

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Läsionen mit unsicherem biologischen Potenzial (B3)

(ADH, LIN, FEA, Papillom, Radiäre Narbe)



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Läsionen mit unklarem biologischen Potenzial (B3)

- **Versionen 2005–2017:**

Albert / Audretsch / Brunnert / Fersis / Friedrich /
Friederichs / Gerber / Huober / Kreipe / Nitz / Rody / Schreer /
Sinn / Thomssen

- **Version 2018:**

Friedrich / Sinn

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

1. AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.0, Aktualisierung 2017
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Pathologische Berichterstellung für minimalinvasive Biopsien

B-Klassifikation*


B1 B2 B3 B4 B5	= = = = =	nicht verwertbar oder ausschließlich normales Gewebe benigne benigne, aber mit unsicherem biologischen Potenzial verdächtig auf Malignität maligne B5a = intraduktal B5b = invasiv B5c = unklar, ob invasiv oder in situ B5d = nicht epithelial, metastatisch
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National Coordinating Group for Breast Screening Pathology (NHBSP),
E.C. Working Group on Breast Screening Pathology, S3-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 2018.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">B3-Läsionen</h2> <ol style="list-style-type: none"> Läsionen mit erhöhtem Risiko eines assoziierten DCIS oder invasiven Karzinoms <ul style="list-style-type: none"> Atypische duktale Hyperplasie (ADH) bzw. atypische Epithelproliferation vom dukталen Typ (in Abhängigkeit von der Ausdehnung ggf. B4) Flache epitheliale Atypie (FEA) Lobuläre Neoplasie, klassischer Typ (LN; ALH und LCIS) Atypische apokrine Adenose Potenziell heterogene Läsionen mit Risiko eines unvollständigen Sampling <ul style="list-style-type: none"> Zellreiche fibroepitheliale Läsion oder Phylloides tumor ohne Malignitätsverdacht Intraduktales Papillom ohne /mit Atypien, nicht sicher vollständig entfernt (bei Atypien in Abhängigkeit von der Ausdehnung ggf. B4) Radiäre Narbe bzw. komplexe sklerosierende Läsion (Ausnahme: wenn radiäre Narbe nicht Ursache der radiologischen Veränderung: B2) Hämangiom Seltene Veränderungen <ul style="list-style-type: none"> Adenomyoepitheliom, Mikroglanduläre Adenose, Mukozelenartige Läsion, Noduläre Faszitis, Fibromatose vom Desmoidtyp, unklare Spindelzellläsion
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B3-Läsionen:	~PPV														
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Management nach minimalinvasiver Biopsie

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Interdisziplinäre Konferenz: Pathologie und Bildgebung konkordant? <ul style="list-style-type: none"> → ja: Vorgehen gemäß histologischem Typ → nein: offene PE 	3a	C	++
	3a	C	++
Vakuumbiopsie (nach Stanzbiopsie)	5	D	+

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Atypische duktale Hyperplasie (ADH)

- **Synonyme:** Atypische intraduktale Epithelproliferation, atypische epitheliale Proliferation vom dukталen Typ (ADP)
- **Definition:** Atypische intraduktale Proliferation mit zytologischen und strukturellen Merkmalen eines gut differenzierten DCIS, wie Ausbildung starrer Brücken oder Mikropapillen, häufig gut erkennbaren Zellgrenzen und höchstens zwei ganz von atypischen Epithelproliferaten ausgefüllte Gängen. Die Summe der Durchmesser aller betroffenen Lumina in einer duktulolobulärer Einheit (TDLUs) nicht mehr als 2 mm. Proliferationen größer 2 mm oder mehr als zwei komplett ausgefüllte Gänge werden als DCIS (low-grade) bezeichnet.
- **Indikator-/Vorläuferläsion:** Ipsi- und kontralateral erhöhtes Brustkrebsrisiko: RR 3 - 5-fach nach 10 Jahren.
- Eine Einteilung in DIN 1 - 3 (dukta intraepitheliale Neoplasie Grad 1 - 3) ist nicht ausreichend validiert.

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Strategie nach Diagnose einer ADH in der Biopsie

ADH in Stanz-/ Vakuumbiopsie:

- Offene Exzisionsbiopsie
- Offene Exzisionsbiopsie verzichtbar, wenn folgende Voraussetzungen erfüllt sind:
 - a) Kein radiologischer Herdbefund
 - b) Fokale Läsion (≤ 2 TDLU*) in Vakuumbiopsie und
 - c) Suspekte Läsion in der Bildgebung komplett entfernt

ADH im Resektionsrand in offener PE:

- Keine Nachresektion, wenn die Veränderung ein intraduktales oder invasives Karzinom begleitet


Oxford		
LoE	GR	AGO
3a	C	++
5a	C	+/-
3a	C	++

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Brustkrebsrisiko nach atypischer Hyperplasie (ADH, ALH)

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Stratifizierung des Brustkrebsrisikos*

▪ Anzahl der Herde:	1 2 ≥ 3	RR = 2.65 (2.06-3.41) RR = 5.19 (3.59-7.52) RR = 8.94 (5.48-14.59)
▪ Mikrokalk (ADH/ALH)	vorhanden nicht vorhanden	RR = 3,21 RR = 4,21
▪ Typ (ADH/ALH)	duktal lobulär beides	RR = 3,83 RR = 3,67 RR = 7,10
▪ Alter (ADH/ALH)	< 45 45–55 > 55	RR = 6,76 RR = 5,10 RR = 2,67

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Lobuläre intraepitheliale Neoplasie (LIN)

- Umfasst: Atypische lobuläre Hyperplasia (ALH), lobuläres Carcinoma in situ (LCIS/CLIS)
- Eine Einteilung in LIN 1 - 3 ist prognostisch nicht ausreichend validiert
- Pleomorphe LIN und LIN mit Komedotyp-Nekrose werden als prämaligne klassifiziert → **B5a**
- Indikator-/Vorläufer-Läsion:
Ipsi- und kontralateral erhöhtes Brustkrebsrisiko:
7-fach nach 10 Jahren

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Statement: Indicator-/ precursor lesion

1. Ansquer Y, Delaney S, Santulli P et al. Risk of invasive breast cancer after lobular intra-epithelial neoplasia: review of the literature. *Eur J Surg Oncol*. 2010 Jul;36(7):604–9.
2. Chuba PJ, Hamre MR, Yap J, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. *J Clin Oncol*. 2005 Aug 20;23(24):5534–41.
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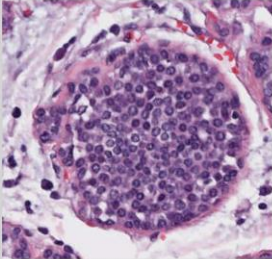
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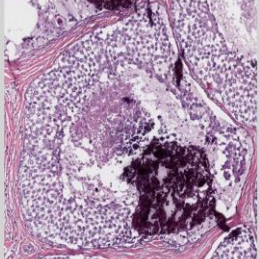
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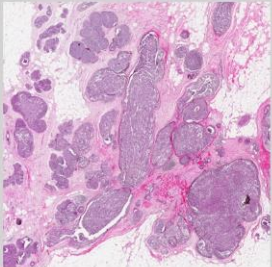
Klassische LIN und Varianten der LIN mit hohem Risiko



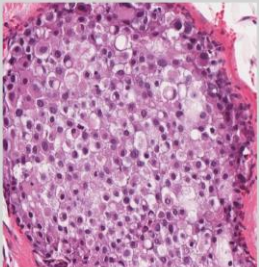
Klass. LIN



LIN mit Komedonekrose




Floride LIN



Pleomorphe LIN

1. Brogi, E., Murray, M. P., & Corben, A. D. (2010). Lobular carcinoma, not only a classic. *Breast Journal*, 16 Suppl 1, S10–4. <http://doi.org/10.1111/j.1524-4741.2010.00994.x>
2. Ginter, P. S., & D'Alfonso, T. M. (2017). Current Concepts in Diagnosis, Molecular Features, and Management of Lobular Carcinoma In Situ of the Breast With a Discussion of Morphologic Variants. *Archives of Pathology & Laboratory Medicine*, 141(12), 1668–1678. <http://doi.org/10.5858/arpa.2016-0421-RA>
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4. Shin SJ, Lal A, De Vries S et al.: Florid lobular carcinoma in situ: molecular profiling and comparison to classic lobular carcinoma in situ and pleomorphic lobular carcinoma in situ. *Hum Pathol*. 2013;44(10):1998-2009.
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LIN mit hohem Risiko

- **Pleomorphes LCIS: höhergradige zelluläre Atypien, häufig Befall der Gänge mit Komedotyp-Nekrosen und Mikroverkalkungen**
- **Florides LCIS: Befall zahlreicher Läppchen mit maximaler Distension bis Konfluenz und Übergreifen auf Duktuli und benachbarter TDLU**
- **Mikroinvasion bei ILC*:**
 - klass. LCIS: n=11
 - florides LCIS: n=4
 - pleomorphes LCIS: n=1

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

Statement: Pleomorphic lobular carcinoma in situ (PLCIS)

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>
2. Chivukula M, Haynik DM, Brufsky A et al. Pleomorphic lobular carcinoma in situ (PLCIS) on breast core needle biopsies: clinical significance and immunoprofile. *Am J Surg Pathol*. 2008;32(11):1721-1726.
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>
4. Khoury, T., Karabakhtsian, R. G., Mattson, D. et al. (2014). Pleomorphic lobular carcinoma in situ of the breast: clinicopathological review of 47 cases. *Histopathology*, 64(7), 981–993. <http://doi.org/10.1111/his.12353>
5. Masannat, Y. A., Bains, S. K., Pinder, S. E et al. (2013). Challenges in the management of pleomorphic lobular carcinoma in situ of the breast. *Breast (Edinburgh, Scotland)*, 22(2), 194–196.
<http://doi.org/10.1016/j.breast.2013.01.003>
6. Monhollen, L., Morrison, C., Ademuyiwa, F. O. et al (2012). Pleomorphic lobular carcinoma: a distinctive clinical and molecular breast cancer type. *Histopathology*, 61(3), 365–377. <http://doi.org/10.1111/j.1365-2559.2012.04230.x>
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Statement: Florid lobular carcinoma in situ (FLCIS)

1. Alvarado-Cabrero, I., Picón Coronel, G., Valencia Cedillo, R et al. (2010). Florid lobular intraepithelial neoplasia with signet ring cells, central necrosis and calcifications: a clinicopathological and immunohistochemical analysis of ten cases associated with invasive lobular carcinoma. *Archives of Medical Research*, 41(6), 436–441. <http://doi.org/10.1016/j.arcmed.2010.08.010>
2. Bagaria, S. P., Shamonki, J., Kinnaird, M. et al.(2011). The florid subtype of lobular carcinoma in situ: marker or precursor for invasive lobular carcinoma? *Annals of Surgical Oncology*, 18(7), 1845–1851. <http://doi.org/10.1245/s10434-011-1563-0>
3. Bratthauer, G., & Tavassoli, F. (2002). Lobular intraepithelial neoplasia: previously unexplored aspects assessed in 775 cases and their clinical implications. *Virchows Archiv : an International Journal of Pathology*, 440(2), 134–138.
4. Fadare, O., Dadmanesh, F., Alvarado-Cabrero, I. et al. (2006). Lobular intraepithelial neoplasia [lobular carcinoma in situ] with comedo-type necrosis: A clinicopathologic study of 18 cases. *The American Journal of Surgical Pathology*, 30(11), 1445–1453. <http://doi.org/10.1097/01.pas.0000213290.58283.82>
5. Shin, S. J., Lal, A., De Vries, S et al. (2013). Florid lobular carcinoma in situ: molecular profiling and comparison to classic lobular carcinoma in situ and pleomorphic lobular carcinoma in situ. *Human Pathology*, 44(10), 1998–2009. <http://doi.org/10.1016/j.humpath.2013.04.004>

Statement: Lobular carcinoma in situ with microinvasion

1. Nemoto, T., Castillo, N., Tsukada, Y et al. (1998). Lobular carcinoma in situ with microinvasion. *Journal of Surgical Oncology*, 67(1), 41–46.
2. Ross, D. S., & Hoda, S. A. (2011). Microinvasive (T1mic) lobular carcinoma of the breast: clinicopathologic profile of 16 cases. *The American Journal of Surgical Pathology*, 35(5), 750–756. <http://doi.org/10.1097/PAS.0b013e318212acd3>



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Strategie nach Diagnose einer LIN

		Oxford		
		LoE	GR	AGO
▪ LIN in Stanz- / Vakuumbiopsie				
▪ Keine weitere Abklärung bei isoliertem oder inzidentellem Befund einer LIN (klassische Variante) in der Stanz- oder Vakuumbiopsie und Konkordanz mit der Bildgebung		2b	C	++
▪ Offene Exzisionsbiopsie bei pleomorpher LIN, florider LIN, LIN mit Komedotypnekrosen, oder wenn Befund nach Korrelation mit der Bildgebung diskordant ist.		2b	C	++
▪ LIN am Resektionsrand von BET				
▪ Keine Nachresektion		2a	C	++
<u>Ausnahmen</u>				
a) Pleomorphe, floride oder LIN mit Nekrosen				
b) Bildgebende Veränderung wurde nicht entfernt				
▪ Komplette Resektion				
		5	D	++

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

1. 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.
2. 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.
3. Buckley, E. S., Webster, F., Hiller, J. E. et al.(2014). ScienceDirect. European Journal of Surgical Oncology, 40(2), 168–175.
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4. 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.
5. 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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7. King, T. A., & Reis-Filho, J. S. (2014). Lobular neoplasia. *Surgical Oncology Clinics of North America*, 23(3), 487–503. <http://doi.org/10.1016/j.soc.2014.03.002>
8. Lakhani, S. R., Audretsch, W., Cleton-Jensen, A.-M. et al. (2006). The management of lobular carcinoma in situ (LCIS). Is LCIS the same as ductal carcinoma in situ (DCIS)? *European Journal of Cancer (Oxford, England : 1990)*, 42(14), 2205–2211. <http://doi.org/10.1016/j.ejca.2006.03.019>
9. Menes TS, Rosenberg R, Balch S et al.: Upgrade of high-risk breast lesions detected on mammography in the Breast Cancer Surveillance Consortium. *Am J Surg*. 2014 Jan;207(1):24-31.
10. Middleton LP, Sneige N, Coyne R et al.: Most lobular carcinoma in situ and atypical lobular hyperplasia diagnosed on core needle biopsy can be managed clinically with radiologic follow-up in a multidisciplinary setting. *Cancer Med*. 2014 Jun;3(3):492-9
11. Neal L, Sandhu NP, Hieken TJ et al.: Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on core needle biopsy. *Mayo Clin Proc*. 2014 Apr;89(4):536-47
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.
13. Purdie CA et al: Management of in situ lobular neoplasia detected on needle core biopsy of breast. *J Clin Pathol*. 2010 Nov;63(11):987-93.
14. 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]
15. Whiffen A: Predictors of Breast Cancer Development in Women with Atypical Ductal Hyperplasia and Atypical Lobular Hyperplasia. *Ann Surg Oncol*. 2010 Sep 28.

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

Flache epitheliale Atypie (FEA)

- **Synonyme:** Kolumnarzellhyperplasie mit Atypien, Kolumnarzellmetaplasie mit Atypien
- **Differenzialdiagnose:**
 - ADH unterscheidet sich durch in das Ganglumen hineinreichende oder ausfüllende Epithelproliferate mit kribriformer oder mikropapillärer Architektur → **B3**
 - DCIS vom Clinging-Typ (clinging carcinoma G2/G3) muss als intraduktales Karzinom eingestuft werden → **B5a**
- **Markerläsion:**
FEA ist häufig mit Mikrokalk assoziiert und es besteht ein Zusammenhang mit dem Auftreten einer FEA und der Entdeckung von ADH und low-grade DCIS. Die stufenartige Aufarbeitung und die Korrelation des pathologischen Befundes mit der Bildgebung sind obligatorisch.

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.
5. Turashvili, G., Hayes, M., Gilks, B et al. (2008). Are columnar cell lesions the earliest histologically detectable non-obligate precursor of breast cancer? *Virchows Archiv : an International Journal of Pathology*, 452(6), 589–598.

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.

<http://doi.org/10.1038/modpathol.3800949>

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.
<http://doi.org/10.1016/j.jamcollsurg.2017.08.022>
4. Noske, A., Pahl, S., Fallenber, 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. <http://doi.org/10.1148/rg.27si075515>
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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Strategie nach Diagnose einer FEA

■ FEA in der Stanz- / Vakuumbiopsie:

- Auf offene Biopsie kann verzichtet werden unter folgenden Voraussetzungen
 - a. Kleinherdiger Befund (≤ 2 TDLU* in Vakuumbiopsie) und
 - b. Entfernung oder weitgehend vollständige Entfernung der auffälligen Läsion in der Bildgebung
- Repräsentative offene Biopsie nur bei radiologisch ausgedehnten begleitenden Verkalkungen oder bei Diskordanz zum radiologischen Befund

■ FEA im Resektionsrand nach Exzisionsbiopsie:

- Keine Nachresektion, außer bei verbliebenem mammographischem Korrelat

Oxford		
LoE	GR	AGO
3b	C	+
5	C	+
3b	C	++


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* TDLU = terminale duktulolobuläre Einheit


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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>
3. Ceugnart, L., Doualliez, V., Chauvet, M. P. et al. (2013). Pure flat epithelial atypia: is there a place for routine surgery? Diagnostic and Interventional Imaging, 94(9), 861–869. <http://doi.org/10.1016/j.diii.2013.01.011>
4. Dialani, V., Venkataraman, S., Frieling, G. et al. (2014). Does Isolated Flat Epithelial Atypia on Vacuum-assisted Breast Core Biopsy Require Surgical Excision? The Breast Journal, 20(6), 606–614. <http://doi.org/10.1111/tbj.12332>
5. Kunju, L. P., & Kleer, C. G. (2007). Significance of flat epithelial atypia on mammotome core needle biopsy: Should it be excised? Human Pathology, 38(1), 35–41. <http://doi.org/10.1016/j.humpath.2006.08.008>
6. Maeda, I., Kanemaki, Y., Tozaki, M. et al. (2015). Positive predictive value for malignancy of pure flat epithelial atypia diagnosis by percutaneous needle biopsy of the breast: management of FEA in ultrasonography. Breast Cancer, 22(6), 634–640. <http://doi.org/10.1007/s12282-014-0530-6>
7. Neal L, Sandhu NP, Hieken TJ et al. Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on core needle biopsy. Mayo Clin Proc. 2014 Apr;89(4):536-47

8. Prowler, V. L., Joh, J. E., Acs, G. et al. (2014). Surgical excision of pure flat epithelial atypia identified on core needle breast biopsy. *Breast (Edinburgh, Scotland)*, 23(4), 352–356. <http://doi.org/10.1016/j.breast.2014.01.013>
9. Uzoaru, I., Morgan, B. R., Liu, Z. G. et al. (2012). Flat epithelial atypia with and without atypical ductal hyperplasia: to re-excise or not. Results of a 5-year prospective study. *Virchows Archiv : an International Journal of Pathology*, 461(4), 419–423. <http://doi.org/10.1007/s00428-012-1312-1>
10. VANCb Study Group, Bianchi, S., Bendinelli, B. et al. (2012). Morphological parameters of flat epithelial atypia (FEA) in stereotactic vacuum-assisted needle core biopsies do not predict the presence of malignancy on subsequent surgical excision. *Virchows Archiv : an International Journal of Pathology*, 461(4), 405–417. <http://doi.org/10.1007/s00428-012-1279-y>
11. Villa, A., Chiesa, F., Massa, T. et al. (2013). Flat epithelial atypia: comparison between 9-gauge and 11-gauge devices. *Clinical Breast Cancer*, 13(6), 450–454. <http://doi.org/10.1016/j.clbc.2013.08.008>

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2018.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Papillom</h2> <ul style="list-style-type: none"> ▪ Umfasst: Zentrales und peripheres Milchgangspapillom > 2 mm, Papillom mit Atypien (B3) ▪ Abzugsgrenzen von peripheren Mikropapillomen, von den TDLUs ausgehend, ≤ 2 mm, gelegentlich multipel ▪ Abzugsgrenzen vom Papillom mit DCIS, vom intraduktalen papillären Karzinom und dem gekapselten papillären Karzinom ▪ Indikator-Läsion: Assoziation mit in situ- oder invasiven Karzinomen (bei atypischen Papillomen bis zu 20%), erhöhtes ipsilaterales Karzinomrisiko (4,6% bis zu 13% bei atypischen Papillomen)
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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.





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Vorgehen nach Diagnose eines zentralen Papilloms

Oxford		
LoE	GR	AGO

- **Solitäres Papillom ohne Atypien in Stanz-/Vakuumbiopsie**
 - Keine weiteren Maßnahmen, wenn Biopsie ausreichend repräsentativ (100 mm²) und keine Diskordanz zur Bildgebung
- **Multiple Papillome**
 - Offene Biopsie
- **Atypisches Papillom in Stanz- / Vakuumbiopsie**
 - Offene Biopsie
- **Papillom am Rand von Resektaten**
 - Keine verfügbaren Daten

3a C ++

3a C ++

3a C ++

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- Collins L, Schnitt S. Papillary lesions of the breast: selected diagnostic and management issues. Histopathology. 2008;52(1):20–9.
- European guidelines for quality assurance in breast cancer screening and diagnosis. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, Karsa von L, editors. 2008
- 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.
- Neal L, Sandhu NP, Hieken TJ et al. Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on core needle biopsy. Mayo Clin Proc. 2014 Apr;89(4):536-47
- 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]
- 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
- 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.
- 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.


Radiäre sklerosierende Läsion

- **Benigne pseudoinfiltrierende Läsion mit zentralem fibroelastischem Kern und radiärem Aufbau.**
- **Beinhaltet:**
 - radiäre Narbe
 - komplexe sklerosierende Läsion (> 1 cm)
- **Zusätzlicher Risikofaktor bei Pat. mit benignen Epithelhyperplasien (proliferierender Mastopathie)**
- **Risiko für Upgrade in offener PE nach Diagnose einer radiär-sklerosierenden Läsion in der Stanzbiopsie: 8,3% (79/948)***

* Bianchi S et al. Breast. (2012) 21: 159–64.

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2. Doyle, E., Banville, N., Quinn, C. et al. (2007). Radial scars/complex sclerosing lesions and malignancy in a screening programme: incidence and histological features revisited. Histopathology, 50(5), 607–614.
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4. Li, Z., Ranade, A., & Zhao, C. (2016). Pathologic findings of follow-up surgical excision for radial scar on breast core needle biopsy. Human Pathology, 48, 76–80. <http://doi.org/10.1016/j.humpath.2015.06.028>
5. Matrai, C., D'Alfonso, T. M., Pharmer, L. et al. (2015). Advocating Nonsurgical Management of Patients With Small, Incidental Radial Scars at the Time of Needle Core Biopsy: A Study of 77 Cases. Archives of Pathology & Laboratory Medicine, 139(9), 1137–1142. <http://doi.org/10.5858/arpa.2014-0550-OA>
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1068.

<div>  <p> © AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2018.1D </p> <p>www.ago-online.de</p> <p> FORSCHEN LEHREN HEILEN </p> </div>	<h2>Vorgehen bei radiärer Narbe, komplexer sklerosierender Läsion (CSL)</h2>									
	<table> <tr> <th></th><th>Oxford</th><th></th><th></th></tr> <tr> <th></th><th>LoE</th><th>GR</th><th>AGO</th></tr> </table>				Oxford				LoE	GR
	Oxford									
	LoE	GR	AGO							
<ul style="list-style-type: none"> Radiäre Narbe / CSL in der Stanz- oder Vakuumbiopsie: <ul style="list-style-type: none"> Auf offene Biopsie kann verzichtet werden, wenn Läsion klein (≤5 mm) oder in der Vakuumbiopsie bereits vollständig oder weitgehend vollständig enthalten Radiäre Narbe / CSL im Resektionsrand nach Exzisionsbiopsie: <ul style="list-style-type: none"> Keine Nachresektion 										
	5a	C	+							
	3b	C	++							

- Andacoglu, O., Kanbour-Shakir, A., Teh, Y.-C. et al. (2013). Rationale of excisional biopsy after the diagnosis of benign radial scar on core biopsy: a single institutional outcome analysis. American Journal of Clinical Oncology, 36(1), 7–11. <http://doi.org/10.1097/COC.0b013e3182354a3f>
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10. Ferreira, A. I., Borges, S., Sousa, A. et al. (2017). Radial scar of the breast: Is it possible to avoid surgery? *European Journal of Surgical Oncology : the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*, 43(7), 1265–1272. <http://doi.org/10.1016/j.ejso.2017.01.238>
11. Hou, Y., Hooda, S., & Li, Z. (2016). Surgical excision outcome after radial scar without atypical proliferative lesion on breast core needle biopsy: a single institutional analysis. *Annals of Diagnostic Pathology*, 21, 35–38. <http://doi.org/10.1016/j.anndiagpath.2015.11.004>
12. Kalife, E. T., Lourenco, A. P., Baird, G. L. et al. (2016). Clinical and Radiologic Follow-up Study for Biopsy Diagnosis of Radial Scar/Radial Sclerosing Lesion without Other Atypia. *Breast Journal*, 22(6), 637–644. <http://doi.org/10.1111/tbj.12645>
13. Leong, R. Y., Kohli, M. K., Zeizafoun, N., Liang, A., & Tartter, P. I. (2016). Radial Scar at Percutaneous Breast Biopsy That Does Not Require Surgery. *Journal of the American College of Surgeons*, 223(5), 712–716. <http://doi.org/10.1016/j.jamcollsurg.2016.08.003>
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19. Tóth, D., Sebő, É., Sarkadi, L. et al. (2012). Role of core needle biopsy in the

treatment of radial scar. *Breast (Edinburgh, Scotland)*, 21(6), 761–763.
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Brustkrebs-Früherkennung: Follow-up nach B3-Läsionen für Frauen im Alter zwischen 50 und 69 Jahren			
	Oxford		
	LoE	GR	AGO
▪ FEA, Papillom ohne Atypien, RN, CSL			
▪ Screening-Mammographie	5	C	++
▪ LIN			
▪ Kurative Mammographie (12 Monate)	3a	C	++
▪ ADH			
▪ Kurative Mammographie (12 Monate)	3a	C	++
▪ Frauen mit LIN und ADH sind über ihr persönlich erhöhtes Brustkrebsrisiko zu informieren	3a	C	++

- Whiffen A: Predictors of Breast Cancer Development in Women with Atypical Ductal Hyperplasia and Atypical Lobular Hyperplasia. Ann Surg Oncol. 2010 Sep 28. [Epub ahead of print]
- Weir R: Risk factors for breast cancer in women:a systematic review of the literature. Christchurch: New Zealand Health Technology Assessment (NZHTA); 2007.
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- Youk J: Sonographically guided 14-gauge core needle biopsy of breast mass: A review of 2.420 cases with long-term follow-up. AJR 2007; 190:202-207
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- O'Connor A: Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-35

Prävention bei Läsionen mit unsicherem biologischem Potenzial (insbes. LIN, ADH)

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen für Frauen > 35 Jahre – Risikoreduktion von DCIS und invasivem Karzinom	1a	A	+
▪ Aromataseinhibitor (Exemestan, Anastrozol) für postmenopausale Frauen	1b	A	+/-
▪ Raloxifen für postmenopausale Frauen – Reduktion nur von invasivem Karzinom	1b	A	+/-*

Eine präventive Medikamentenbehandlung sollte nur nach ausführlicher individueller Beratung angeboten werden: Der Netto-Benefit ist stark abhängig vom Risikostatus, Lebensalter und vorbestehenden Risiken für Nebenwirkungen.

* Risiko entsprechend der Definition des NSABP P1-trial (1,66% in 5 years)

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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 IBIS-I trial. J Natl Cancer Inst 2007; 99:272-282
3. O'Connor A: Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-354
4. Bozovic-Spasojevic I, Azambuja E, McCaskill-Stevens W et al.: Chemoprevention for breast cancer. Cancer Treat Rev. 2012 Aug;38(5):329-39.

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.


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

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Prävention bei Läsionen mit unsicherem biologischem Potenzial (Tamoxifen)

	Placebo Rate / 1000 WE	Tamoxifen Rate / 1000 WE	RR	95% CI
Alle Frauen	6.29	3.59	0.57	0.46-0.70
Mit/ohne LCIS	5.93	3.41	0.58	0.46-0.72
Mit LIN	11.70	6.27	0.54	0.27-1.02
w/o ADH	5.87	3.69	0.63	0.50-0.78
Mit ADH	10.42	2.55	0.25	0.10-0.52
5-Jahresrisiko <2%	4.77	3.18	0.67	0.43-1.01
5 Jahresrisiko > 5%	11.98	5.15	0.43	0.28-0.64
Eine Verwandte 1. Grades	6.47	3.48	0.54	0.34-0.83
Mehr als drei Verwandte 1. Grades	11.24	5.48	0.49	0.16-1.34
Frakturen	2.88	1.97	0.91	0.51-0.92
Endometriumkarzinom	0.68	2.24	3.28	1.87-6.03


Angebote nur für Frauen mit erhöhtem Brustkrebsrisiko (Gail $\geq 1,66\%$):

- mit LIN , mit ADH
- mit genetischer Belastung

Sollte Frauen nicht angeboten werden:

- mit moderatem Risiko nach dem 50. Lebensjahr
- mit erhöhtem Thromboembolierisiko

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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Prävention bei Läsionen mit unsicherem biologischem Potenzial (Tamoxifen) - NW

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)

Inzidenz	RR	95% CI	AR je 1000*	NNT / NNH**
Brustkrebs	0.73	0.58-0.91	15	68
Invasives Karzinom	0.74	0.58-0.94	12	81
Thromboembolie	1.72	1.27-2.36	14	73
Tiefe Beinvenenthrombose	1.84	1.21-2.82	9	115
Kopfschmerzen	0.93	0.87-0.99	25	39
Gynäkologische / vasomotorische Symptome	1.08	1.06-1.10	64	16
Brustbeschwerden	0.77	0.70-0.84	58	17

Risikokommunikation
AR*: Absolutes Risiko je 1000 Frauen. NNT/NNH** = number needed to treat oder number needed to harm

Ausgewiesen sind nur statistisch signifikante Daten über den Follow-up-Zeitraum von 96 Monaten.
Die Datenberechnung erfolgte von den Leitlinienautoren. 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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Prävention bei Läsionen mit unsicherem biologischem Potenzial (Raloxifen)

NSABP-P2 Study, STAR trial 2006

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


Angebote nur für Frauen mit erhöhtem Brustkrebsrisiko:

- ≥ 35 J. Gail 1,66% oder postmenopausal

Sollte Frauen nicht angeboten werden:

- mit moderatem Risiko nach dem 50. Lebensjahr
- mit erhöhtem Thromboembolierisiko

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 2018.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Prävention bei Läsionen mit unsicherem biologischem Potenzial (Aromatasehemmer)</h2> <table border="1" style="width: 100%;"> <thead> <tr> <th style="text-align: left;">Einschlusskriterien:</th><th style="text-align: left;">Results for prior ALH, ADH, LCIS (HR AI vs Plac):</th></tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> ▪ IBIS.2: <ul style="list-style-type: none"> ▪ Zuvor ADH, ALH, or LCIS Anastrozol: 154 (8,0%); Placebo: 190 (9,7%) ▪ MAP.3: <ul style="list-style-type: none"> ▪ Zuvor ADH, ALH, or LCIS: Exemestan: 185 (8,1%); Placebo: 188 (8,3%) </td><td> <ul style="list-style-type: none"> ▪ Ja (7J-MaCa-Risiko 12,1%): HR 0,31 (0,12–0,84) ▪ No (7J-MCa-Risiko 4,9%): HR 0,52 (0,31–0,78) <ul style="list-style-type: none"> ▪ Yes: HR=0,61 (0,20–1,82) ▪ No: HR=0,26 (0,11–0,64) </td></tr> </tbody> </table> <p style="font-size: small;">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>	Einschlusskriterien:	Results for prior ALH, ADH, LCIS (HR AI vs Plac):	<ul style="list-style-type: none"> ▪ IBIS.2: <ul style="list-style-type: none"> ▪ Zuvor ADH, ALH, or LCIS Anastrozol: 154 (8,0%); Placebo: 190 (9,7%) ▪ MAP.3: <ul style="list-style-type: none"> ▪ Zuvor ADH, ALH, or LCIS: Exemestan: 185 (8,1%); Placebo: 188 (8,3%) 	<ul style="list-style-type: none"> ▪ Ja (7J-MaCa-Risiko 12,1%): HR 0,31 (0,12–0,84) ▪ No (7J-MCa-Risiko 4,9%): HR 0,52 (0,31–0,78) <ul style="list-style-type: none"> ▪ Yes: HR=0,61 (0,20–1,82) ▪ No: HR=0,26 (0,11–0,64)
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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>