Early Detection and Diagnosis
Early Detection and Diagnosis

- **Versions 2005–2014:**
  - Albert / Blohmer / Fersis / Junkermann / Maass / Scharl / Schreer

- **Version 2015:**
  - Schreer / Albert
# Early Detection Mammography

<table>
<thead>
<tr>
<th>Age</th>
<th>Interval</th>
<th>Oxford LOE</th>
<th>AGO GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>na</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40–50</td>
<td>12–18</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>50–70*</td>
<td>24</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>&gt;70</td>
<td>24</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>

* National Mammography-Screening-Program
## Breast Cancer Mortality Reduction

<table>
<thead>
<tr>
<th>Metaanalyses</th>
<th>RR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent UK Panel, 2012</strong></td>
<td></td>
</tr>
<tr>
<td>13-year metaanalysis</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td><strong>Cochrane Review, 2011</strong></td>
<td></td>
</tr>
<tr>
<td>Fixed-effect metaanalysis of 9 RCT-trials</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>As above, but excluding women &lt;50 years</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td><strong>US Task Force, 2009</strong></td>
<td></td>
</tr>
<tr>
<td>Women 50–59 years</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td>Women 60–69 years</td>
<td>0.68 (0.54–0.87)</td>
</tr>
<tr>
<td>Estimates weighted average</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Canadian Task Force, 2011</strong></td>
<td></td>
</tr>
<tr>
<td>Women aged 50–69 years</td>
<td>0.79 (0.68–0.90)</td>
</tr>
<tr>
<td><strong>Duffy et al., 2012</strong></td>
<td></td>
</tr>
<tr>
<td>Review of all trials and age groups</td>
<td>0.79 (0.73–0.86)</td>
</tr>
</tbody>
</table>
Mammography-Screening
Women 40–49 Years

RR (invited women) | 0.74 (95%CI 0.66-0.83)
40–44 J | 0.83 (95%CI 0.67-1.00)
45–49 J | 0.68 (95%CI 0.59-0.78)
Participants | 0.71 (95%CI 0.62-0.80)

NNS | 1252 (95%CI 958-1915)
(1 live saved / 10 years screening)

Hellquist BN et al. Cancer 2011; 117(4) : 714-722
### Early Detection Sonography

<table>
<thead>
<tr>
<th><strong>Screening-Breast Sonography</strong></th>
<th><strong>Oxford / AGO LOE / GR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated 3D-Sonography</td>
<td>3b C ++</td>
</tr>
</tbody>
</table>

#### As an adjunct:

- **Dense mammogram (ACR 3–4)**
  - Elevated risk: 1b C ++
- **Mammographic lesion**: 2b B ++
- **Second-look US (MRI-only detected lesions)**: 2b C ++
Early Detection
Clinical Examination

As stand alone procedure

- **Self-examination**
  - Oxford / AGO LOE / GR: 1a A -*

- **Clinical breast examination (CBE) by health professionals**
  - Oxford / AGO LOE / GR: 3b C -*

- **CBE because of mammo/sonographic lesion**
  - Oxford / AGO LOE / GR: 5 D ++

**CBE in combination with imaging**

- Oxford / AGO LOE / GR: BCP ++

* May increase breast awareness
## Assessment of Breast Symptoms or Lesions

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / LOE / AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>3b B ++</td>
</tr>
<tr>
<td>Mammography</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Additional Tomosynthesis</td>
<td>2b B +</td>
</tr>
<tr>
<td>(vs spot compression)</td>
<td></td>
</tr>
<tr>
<td>Sonography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Elastography (shear-wave)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Automated 3D-sonography</td>
<td>3b B +/-</td>
</tr>
<tr>
<td>MRI*</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Minimally invasive biopsy</td>
<td>1c A ++</td>
</tr>
</tbody>
</table>

*If clinical examination, mammography and sonography do not allow a definite diagnosis*
Pretherapeutic Assessment of Lesion Extension and Staging

- Clinical examination
  - Oxford / AGO LOE / GR
  - 5 / D ++

- Mammography
  - 2b / B ++

- Sonography
  - 2b / B ++

- Axilla + FNP/CNB
  - 2b / B +

- MRI *
  - 1b / B +/-

- Minimally invasive biopsy**
  - 1b / A ++

* Weak reduction in reexcision rate in lobular-invasive cancer but sign. higher rate of initial mastectomy. Lobular invasive tumors, suspicion of multilocular disease, high-risk patients. MRI-guided vacuum biopsy mandatory in case of MRI-detected additional lesions.

** If clinical examination, mammography and sonography (e.g. plus MRI) do not allow assessment of lesion extension.
MRI: Preoperative Staging

- 9 eligible studies (2 randomized trials; 7 comparative cohorts)
- 3112 patients with BC
- MRI versus no-MRI:
  - Initial mastectomy 16.4% versus 8.1% [OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)]
  - Re-excision after initial breast conservation 11.6% versus 11.4% [OR, 1.02 (P = 0.87); adjusted OR, 0.95 (P = 0.71)]
  - Overall mastectomy 25.5% versus 18.2% [OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)]

MRI: Preoperative Staging in Lobular Invasive Breast Cancer

- 766 patients with invasive lobular cancer (ILC)
  - Initial mastectomy: 31.1% versus 24.9% [OR, 1.36 (P = 0.056); adjusted OR, 2.12 (P = 0.008)]
  - Re-excision after initial breast conservation 10.9% versus 18.0% [OR, 0.56 (P = 0.031); adjusted OR, 0.56 (P = 0.09)]
  - Overall mastectomy 43.0% versus 40.2% [OR, 1.12 (P = 0.45); adjusted OR, 1.64 (P = 0.034)]

MRI Screening (High-risk) Benefit

- Early detection of cancer cases additionally to conventional imaging
- Improved patient prognosis? (Mortality reduction? Reduction of interval cancers?)
### MRI Screening in Women with High Familiar Risk

<table>
<thead>
<tr>
<th>Author</th>
<th>Hochrisiko / Mutation</th>
<th>Anzahl Frauen</th>
<th>Anzahl Karzinome</th>
<th>Sensitivität (%)</th>
<th>Spezifität (%)</th>
<th>MRT</th>
<th>Mammographie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kriege 2004</td>
<td>M</td>
<td>1909</td>
<td>50</td>
<td>80</td>
<td>90</td>
<td>33</td>
<td>95</td>
</tr>
<tr>
<td>Warner 2004</td>
<td>M</td>
<td>236</td>
<td>22</td>
<td>77</td>
<td>95</td>
<td>36</td>
<td>99</td>
</tr>
<tr>
<td>Hagen 2004</td>
<td>M</td>
<td>491</td>
<td>25</td>
<td>86</td>
<td>-</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Leach 2005</td>
<td>H / M</td>
<td>649</td>
<td>35</td>
<td>94</td>
<td>77</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>Riedl 2007</td>
<td>H / M</td>
<td>327</td>
<td>28</td>
<td>50</td>
<td>98</td>
<td>85,7</td>
<td>92</td>
</tr>
<tr>
<td>Kuhl 2010</td>
<td>H / M</td>
<td>687</td>
<td>27</td>
<td>93</td>
<td>98,4</td>
<td>33</td>
<td>99,1</td>
</tr>
<tr>
<td>Rijnsburger 2010</td>
<td>M</td>
<td>594</td>
<td>97</td>
<td>77,4</td>
<td>89,7</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>Sardanelli 2011</td>
<td>H / M</td>
<td>501</td>
<td>52</td>
<td>91</td>
<td>97</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Passaperuma 2012</td>
<td>M</td>
<td>496</td>
<td>57</td>
<td>90</td>
<td>97</td>
<td>19</td>
<td>97</td>
</tr>
<tr>
<td>Gareth 2014</td>
<td>H / M</td>
<td>649</td>
<td>139</td>
<td>93</td>
<td>63</td>
<td>60</td>
<td>-</td>
</tr>
</tbody>
</table>

Prospective study results for MRI screening in women with high familiar risk (H) and mutation carriers (M)
## MRI Screening (High-risk) Problems

<table>
<thead>
<tr>
<th>MRI in addition to mammography</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment of benign lesions</strong></td>
<td>3.43–4.86</td>
</tr>
<tr>
<td><strong>Benign biopsies</strong></td>
<td>1.22–9.50</td>
</tr>
<tr>
<td><strong>Benign surgical biopsies (MARIBS)</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>False-negative MRI (MRISC)</strong></td>
<td>22%</td>
</tr>
</tbody>
</table>
### MRI and DCIS

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Cases</th>
<th>Overall accuracy (%)</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilles et al 1995</td>
<td>172</td>
<td>70</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Westerhof et al 1998</td>
<td>63</td>
<td>56</td>
<td>45</td>
<td>72</td>
</tr>
<tr>
<td>Bazzocchi et al 2006</td>
<td>112</td>
<td>80</td>
<td>79</td>
<td>68</td>
</tr>
<tr>
<td>Kuhl et al 2007</td>
<td>75</td>
<td>-</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>Baur et al 2013</td>
<td>58</td>
<td>-</td>
<td>79,3</td>
<td>-</td>
</tr>
</tbody>
</table>

„Negative breast MRI findings should not be considered a sure marker of benignancy.“
Further information and references:

Screened data bases:
- Pubmed 2009 - 2014
- ASCO 2009 - 2014
- Cochrane 2009 - 2014
- Medline 2009 - 2014
- GIN 2009 - 2014

Guidelines:
- S3 Brustkrebsfrüherkennung
- S3 Diagnostik, Therapie, Nachsorge

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies
Early Detection – Mammography (3/15)

Further information:

The aim of early detection and screening of breast cancer is to reduce the risk of dying from the disease. Detecting invasive breast cancer at an early stage (Stage I-IIA) offers the chance of survival with less treatment impairment and better quality of life. Professionals and women need to be informed about the benefits and harms of cancer screening tests before making medical decisions. This includes clear and understandable information in absolute terms about false positives, false negatives, overdiagnosis and overtreatment.

Meta-analysis and reviews from randomised trials:
Conclusion of the meta-analysis of the Independen UK Panel on Breast Cancer Screening: “Considering the internal bias in the trials, which were done a long time ago, the relative risk reduction in breast cancer mortality from invitation to mammography screening is estimated to be 20%.”

Data from observational studies and registries:
The EUROCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: 1. “the best “European” estimate of of breast cancer reduction is 25-31% for women invited for screening, and 28-38% for women actually screened. The estimate of overdiagnosis range from 1-10%. The chance for saving a woman’s life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis”.

The population-based data from the United States (SEER-Cancer Statistics 1976 - 2008) showed an increase in number of early-stage breast cancer, a marginal reduction at advanced stage. The authors conclude “the imbalance suggests that there is substantial overdiagnosis, and that screening at best, only has a small effect on the rate of death from breast cancer”.

Since 2006 mammography screening is offered to women age 50-69 in Germany within a population-based organised quality assured program in accordance with the European Guidelines for Quality Assurance in Mammography Screening.
References:


Breast Cancer Mortality Reduction (4/15)

No further information

References:

Mammography Screening Women 40–49 years (5/15)

Further information:

On the basis of randomized controlled trials there is evidence of a 26% mortality reduction. The only one especially designed for this age group (“Age-Trial”) achieved a mortality reduction of 17% for those invited and 24% for those participating. These results were not yet statistically significant (95% CI, 0.66-1.04), because the follow-up time is too short for this young age group. The data have been underlined by study results of several service screening studies.

To estimate overdiagnosis within the “Age-Trial” Markov-modelling was performed and yielded the following results (Gunsoy N, 2012): “The sensitivity of mammography for invasive and in-situ breast cancers was 90% (95% CI, 72-99) and 82% (43-99), respectively. The screen-detectable mean sojourn time of preclinical non-progressive and progressive in-situ cancers was 1.3 (0.4-3.4) and 0.11 (0.05-0.19) years, respectively, and 0.8 years (0.6-1.2) for preclinical invasive breast cancer. The proportion of screen-detected in-situ cancers that were non-progressive was 55% (25-77) for the first and 40% (22-60) for subsequent screens. In our main analysis, overdiagnosis was estimated as 0.7% of screen-detected cancers. A sensitivity analysis, covering a wide range of alternative scenarios, yielded a range of 0.5% to 2.9%.” The authors conclude: “The extent of overdiagnosis due to screening in women aged 40-49 was small. Results also suggest annual screening is most suitable for women aged 40-49 in the United Kingdom due to short cancer sojourn times.”

References:


4. FH01 Collaborative Teams Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncol 2010;11:1127-1134


Results from the systematic review (Nothacker et al): The systematic search identified no randomized controlled trials or systematic reviews, six cohort studies of intermediate level of evidence (3b) were found. Only two of the studies included adequate follow-up of subjects with negative or benign findings. Supplemental breast ultrasound after negative mammographic screening permitted diagnosis of primarily invasive carcinomas in 0.32% of women in breast density type categories 2-4 of the American College of Radiology (ACR); mean tumor size for those identified was 9.9 mm, 90% with negative lymph node status. Most detected cancers occurred in mammographically dense breast ACR types 3 and 4. Biopsy rates were in the range 2.3%-4.7%, with PPV of 8.4-13.7% for those biopsied due to positive ultrasound, or about one third of the PPV of biopsies due to mammography. Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3 and 4) permits detection of small, otherwise occult, breast cancers. Potential adverse impacts for women in this intermediate risk group are associated with an increased biopsy rate. Automated ultrasound (ABUS/AVUS) is a potentially feasible way to meet the increasing demands for screening ultrasound in women with dense breasts as it shows a comparable diagnostic performance to hand held ultrasound examination.

The arguments against ultrasound use as stand alone screening modality are reproducibility, high false-positive rate, low ppv for biopsy, inability to detect most DCIS cases, operator dependency and lack of quality assurance.

References:


**Early Detection Clinical Examination (7/15)**

**Further information:**

In a large well performed randomized study no difference in breast cancer mortality emerged after 11 years of follow-up. The only difference was that women in the self-examination arm had nearly twice as many biopsies for benign lesions than women in the control arm. Therefore based on current evidence breast self-examination cannot be recommended anymore. No randomized studies have been performed, where screening-examination by health professionals is compared to no screening. One Japanese case-control study suggests that examination by health professionals might reduce mortality from breast cancer. A randomized trial in Canada showed no difference in breast cancer mortality between a group of women offered clinical breast examination or mammography combined with clinical breast examination. Nevertheless in asymptomatic women participating in mammography screening programs there is the risk of interval cancer development. This is the reason why in the US mammography screening is recommended in close connection with clinical examination. Recent data (Haakinson and coauthors 2010) underscore this strategy.

**References:**

Assessment of Breast Symptoms or Lesions (8/15)

Further information:

If clinical examination, mammography and ultrasound are not conclusive, morphological diagnosis based on biopsy material is warranted. MRI has a high sensitivity but a low specificity to allow definitive diagnosis. Digital breast tomosynthesis allows an increased breast cancer detection rate and its use is recommended for screening centers in population-based trials. Shear wave elastography (SWE) is a promising adjunct to greyscale ultrasound in differentiating benign from malignant breast masses (improved specificity of breast US mass assessment without loss of sensitivity thus reducing the need for core biopsy by downstaging US-BIRADS III and IVa lesions). Automated ultrasound (ABUS/AVUS) is a potentially feasible way to meet the increasing demands for screening ultrasound in women with dense breasts as it shows a comparable diagnostic performance to hand held ultrasound examination. Minimally invasive biopsy allows definitive diagnosis in most cases at reduced expenditure. In case of suspicious microcalcifications extensively distributed in mammography several percutaneous biopsies should be performed before deciding upon mastectomy.

References:


**Tomosynthesis**


Elastography


**Automated Breast Ultrasound (ABUS)**


Pretherapeutic Assessment of Lesion Extension and Staging (9/15)

Further information:

Sonography corresponds better than mammography with the pathological tumor size of the invasive component of breast tumours. Mammography delineates the in situ component better if microcalcifications are present. In these cases magnification mammography is warranted. MRI is the most sensitive method for both invasive and non-invasive tumors, but lacks specificity. Thus MRI findings should be verified by percutaneous biopsy before definite treatment. The effect of MRI on the success of breast conserving therapy neither concerning short-time outcome parameter, i.e. reduction of re-excision rate nor long time outcome parameter, i.e. ipsilateral recurrence and overall survival have not been assessed in randomized studies. Therefore the overall contribution of MRI to successful breast conserving therapy cannot be assessed yet.

MRI for preoperative staging may be helpful in individual cases (high-risk women, multifocality/multicentricity demonstrated at conventional imaging and pathologically proven, invasive lobular cancer with inconclusive findings at conventional imaging), but considering the present evidence no general recommendation can be given for preoperative MRI in patients before breast conservation.

In case of large areas of highly suspicious microcalcifications on mammography several percutaneous biopsies to define tumour size should be performed before deciding upon mastectomy.

Preoperative ultrasound of the axilla and guided lymphnode biopsy prevent completion axillary lymphnode dissection in breast cancer. Elastography of lymph nodes might add prognostic information additional to that provided by conventional preoperative tumor assessment and staging. A general recommendation for the use of lymph node elastography cannot be given as data on quality assurance is lacking.

References:

8. Houssami N, Hayes DF Review of preoperative magnetic resonance imaging (MRI) in breast cancer: Should MRI be performed on all women with newly diagnosed early stage breast cancer. CA Cancer J Clin 2009; 59:290-302
MRI: Preoperative Staging (10/15)

No further information

References:


2. Sardanelli F Overview of the role of preoperative breast MRI in the absence of evidence on patient outcomes. Breast 2010; 19: 3-6


MRI Preoperative Staging in Lobular Invasive Breast Cancer (11/15)

No further information

References:

MRI Screening (High-risk) – Benefit (12/15)

No further information

No references
MRI Screening in Women with High Familiar Risk (13/15)

Further information:

Six prospective multicentre studies and further systematic reviews showed that additional use of MRI increased the sensitivity significantly and that cancers could be detected at a better stage. Overall sensitivity levels ranged from 77% - 100%. About 33% of malignancies were detected by MRI alone, about 11% by mammography alone and only 3% by ultrasound alone. Therefore MRI should be the first imaging method used for intensified screening in high-risk women. It is still unclear whether early detection by MRI will translate into improved disease-free and overall survival.

References:

No further information

No references
MRI and DCIS (15/15)

No further information

References: