


# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)



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## Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **Versions 2005–2018:**  
**Albert / Audretsch / Brunnert / Fersis / Friedrich /  
Friederichs / Gerber / Kreipe / Nitz / Rody / Schreer /  
Sinn / Thomssen / Huober / Kreipe/ Friedrich / Sinn**
  
- **Version 2019:**  
**Ditsch / Kreipe**

### Pubmed 2010-2018 queries

#### Lobular neoplasia (119 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2010/01/01"[dp] : "2018/01/01"[dp]) AND ("lobular neoplasia"[ti] OR "lobular intraepithelial neoplasia"[ti] OR "atypical lobular hyperplasia"[ti] OR "lobular carcinoma in situ"[ti] OR "LIN"[ti] OR "ALH"[ti] OR "LCIS"[ti]) AND ("english"[la] OR "german"[la])

#### Atypical ductal hyperplasia (57 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2010/01/01"[dp] : "2018/01/01"[dp]) AND ("atypical ductal hyperplasia"[ti] OR "atypical hyperplasia"[ti] OR "ADH"[ti]) AND ("english"[la] OR "german"[la])

#### Flat epithelial atypia (55 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2010/01/01"[dp] : "2018/01/01"[dp]) AND ("flat epithelial atypia"[ti] OR "columnar cell"[ti] OR "FEA"[ti]) AND ("english"[la] OR "german"[la])

#### Papilloma (181 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2010/01/01"[dp] : "2018/01/01"[dp]) AND ("papilloma"[ti] OR "papillary"[ti]) AND ("english"[la] OR "german"[la]) NOT virus[Title]


#### Radial scar (15 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2010/01/01"[dp] : "2018/01/01"[dp]) AND ("radial scar"[ti] OR "complex sclerosing lesion"[ti] OR "radial sclerosing lesion"[ti]) AND ("english"[la] OR "german"[la])

#### National and international guidelines

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## Pathology Reporting for Minimal Invasive Biopsies

### B-Classification\*

**B1 =** unsatisfactory or normal tissue only

**B2 =** benign lesion

**B3 =** lesion of uncertain malignant potential

**B4 =** suspicion of malignancy

**B5 =** malignant

B5a = non-invasive


B5b = invasive

B5c = in situ/invasion not assessable

B5d = non epithelial, metastatic


\* National Coordinating Group for Breast Screening Pathology (NHSBSP),  
E.C. Working Group on Breast Screening Pathology, 53-Leitlinie Mammakarzinom der DKG

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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">B3-Lesions</h2> <ol style="list-style-type: none"> <li><b>1. Lesions with increased risk of associated DCIS or invasive carcinoma</b> <ul style="list-style-type: none"> <li>▪ Atypical ductal hyperplasia (ADH) or atypical epithelial proliferation of ductal type (classification possibly as B4, depending on extent of lesion)</li> <li>▪ Flat epithelial atypia (FEA)</li> <li>▪ Lobular neoplasia (LIN; LN; now subdivided into ALH and LCIS, no differentiation according to older nomenclature) classical and non-classical type</li> <li>▪ Atypical apocrine adenosis</li> </ul> </li> <li><b>2. Potentially heterogeneous lesions with risk of incomplete sampling</b> <ul style="list-style-type: none"> <li>▪ Cellular fibroepithelial lesion or phyllodes tumour without evidence of malignancy</li> <li>▪ Intraductal papilloma with/without atypia (possibly also B4, depending on the extent of the lesion)</li> <li>▪ Radial scar or complex sclerosing lesion (unless the radial scar only microscopically, not radiologically detected: B2)</li> <li>▪ Hemangioma</li> </ul> </li> <li><b>3. Rare Lesions</b> <ul style="list-style-type: none"> <li>▪ Adenomyoepithelioma, microglandular adenosis, mucocele-like lesion, nodular fasciitis, desmoid-type fibromatosis, spindle cell lesion of unknown significance</li> </ul> </li> </ol>
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Main types of B3-Lesions and Prospective Predictive Value (PPV) of Malignancy in Resection Specimen (DCIS/inv. Ca.)		
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	▪ Atypical ductal hyperplasia (ADH)	20–30 %
	▪ Lobular intraepithelial neoplasia (LN/LIN)	0–10 %
	▪ Flat epithelial atypia (FEA)	0–10 %
	▪ Radial scar / Complex sclerosing lesion	0–10 %
	▪ Papilloma without atypia	0–10 %
	▪ Cellular fibroepithelial tumors / phyllodes tumors	0%

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## Management after Minimally Invasive Biopsy

Oxford

LoE	GR	AGO
3a	C	++
3a	C	++
5	D	+


■ **Interdisciplinary conference:**  
**Concordant findings in pathology and imaging?**

- yes: proceed according to histologic type
- no: open biopsy
- Vacuum-assisted biopsy (after core biopsy)

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## Atypical ductal Hyperplasia (ADH)

- **Synonyms:** Atypical intraductal epithelial proliferation (AIDEP), atypical epithelial proliferation of ductal type
- **Definition:** Atypical intraductal proliferations with cytological and structural features of well differentiated DCIS, such as rigid bridging or micropapillae, well demarcated cell borders and occupy less than two separate duct spaces. The extension of all involved lumens within one ductulo-lobular unit is less than 2 mm. Atypical ductal proliferations larger than 2 mm or in at least two ductules are classified as DCIS (low-grade).
- **Indicator/Precursor lesion:** Ipsilateral and contralateral breast cancer risk: RR 3 - 5 x after 3 - 5 years.
- Particularly high risk for breast cancer when combined with BIRADS IV / V and high breast volume.

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# Strategy after Diagnosis of ADH in Biopsy Specimen

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	LoE	GR	AGO
<b>ADH in core- / vacuum-assisted biopsy:</b>			
→ <b>Open excisional biopsy</b>	3a	C	++
→ <b>Open excisional biopsy may be omitted, with:</b>			
a) No mass-lesion radiologically, and			
b) a small lesion ( $\leq 2$ TDLU*) in vacuum biopsy, and	5a	C	+/-
c) complete removal of imaging abnormality			
<b>ADH at margins in open biopsy specimen:</b>			
→ <b>No further surgery, if incidental finding     accompanies invasive or intraductal     carcinoma</b>	3a	C	++

\* Terminal ductal-lobular unit

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## Risk of Breast Cancer after Atypical Hyperplasy (ADH, ALH)

### Stratification of breast cancer risk\*

■ Number of Foci:	1	RR = 2.65 (2.06–3.41)
	2	RR = 5.19 (3.59–7.52)
	≥ 3	RR = 8.94 (5.48–14.59)
■ Microcalcifications	present	RR = 3,21
	not present	RR = 4,21
■ Type	ductal	RR = 3,83
	lobular	RR = 3,67
	both	RR = 7,10
■ Age	< 45	RR = 6,76
	45–55	RR = 5,10
	> 55	RR = 2,67

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## Lobular Intraepithelial Neoplasia (LIN)

- Includes: Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS
- LIN 1–3 classification is not sufficiently validated prognostically
- Pleomorphic LIN and LIN with comedo-type necrosis are classified as premalignant → **B5a**
- Indicator/Precursor lesion:  
Ipsi- and contralaterally increased breast cancer risk:  
7 x after 10 years


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Statement: Indicator-/ precursor lesion

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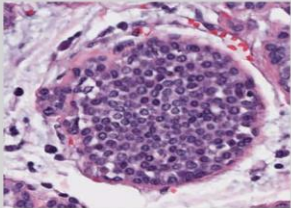
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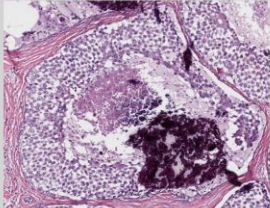
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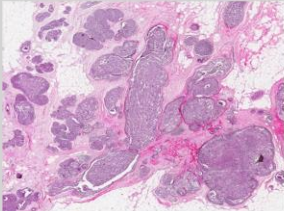
## Classical LIN and Variants of LIN with increased risk



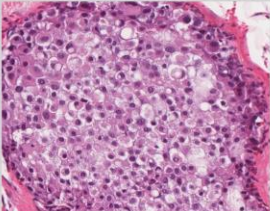
Classical LIN



LIN with comedo type necrosis




Florid LIN



Pleomorphic LIN

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## LIN with High Risk

- **Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necrosis, microcalcifications**
- **Florid LCIS: Involvement of numerous lobuli with distension and near confluence, extension to ductules and neighbouring TDLU**
- **Type of LCIS with 21 cases of LCIS with microinvasion\*:**
  - classical LCIS: n = 11
  - florid LCIS: n = 4
  - pleomorphic LCIS: n = 1

\* Ross DS. Am J Surg Pathol 2011 35: 750–6.

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1. Carder, P. J., Shaaban, A., Alizadeh, Y. et al. (2010). Screen-detected pleomorphic lobular carcinoma in situ (PLCIS): risk of concurrent invasive malignancy following a core biopsy diagnosis. *Histopathology*, 57(3), 472–478. <http://doi.org/10.1111/j.1365-2559.2010.03634.x>
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3. Downs-Kelly, E., Bell, D., Perkins, G. H. et al. (2011). Clinical implications of margin involvement by pleomorphic lobular carcinoma in situ. *Archives of Pathology & Laboratory Medicine*, 135(6), 737–743. <http://doi.org/10.1043/2010-0204-OA.1>
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Statement: Florid lobular carcinoma in situ (FLCIS)

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Statement: Lobular carcinoma in situ with microinvasion

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## Strategy after Diagnosis of LIN

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li><b>LIN in core- / vacuum-assisted biopsy:</b> <ul style="list-style-type: none"> <li>→ No further studies when LIN (classical variant) represents an incidental or isolated finding in core or vacuum biopsy and concordance in imaging</li> <li>→ Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or when not concordant with imaging findings</li> </ul> </li> <li><b>LIN at margins of resection specimen (BCT):</b> <ul style="list-style-type: none"> <li>→ No further surgery</li> </ul> </li> <li><b>Exceptions:</b> <ul style="list-style-type: none"> <li>a) Pleomorphic LIN, florid LIN, or LIN with necrosis</li> <li>b) Imaging abnormality is not removed</li> </ul> </li> </ul>	2b	C	++
	2b	C	++
	2a	C	++


### LIN in core- / vacuum-assisted biopsy (LoE 2b)

- Atkins KA, Cohen MA, Nicholson B et al. Atypical lobular hyperplasia and lobular carcinoma in situ at core breast biopsy: use of careful radiologic-pathologic correlation to recommend excision or observation. Radiology. 2013 Nov;269(2):340-7.
- Bianchi S, Bendinelli B, Castellano I et al.: VANCb Study Group. Morphological parameters of lobular in situ neoplasia in stereotactic 11-gauge vacuum-assisted needle core biopsy do not predict the presence of malignancy on subsequent surgical excision. Histopathology. 2013 Jul;63(1):83-95.
- Buckley, E. S., Webster, F., Hiller, J. E. et al.(2014). ScienceDirect. European Journal of Surgical Oncology, 40(2), 168–175. <http://doi.org/10.1016/j.ejso.2013.10.024>
- D'Alfonso TM, Wang K, Chiu YL et al. Pathologic upgrade rates on subsequent excision when lobular carcinoma in situ is the primary diagnosis in the needle core biopsy with special attention to the radiographic target. Arch Pathol Lab Med. 2013 Jul;137(7):927-35.
- Hussain, M., & Cunnick, G. H. (2011). Management of lobular carcinoma in-situ and atypical lobular hyperplasia of the breast--a review. European Journal of Surgical Oncology : the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 37(4), 279–289. <http://doi.org/10.1016/j.ejso.2011.01.009>
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<http://doi.org/10.1016/j.soc.2014.03.002>
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12. Parkin CK, Garewal S, Waugh P et al.: Outcomes of patients with lobular in situ neoplasia of the breast: the role of vacuum-assisted biopsy. *Breast*. 2014 Oct;23(5):651-5. doi: 10.1016/j.breast.2014.06.016.
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15. Whiffen A: Predictors of Breast Cancer Development in Women with Atypical Ductal Hyperplasia and Atypical Lobular Hyperplasia. *Ann Surg Oncol*. 2010 Sep 28.
16. NCCN Guidelines 03/2018. Breast cancer screening and diagnosis.

LIN accompanying intraductal or invasive carcinoma in patients with BCT (LoE 2a)

1. Ciocca R: Presence of lobular carcinoma in situ does not increase recurrence in patients treated with breast-conserving therapy. *Ann Surg Oncol* 2008; 15:2263-2271



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## Flat Epithelial Atypia (FEA)

- **Synonyms:** Columnar cell hyperplasia with atypia, columnar cell metaplasia with atypia, ductal intraepithelial neoplasia grade 1A (DIN 1A)
- **Differential diagnosis:**
  - ADH is discriminated by architectural features (micropapillary, cribriform) → **B3**
  - Clinging carcinoma is discriminated by high grade nuclear atypia (G2/G3) and classified as ductal carcinoma in situ → **B5a**
- **Marker lesion:**  
FEA frequently is associated with calcifications and may be associated with low-grade intraductal carcinoma. Frequent occurrence in combination with high density of the breast (OR1.3). High risk for associated breast cancer in the presence of extensive calcifications (also when 75% of calcification remained after biopsy), age >= 57J, > 1 cm in imaging, >= 4 foci.

### General

1. Böcker, W., Hungermann, D., Tio, J. et al. (2009). Flache epitheliale Atypie. *Der Pathologe*, 30(1), 36–41. <http://doi.org/10.1007/s00292-008-1123-y>
2. Elif, A., Burcu, S., Nazan, C. et al. (2015). Columnar cell lesions of the breast: radiological features and histological correlation. *Medical Ultrasonography*, 17(2), 147–154. <http://doi.org/10.11152/mu.2013.2066.172.ccl>
3. Moinfar, F. (2009). Flat ductal intraepithelial neoplasia of the breast: a review of diagnostic criteria, differential diagnoses, molecular-genetic findings, and clinical relevance--it is time to appreciate the Azzopardi concept! *Archives of Pathology & Laboratory Medicine*, 133(6), 879–892.
4. Schnitt, S., & Vincent-Salomon, A. (2003). Columnar cell lesions of the breast. *Advances in Anatomic Pathology*, 10(3), 113–124.
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### Statement: Marker Lesion

1. Boulos, F. I., Dupont, W. D., Simpson, J. F. et al. (2008). Histologic associations and long-term cancer risk in columnar cell lesions of the breast: a retrospective cohort and a nested case-control study. *Cancer*, 113(9), 2415–2421. <http://doi.org/10.1002/cncr.23873>
2. Collins, L. C., Achacoso, N. A., Nekhlyudov, L. et al. (2007). Clinical and pathologic features of ductal carcinoma in situ associated

- with the presence of flat epithelial atypia: an analysis of 543 patients. *Modern Pathology*, 20(11), 1149–1155.  
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3. Lamb, L. R., Bahl, M., Gadd, M. A et al. (2017). Flat Epithelial Atypia: Upgrade Rates and Risk-Stratification Approach to Support Informed Decision Making. *Journal of the American College of Surgeons*, 225(6), 696–701.  
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  4. Noske, A., Pahl, S., Fallenberg, E. et al. (2010). Flat epithelial atypia is a common subtype of B3 breast lesions and is associated with noninvasive cancer but not with invasive cancer in final excision histology. *Human Pathology*, 41(4), 522–527.  
<http://doi.org/10.1016/j.humpath.2009.09.005>
  5. Pandey, S., Kornstein, M. J., Shank et al. (2007). Columnar cell lesions of the breast: mammographic findings with histopathologic correlation. *Radiographics : a Review Publication of the Radiological Society of North America, Inc*, 27 Suppl 1, S79–89.  
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  6. Said, S. M., Visscher, D. W., Nassar, A et al. (2015). Flat epithelial atypia and risk of breast cancer: A Mayo cohort study. *Cancer*, 121(10), 1548–1555. <http://doi.org/10.1002/cncr.29243>
  7. Verschuur-Maes, A. H. J., Witkamp, A. J., de Bruin, P. C. et al. (2011). Progression risk of columnar cell lesions of the breast diagnosed in core needle biopsies. *International Journal of Cancer Journal International Du Cancer*, 129(11), 2674–2680.  
<http://doi.org/10.1002/ijc.25926>
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  9. Ghosh K, Vierkant RA, Frank RD et al: Association between mammographic breast density and histologic features of benign breast disease. *Breast Cancer Res* , 2017, 19:134
  10. Alencherry E, Goel R, Gore S et al.: Clinical, imaging, and intervention factors associated with the upgrade of isolated flat epithelial atypia. *Clinical Imaging* 2019, 54:21-24




## Strategy after Diagnosis of FEA

	Oxford		
	LoE	GR	AGO
<b>FEA in core biopsy/vacuum-assisted biopsy:</b> → Open excisional biopsy may be omitted under the following circumstances: a) a small lesion ( $\leq 2$ TDLU* in vacuum biopsy) <b>and</b> b) Complete or near complete removal of imaging abnormality → Representative open excisional biopsy in radiologically extensive microcalcifications or discordance to the radiological result	3b	C	+
<b>FEA at margins in resection specimen:</b> → No further surgery, unless calcifications have not been completely removed	5	C	+
	3b	C	++

\* Terminal ductal-lobular unit

1. Becker, A. K., Gordon, P. B., Harrison, D. A. et al. (2013). Flat Ductal Intraepithelial Neoplasia 1A Diagnosed at Stereotactic Core Needle Biopsy: Is Excisional Biopsy Indicated? American Journal of Roentgenology, 200(3), 682–688. <http://doi.org/10.2214/AJR.11.8090>
2. Calhoun, B. C., Sobel, A., White, R. L et al. (2015). Management of flat epithelial atypia on breast core biopsy may be individualized based on correlation with imaging studies. Modern Pathology, 28(5), 670–676. <http://doi.org/10.1038/modpathol.2014.159>
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## Papilloma

- **Includes:** Central and peripheral papilloma > 2 mm, atypical intraductal papilloma (B3)
- To be **distinguished from** peripheral micropapilloma arising in the TDLU, size ≤ 2 mm, may be multiple
- To be distinguished from papilloma with DCIS, from intraductal papillary carcinoma, and from encapsulated papillary carcinoma
- **Indicator lesion:**  
May be associated with in-situ or invasive cancer (up to 6% without atypia if concordant imaging, up to 30% with atypia), increased ipsilateral risk for cancer (up to 4.6% and up to 13% in case of atypical papilloma) .

1. World Health Organization. Who Classification of Tumours of the Breast. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, editors. World Health Organization; 2012.
2. Bilous M. Breast core needle biopsy: issues and controversies. Mod Pathol. 2010 May 1;23 Suppl 2:S36–45.
3. Page DL, Salhany KE, Jensen RA et al. Subsequent breast carcinoma risk after biopsy with atypia in a breast papilloma. Cancer. 1996 Jul 14;78(2):258–66.
4. Khan S, Diaz A, Archer KJ et al. Papillary lesions of the breast: To excise or observe? Breast J. 2018 May;24(3):350-355.
5. Leithner D, Kaltenbach B, Hödl P et al. Intraductal Papilloma Without Atypia on Image- Guided Breast Biopsy: Upgrade Rates to Carcinoma at Surgical Excision. Breast Care (Basel). 2018 Oct;13(5):364-368.

Strategy after Diagnosis of Papilloma			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Papilloma without atypia in core needle or vacuum biopsy:</b> <ul style="list-style-type: none"> <li>→ no further therapy, when biopsy sufficiently representative (100 mm<sup>2</sup>) and no discordance to imaging</li> </ul> </li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>■ <b>Multiple papillomas</b> <ul style="list-style-type: none"> <li>→ open biopsy</li> </ul> </li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>■ <b>Papilloma with atypia in core needle or vacuum biopsies:</b> <ul style="list-style-type: none"> <li>→ open biopsy</li> </ul> </li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>■ <b>Papilloma at resection margin:</b> <ul style="list-style-type: none"> <li>→ no published data available</li> </ul> </li> </ul>			



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3. Lewis, J., Hartmann, L., Vierkant, R. et al. (2006). An analysis of breast cancer risk in women with single, multiple, and atypical papilloma. *Am J Surg Pathol*, 30(6), 665–672.
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5. Rakha EA et al: Characterisation and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. *Int J Cancer*. 2010 Dec 2. [Epub ahead of print]
6. Shamonki J, Chung A, Huynh KT et al. Management of papillary lesions of the breast: can larger core needle biopsy samples identify patients who may avoid surgical excision? *Ann Surg Oncol*. 2013 Dec;20(13):4137-44
7. Swapp RE, Glazebrook KN, Jones KN et al. Management of benign intraductal solitary papilloma diagnosed on core needle biopsy. *Ann Surg Oncol*. 2013 Jun;20(6):1900–5.
8. Wen X, Cheng W. Nonmalignant Breast Papillary Lesions at Core-Needle Biopsy: A Meta-analysis of Underestimation and Influencing Factors. *Ann Surg Oncol*. 2012 Aug 10;20(1):94–101.
9. Wyss P, Varga Z, Rössle M et al.: Papillary lesions of the breast: outcomes of 156 patients managed without excisional biopsy.


Breast J. 2014 Jul-Aug;20(4):394-401.

## Radially Sclerosing Lesion

- **Benign pseudoinfiltrative lesion with central fibroelastic core and radical configuration.**
- **Includes:**
  - radial scar
  - complex sclerosing lesion (> 1 cm)
- **Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)**
- **Risk for upgrade in open biopsy after diagnosis of a radial sclerosing lesion, depending on the size of the needle (CNB) or method (VAB) and additional atypia: 1–18%**

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## Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

Oxford		
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- **Radial scar / CSL in core- / vacuum-assisted biopsy:**
  - Open excisional biopsy may be omitted with a small (< 5mm) lesion or complete removal or near complete removal of imaging abnormality
  
- **Radial scar / CSL at margins in resection specimen:**
  - No further surgery


	5a	C	+
→ Open excisional biopsy may be omitted with a small (< 5mm) lesion or complete removal or near complete removal of imaging abnormality			
	3b	C	++

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## Management Radial Scar


- “When RS (radial scar) is associated to atypia (such as flat epithelial atypia (FEA), atypical ductal (ADH), or lobular neoplasia (classical LN)), management can the same as recommended in cases of atypia alone.

**Rageth CJ, O’Flynn EAM, Pinker K et al.: Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Review, Breast Cancer Res Treat, 2018, doi: 10.1007/s10549-018-05071-1**

1. Rageth CJ, O’Flynn EAM, Pinker K et al.: Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Review, Breast Cancer Res Treat, 2018, doi: 10.1007/s10549-018-05071-1

Follow-up Imaging for Women Age 50–69 Years with B3-Lesions			
	Oxford		
	LoE	GR	AGO
<div> <div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div> <div> <ul style="list-style-type: none"> <li>▪ <b>FEA, non-atypical papilloma</b> <ul style="list-style-type: none"> <li>▪ Screening mammography</li> </ul> </li> <li>▪ <b>LIN</b> <ul style="list-style-type: none"> <li>▪ Mammography (12 months)</li> </ul> </li> <li>▪ <b>ADH</b> <ul style="list-style-type: none"> <li>▪ Mammography (12 months)</li> <li>▪ Women with LIN and ADH should be informed about their elevated risk of breast cancer</li> </ul> </li> </ul> </div> </div>	5	C	++
	3a	C	++
	3a	C	++
	3a	C	++

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## Medical Prevention for Lesions with Uncertain Biological Behavior (incl. LIN, ADH)

	Oxford LoE	GR	AGO
■ Tamoxifen for women > 35 years – Risk reduction of invasive BrCa and DCIS	1a	A	+
■ Aromatase inhibitors (Exemestan, Anastrozole) for postmenopausal women	1b	A	+/-
■ Raloxifen for postmenopausal women – Risk reduction of invasive BrCa only	1b	A	+/-*

**Medical prevention should only be offered after individual and comprehensive counseling; the overall benefit is dependent on classification, age and pre-existing conditions that may influence the occurrence of side effects.**

\* Risk situation as defined in NSABP P1-trial (1,66% in 5 years)

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2. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 2007; 99:272-282
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4. Bozovic-Spasojevic I, Azambuja E, McCaskill-Stevens W et al.: Chemoprevention for breast cancer. Cancer Treat Rev. 2012 Aug;38(5):329-39.
5. Lobular Carcinoma in Situ: A 29-Year Longitudinal Experience Evaluating Clinicopathologic Features and Breast Cancer Risk.

Tamoxifen für Frauen > 35 Jahre –Reduktion von DCIS und invasivem Karzinom

NSABP.P1

1. Fischer B: Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. *J Natl Cancer Inst* 2005, 97:1652-1662

#### IBIS.1

1. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007; 99:272-282.

Royal Marsden  
Italian Trial

#### Aromataseinhibitor (Exemestan, Anastrozol) für postmenopausale Frauen

#### MAP.3

1. Goss PE, Ingle JN, Alés-Martínez JE et al.: Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. 2011 Jun 23;364(25):2381-91.
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#### IBIS.2

1. Cuzick J, Sestak I, Forbes JF et al.: Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial *Lancet* 2014; 383: 1041–48

## Prevention for Lesions with Uncertain Biological Behavior (Tamoxifen)

### NSABP-P2 Study, STAR trial 2006

	Placebo Rate / 1000 WE	Tamoxifen Rate / 1000 WE	RR	95% CI
All women	6.29	3.59	0.57	0.46-0.70
± LCIS	5.93	3.41	0.58	0.46-0.72
+ LIN	11.70	6.27	0.54	0.27-1.02
w/o ADH	5.87	3.69	0.63	0.50-0.78
+ ADH	10.42	2.55	0.25	0.10-0.52
5-year-risk <2%	4.77	3.18	0.67	0.43-1.01
5-year-risk > 5%	11.98	5.15	0.43	0.28-0.64
Relative 1. grade	6.47	3.48	0.54	0.34-0.83
> 3 relatives 1. grade	11.24	5.48	0.49	0.16-1.34
Fractures	2.88	1.97	0.91	0.51-0.92
Endometrial cancer	0.68	2.24	3.28	1.87-6.03


**Should only be offered to women with enhanced breast cancer risk (Gail  $\geq 1.66\%$ ):**

- LIN , with ADH
- Family history of breast cancer

**Should not be offered to women:**

- With moderate risk and > 50 year of age
- With enhanced risk for thrombembolism

1. Visvanathan, K., Hurley, P., Bantug, E. et al. (2013). Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31(23), 2942–2962. <http://doi.org/10.1200/JCO.2013.49.3122>
2. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized INIS-I trial. J Natl Cancer Inst 2007; 99:272-282
3. Vogel V: Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial. JAMA 2006; 295(23):2727-2741.
4. Fischer B: Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst 2005, 97:1652-1662



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## Prevention for Lesions with Uncertain Biological Behavior (Tamoxifen, Side Effects)

**Risks and Benefits with long-term Tamoxifen use compared with placebo:  
results from the IBIS-I Trial 96 months median follow-up  
(Cuzick J et al J Natl Cancer Inst 2007:272-282)**

Incidence	RR	95% CI	AR je 1000*	NNT / NNH**
Breast cancer	0.73	0.58-0.91	15	68
Invasive carcinoma	0.74	0.58-0.94	12	81
Thrombembolism	1.72	1.27-2.36	14	73
Deep vein thrombosis leg	1.84	1.21-2.82	9	115
Headache	0.93	0.87-0.99	25	39
Gynecological-/ vasom- otoric symptoms	1.08	1.06-1.10	64	16
Chest pain	0.77	0.70-0.84	58	17


**AR\*:Absolute risk per 1000 women. NNT/NNH\*\* = number needed to treat or number needed to harm**

**Data shown are statistically significant associations for a follow-up-period of 96 month.**

**Calculations by the authors of the guideline. Visvanathan K et al. JCO 2009;27:3235-3258.**

1. Visvanathan, K., Hurley, P., Bantug, E. et al. (2013). Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31(23), 2942–2962. <http://doi.org/10.1200/JCO.2013.49.3122>
2. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized INIS-I trial. J Natl Cancer Inst 2007; 99:272-282
3. Stacey, D., Légaré, F., Lewis, K. et al. (2017). Decision aids for people facing health treatment or screening decisions. The Cochrane Database of Systematic Reviews, 4, CD001431. <http://doi.org/10.1002/14651858.CD001431.pub5>





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## Prevention for Lesions with Uncertain Biological Behavior (Raloxifen)

### NSABP-P2 Study, STAR Trial 2006

	Tamoxifen: Rate / 1000 WE	Raloxifen Rate / 1000 WE	RR	95% CI
All women	4.30	4.41	1.02	0.82-1.28
± LIN	3.76	3.89	1.03	0.81-1.33
+ LIN	9.83	9.61	0.98	0.58-1.63
± ADH	4.06	4.03	0.99	0.76-1.28
+ ADH	5.21	5.81	1.12	0.72-1.74


**Should only be offered to women with enhanced breast cancer risk :**

- (Gail ≥ 1,66%) or postmenopausal

**Should not be offered to women:**

- With moderate risk > 50 year of age
- With enhanced risk for thromboembolism

1. Visvanathan, K., Hurley, P., Bantug, E. et al. (2013). Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31(23), 2942–2962. <http://doi.org/10.1200/JCO.2013.49.3122>
2. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized INIS-I trial. J Natl Cancer Inst 2007; 99:272-282
3. Vogel V: Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial. JAMA 2006; 295(23):2727-2741.
4. Fischer B: Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst 2005, 97:1652-1662

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Prevention for Lesions with Uncertain Biological Behavior (Aromatase Inhibitors)</h2> <table border="1"> <thead> <tr> <th data-bbox="674 189 840 211">Inclusion criteria:</th><th data-bbox="1129 189 1415 237">Results for prior ALH, ADH, LCIS (HR AI vs Plac):</th></tr> </thead> <tbody> <tr> <td data-bbox="674 255 989 368"> <b>IBIS.2:</b> <ul style="list-style-type: none"> <li>Prior ADH, ALH, or LCIS Anastrozole: 154 (8,0%); Placebo: 190 (9,7%)</li> </ul> </td><td data-bbox="1129 294 1415 394"> <ul style="list-style-type: none"> <li>Yes (7J-MaCa-Risiko 12,1%): HR 0,31 (0,12–0,84)</li> <li>No (7J-MCa-Risiko 4,9%): HR 0,52 (0,31–0,78)</li> </ul> </td></tr> <tr> <td data-bbox="674 418 989 531"> <b>MAP.3:</b> <ul style="list-style-type: none"> <li>Prior ADH, ALH, or LCIS: Exemestane: 185 (8,1%); Placebo: 188 (8,3%)</li> </ul> </td><td data-bbox="1129 455 1415 502"> <ul style="list-style-type: none"> <li>Yes: HR=0,61 (0,20–1,82)</li> <li>No: HR=0,26 (0,11–0,64)</li> </ul> </td></tr> </tbody> </table> <p>Cuzick J et al. Lancet 2014; 383: 1041–48 Goss PE et al. N Engl J Med. 2011 Jun 23;364(25):2381-91</p>	Inclusion criteria:	Results for prior ALH, ADH, LCIS (HR AI vs Plac):	<b>IBIS.2:</b> <ul style="list-style-type: none"> <li>Prior ADH, ALH, or LCIS Anastrozole: 154 (8,0%); Placebo: 190 (9,7%)</li> </ul>	<ul style="list-style-type: none"> <li>Yes (7J-MaCa-Risiko 12,1%): HR 0,31 (0,12–0,84)</li> <li>No (7J-MCa-Risiko 4,9%): HR 0,52 (0,31–0,78)</li> </ul>	<b>MAP.3:</b> <ul style="list-style-type: none"> <li>Prior ADH, ALH, or LCIS: Exemestane: 185 (8,1%); Placebo: 188 (8,3%)</li> </ul>	<ul style="list-style-type: none"> <li>Yes: HR=0,61 (0,20–1,82)</li> <li>No: HR=0,26 (0,11–0,64)</li> </ul>
Inclusion criteria:	Results for prior ALH, ADH, LCIS (HR AI vs Plac):						
<b>IBIS.2:</b> <ul style="list-style-type: none"> <li>Prior ADH, ALH, or LCIS Anastrozole: 154 (8,0%); Placebo: 190 (9,7%)</li> </ul>	<ul style="list-style-type: none"> <li>Yes (7J-MaCa-Risiko 12,1%): HR 0,31 (0,12–0,84)</li> <li>No (7J-MCa-Risiko 4,9%): HR 0,52 (0,31–0,78)</li> </ul>						
<b>MAP.3:</b> <ul style="list-style-type: none"> <li>Prior ADH, ALH, or LCIS: Exemestane: 185 (8,1%); Placebo: 188 (8,3%)</li> </ul>	<ul style="list-style-type: none"> <li>Yes: HR=0,61 (0,20–1,82)</li> <li>No: HR=0,26 (0,11–0,64)</li> </ul>						

### Exemestane for breast-cancer prevention in postmenopausal women

1. Goss, P. E., Ingle, J. N., Alés-Martínez, J. E. et al. (2011). Exemestane for breast-cancer prevention in postmenopausal women. The New England Journal of Medicine, 364(25), 2381–2391. <http://doi.org/10.1056/NEJMoa1103507>

### Chemoprevention for breast cancer

1. Bozovic-Spasojevic, I., Azambuja, E., McCaskill-Stevens, W. et al. (2012). Chemoprevention for breast cancer. Cancer Treatment Reviews, 38(5), 329–339. <http://doi.org/10.1016/j.ctrv.2011.07.005>