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

- **Version 2005:**
  Audretsch / Thomssen

- **Version 2006–2009:**
  Albert / Brunnert / Fersis / Friedrich / Kreipe / Nitz / Schreer

- **Version 2010:**
  Albert / Kreipe
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 = 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 Malignant Potential

Type of B3-lesions:
- Flat epithelial atypia (FEA)
- Lobular intraepithelial Neoplasia (LN/LIN)
- Atypical ductal hyperplasia (ADH)
- Radial scar
- Complex sclerosing lesion
- Papillary lesions
- Fibroepithelial lesions
- Adenomyoepithelial lesions

B3 – Malignancy:
PPV = 35,1% (95%CI 29,5 – 40,7)*

* Houssami N et al. 2007
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?
      - yes: Management according to type of lesion
      - no: Diagnostic approach: tissue acquisition

Definition of standard elements:
- Clinical status
- decision
- action
- Logical consequence
Flat Epithelial Atypia (FEA)

- **Synonyma:** 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

哌 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

哌 FEA at margins in resection specimen:
→ No further surgery, unless calcifications have not been completely removed
Lobular Intraepithelial Neoplasia (LIN)

- **Synonyma:** Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS. LIN1-3 is not recommended by WHO.

- **Differential diagnosis:**
  - Pleomorphic LIN and LIN with necrosis and extensive involvement of lobules with confluence are classified as → **B5a**

- **Indicator-/Precursor-lesion:**
  - Ipsilateral and contralateral enhanced breast cancer risk: 7x 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

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- 2b C ++
- 3a C ++
- 2a C ++
- 5 D ++
Atypical Ductal Hyperplasia (ADH)

- **Synonyma:** 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:** Ipsi- 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.

➢ **ADH at margins in resection specimen:**
  → No further surgery, if incidental finding accompanying invasive or intraductal carcinoma

Oxford / AGO LoE / GR

3a  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

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Level</th>
<th>Evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening mammography</td>
<td>5</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Mammography (12 months)</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Mammography (12 months)</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Women with LIN and ADH should be informed about their elevated risk of breast cancer</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
</tbody>
</table>
# Medical Prevention for Women at Increased Risk (including Women with LIN and ADH)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Level</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>for women &gt;35 years — Risk reduction of invasive BrCa and DCIS</td>
<td>1a</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>Raloxifen</td>
<td>for postmenopausal women - Risk reduction of invasive BrCa only</td>
<td>1b</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>for postmenopausal women</td>
<td>5</td>
<td>D</td>
<td>+/-**</td>
</tr>
</tbody>
</table>

*Risk situation as defined in NSABP P1-trial (1.66% in 5 years)  
** Study participation recommended

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.
### 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;= three 1st° 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>3.89</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;= two 1st° 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>Thromboembolisms</td>
<td>3.71</td>
<td>2.61</td>
<td>0.70</td>
<td>0.54-0.91</td>
</tr>
<tr>
<td>Developing Cataracts</td>
<td>12.30</td>
<td>9.72</td>
<td>0.79</td>
<td>0.068-0.92</td>
</tr>
</tbody>
</table>

**Outcome of Medical Prevention (1)**

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.