Lesions of Uncertain Malignant Potential (B3) – ADH, LIN, FEA –
Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **Version 2005:**
  Audretsch / Thomssen

- **Versions 2006–2011:**
  Albert / Brunnert / Fersis / Friedrich / Gerber / Kreipe / Nitz / Schreer

- **Version 2012:**
  Sinn / Schreer
Pathology Reporting for Minimal Invasive Biopsies

B – Classification*

B1 = unsatisfactory / 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, S3-Leitlinien
### Major Type of B3 Lesions and their Prospective Predictive Value (PPV) for Malignancy in Resection Specimen

<table>
<thead>
<tr>
<th>Type of B3-lesions</th>
<th>~PPV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>40%</td>
</tr>
<tr>
<td>Lobular intraepithelial neoplasia (LN/LIN)</td>
<td>21%</td>
</tr>
<tr>
<td>Flat epithelial atypia (FEA)</td>
<td>21%</td>
</tr>
<tr>
<td>Radial scar</td>
<td>12%</td>
</tr>
<tr>
<td>Complex sclerosing lesion</td>
<td>9%</td>
</tr>
<tr>
<td>Papillary lesions</td>
<td>13%</td>
</tr>
<tr>
<td>Cellular fibroepithelial lesions / phylloides tu.</td>
<td></td>
</tr>
<tr>
<td>Adenomyoepithelioma</td>
<td></td>
</tr>
</tbody>
</table>

B3 – risk of upgrade after minimally invasive biopsy: PPV = 35,1% (95%CI 29,5–40,7)*

* Houssami N et al. 2007
** Rakha EA et al. 2010
Management after Minimal Invasive Biopsy

Imaging guided minimal invasive biopsy

Imaging of specimen

Pathology of specimen

B 3 lesion

Multi-disciplinary conference: pathology and imaging results concordant?

Diagnostic approach: tissue acquisition

Management according to type of lesion

Definition of standard elements: Clinical status \[\xleftarrow{\text{decision}}\] Action \[\rightarrow\] Logical consequence
Atypical Ductal Hyperplasia (ADH)

- **Synonyms:** Atypical intraductal proliferation, ductal intraepithelial neoplasia grade 1B (DIN1B)

- **Definition:** Any architectural atypia with micropapillary or cribriform proliferations and non-high grade nuclear atypia not exceeding 2 mm in diameter or two completely filled ducts is ADH.
  - Proliferation exceeding 2 mm or two completely filled ducts has to be considered as low-grade intraductal carcinoma (low-grade DCIS)
  - Due to poor reproducibility 2nd opinion may be considered

- **Indicator-/Precursor-lesion:** Ipsilateral and contralateral enhanced breast cancer risk: unifocal 4 x at 10 years, multifocal (more than 3 foci) 10 x at 10 years. Enhanced breast cancer risks at diagnosis before age 45 yrs.: 6 x at 10 years.
Risk of Breast Cancer after ADH

Stratification of breast cancer risk*

- 1 lesion: RR 3.88 (95%CI 3.00–4.94)
- 3 lesions: RR 10.35 (95% CI 6.13–16.4)
- less than 45 years at diagnosis: RR 6.78 (95%CI 3.24–12.4)

Strategy after Diagnosis of ADH

ADH in core- / vacuum-assisted biopsy:

→ open excisional biopsy
→ open excisional biopsy may be omitted, with:
  a) a small lesion (≤ 2 TDLU* in vacuum biopsy) and
  b) complete removal of imaging abnormality

ADH at margins in resection specimen:

→ no further surgery, if incidental finding accompanying invasive or intraductal carcinoma

* Terminal ductal-lobular unit
Lobular Intraepithelial Neoplasia (LIN)

- **Includes:** Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS
- LIN1–3 classification is not sufficiently validated
- Pleomorphic LIN and LIN with necrosis or with distension and confluence of lobules are classified as → **B5a**
- **Indicator-/Precursor-lesion:** Ipsilateral and contralateral enhanced breast cancer risk: 7 x at 10 years
Strategy after Diagnosis of LIN

- **LIN in core- / vacuum-assisted biopsy:**
  - open excisional biopsy, if careful correlation with imaging is not conclusive
  - LIN is frequently associated with invasive cancer which may be not represented in core- or vacuum-assisted biopsy

- **LIN at margins of resection specimen:**
  - no further surgery / re-excision unless imaging abnormality is not removed

- **LIN accompanying intraductal or invasive carcinoma in patients with BCT**
  - no further resection

- **Exception:** Pleomorphic LIN and LIN with necrosis
  - complete resection

Oxford / AGO LoE / GR:

- 2b C ++
- 3a C ++
- 2a C ++
- 5 D ++
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 → **B5a**

- **Marker lesion:**
  FEA is frequently associated with calcifications and may be associated with intraductal carcinoma. Therefore, correlation with imaging is mandatory.
Strategy after Diagnosis of FEA

- **FEA in core biopsy:**
  - No further biopsy if calcifications are completely removed
  - Exception: calcifications not removed
    → Radiographic guided vacuum-assisted biopsy can follow core biopsy

- **FEA at margins in resection specimen:**
  - No further surgery, unless calcifications have not been completely removed

Oxford / AGO LoE / GR

3a  C  ++

3b  C  ++
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions

**FEA**
- Screening mammography

**LIN**
- Mammography (12 months)

**ADH**
- Mammography (12 months)

- Women with LIN and ADH should be informed about their elevated risk of breast cancer
Medical Prevention for Women at Increased Risk (including Women with LIN and ADH)

- Tamoxifen for women >35 years – Risk reduction of invasive BrCa and DCIS: 1a A +*
- Raloxifene for postmenopausal women - Risk reduction of invasive BrCa only: 1b A +*
- Aromatase inhibitors for postmenopausal women: 5 D +/-**

Medical prevention should only be offered after individual and comprehensive counseling; the net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

*Risk situation as defined in NSABP P1-trial (1.66% in 5 years)
**Study participation recommended
Outcome of Medical Prevention (1)

### NSABP-P1 Study, update 2005

<table>
<thead>
<tr>
<th></th>
<th>Placebo Rate / 1000 WE</th>
<th>Tamoxifen Rate / 1000 WE</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>6.29</td>
<td>3.59</td>
<td>0.57</td>
<td>0.46-0.70</td>
</tr>
<tr>
<td>w/o LCIS</td>
<td>5.93</td>
<td>3.41</td>
<td>0.58</td>
<td>0.46-0.72</td>
</tr>
<tr>
<td>W LCIS</td>
<td>11.70</td>
<td>6.27</td>
<td>0.54</td>
<td>0.27-1.02</td>
</tr>
<tr>
<td>w/o AH</td>
<td>5.87</td>
<td>3.69</td>
<td>0.63</td>
<td>0.50-0.78</td>
</tr>
<tr>
<td>w AH</td>
<td>10.42</td>
<td>2.55</td>
<td>0.25</td>
<td>0.10-0.52</td>
</tr>
<tr>
<td>5 y risk &lt;2%</td>
<td>4.77</td>
<td>3.18</td>
<td>0.67</td>
<td>0.43-1.01</td>
</tr>
<tr>
<td>5 y risk &gt; 5%</td>
<td>11.98</td>
<td>5.15</td>
<td>0.43</td>
<td>0.28-0.64</td>
</tr>
<tr>
<td>One 1st ° relatives</td>
<td>6.47</td>
<td>3.48</td>
<td>0.54</td>
<td>0.34-0.83</td>
</tr>
<tr>
<td>&gt;= three1st ° relatives</td>
<td>11.24</td>
<td>5.48</td>
<td>0.49</td>
<td>0.16-1.34</td>
</tr>
<tr>
<td>Fractures</td>
<td>2.88</td>
<td>1.97</td>
<td>0.91</td>
<td>0.51-0.92</td>
</tr>
<tr>
<td>Endometrial Ca</td>
<td>0.68</td>
<td>2.24</td>
<td>3.28</td>
<td>1.87-6.03</td>
</tr>
</tbody>
</table>

### NSABP-P2 Study, STAR trial 2006

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen Rate / 1000 WE</th>
<th>Raloxifen Rate / 1000 WE</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>4.30</td>
<td>4.41</td>
<td>1.02</td>
<td>0.82-1.28</td>
</tr>
<tr>
<td>W/O LCIS</td>
<td>3.76</td>
<td>4.03</td>
<td>1.03</td>
<td>0.81-1.33</td>
</tr>
<tr>
<td>W LCIS</td>
<td>9.83</td>
<td>9.61</td>
<td>0.98</td>
<td>0.58-1.63</td>
</tr>
<tr>
<td>W/O AH</td>
<td>4.06</td>
<td>4.03</td>
<td>0.99</td>
<td>0.76-1.28</td>
</tr>
<tr>
<td>W AH</td>
<td>5.21</td>
<td>5.81</td>
<td>1.12</td>
<td>0.72-1.74</td>
</tr>
<tr>
<td>5 y risk &lt;3%</td>
<td>2.03</td>
<td>2.83</td>
<td>1.40</td>
<td>0.87-2.28</td>
</tr>
<tr>
<td>5 y risk &gt; 5%</td>
<td>6.77</td>
<td>7.35</td>
<td>1.09</td>
<td>0.78-1.52</td>
</tr>
<tr>
<td>One 1st ° relatives</td>
<td>4.99</td>
<td>5.18</td>
<td>1.04</td>
<td>0.69-1.55</td>
</tr>
<tr>
<td>&gt;= two1st ° relatives</td>
<td>5.16</td>
<td>5.00</td>
<td>0.97</td>
<td>0.60-1.56</td>
</tr>
<tr>
<td>Endometrial CA</td>
<td>2.00</td>
<td>1.25</td>
<td>0.62</td>
<td>0.35-1.08</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>3.71</td>
<td>2.61</td>
<td>0.70</td>
<td>0.54-0.91</td>
</tr>
<tr>
<td>Develeoping</td>
<td>12.30</td>
<td>9.72</td>
<td>0.79</td>
<td>0.68-0.92</td>
</tr>
<tr>
<td>Cataracts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Should only be offered to women at high risk, e.g.
- with LIN
- with ADH
- with a strong family history

Should **not** be offered to women
- with a moderate risk over the age of 50
- with an increased risk for thromboembolic events
## Outcome of Medical Prevention (2)

Risks and benefits with long-term Tamoxifen use compared with placebo: results from the IBIS-I Trial, 96 months median follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>RR</th>
<th>95% CI</th>
<th>AR per 1000*</th>
<th>NNT / NNH**</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC Incidence</td>
<td>0.73</td>
<td>0.58-0.91</td>
<td>15</td>
<td>68</td>
</tr>
<tr>
<td>Invasive BC</td>
<td>0.74</td>
<td>0.58-0.94</td>
<td>12</td>
<td>81</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1.72</td>
<td>1.27-2.36</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.84</td>
<td>1.21-2.82</td>
<td>9</td>
<td>115</td>
</tr>
<tr>
<td>Headache</td>
<td>0.93</td>
<td>0.87-0.99</td>
<td>25</td>
<td>39</td>
</tr>
<tr>
<td>Gynecological / vasomotoric symptoms</td>
<td>1.08</td>
<td>1.06-1.10</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>Breast complains</td>
<td>0.77</td>
<td>0.70-0.84</td>
<td>58</td>
<td>17</td>
</tr>
</tbody>
</table>

Risk communication:

AR*: absolute risk difference per 1000 women
NNT/NNH** number needed to treat or number needed to harm only shown for statistically significant events over the entire follow-up period

Data computed by guideline authors Visvanathan K et al. JCO 2009;27:3235-3258