Breast Cancer Risk and Prevention
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- **Versions 2003–2019:**
  Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen /

- **Version 2020:**
  Fasching / Rhiem
Principles of Prevention

- Women at increased risk for breast cancer are not considered patients but healthy women or counselees

- A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures

- Highest priority: „First, do no harm!“

(Primum nil nocere)
Who Should be Tested for BRCA1/2 Mutations and Possibly Further Risk Genes? (Part 1 of 2)

**Oxford LoE: 2b**  **GR: B**  **AGO: ++**

**Families with (each from one family branch)**

- at least three women with breast cancer independent of age or
- at least two women with breast cancer, one < 50 yrs. or
- at least one woman affected by breast and one by ovarian cancer or
- at least one woman affected by breast and ovarian cancer or
- at least two women affected by ovarian cancer or
- at least one woman affected by bilateral breast cancer, first < 50 yrs. or

*Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a BRCA1/2 mutation prevalence ≥ 10% tested in 21,401 families. All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).*


11. Couch FJ, Hu C, Hart SN et al.: Age-related breast cancer risk estimates for the general population based on sequencing of cancer predisposition genes in 19,228 breast cancer patients and 20,211 matched unaffected controls from US based cohorts in the CARRIERS study GS2-01, oral presentation, SABCS 2018


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Breast Cancer Risk Genes with moderate to high Lifetime Risk

For following genes, risk calculations are available with varying degree of evidence. The clinical benefit must be proven by the effectiveness of preventive measures. ORs from studies with selected populations cannot be transferred to other populations.

<table>
<thead>
<tr>
<th>Clinical benefit of genetic test</th>
<th>Oxford LoE</th>
<th>Oxford GR</th>
<th>Oxford AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong>, <strong>BRCA2</strong></td>
<td>1b</td>
<td>A</td>
<td>++°</td>
</tr>
<tr>
<td><strong>PALB2</strong>, <strong>CDH1</strong>, <strong>TP53</strong></td>
<td>3a</td>
<td>B</td>
<td>+/-°</td>
</tr>
<tr>
<td><strong>ATM</strong>, <strong>CHEK2</strong>, <strong>BARD1</strong>, <strong>RAD51C</strong>, <strong>RAD51D</strong></td>
<td>3a</td>
<td>B</td>
<td>+/-°</td>
</tr>
</tbody>
</table>

* **BRCA1/2** are genes with a high lifetime risk. Furthermore genes with a medium and a low lifetime risk have been described.
** High ORs allow for the assumption that these are high risk genes. Prospective and age-related penetrances are not yet available.
*** These genes are classified as genes with a moderate lifetime risk based on currently available data.
(# These genes are associated with an increased risk of triple-negative breast cancer.
° Participation in prospective registries or studies is highly recommended.

8. Leila Dorling, Sara Carvalho, Jamie Allen et al. Breast cancer risk genes: association analysis of rare coding variants in 34 genes in 60,466 cases and 53,461 controls, submitted
Current Clinical Impact of Further Risk Genes

- Further moderate and low-risk gene variants are most likely transmitted by an oligo- or polygenic trait.
- The penetrance of such genes depends on the own and family cancer history.
- Single low-risk variants confer only small risk elevations and also seem to be associated with specific tumor subtypes. Potential multiplicative effects that may be relevant for risk stratification and provision of clinical prevention strategies remain to be elucidated. Therefore, the analysis of multiple gene regions may be of clinical relevance in the future.
- Therefore, genetic testing of moderate and low-risk genes and variants should only be performed within large prospective cohort studies like the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC).

<table>
<thead>
<tr>
<th>Clinical genetic testing of moderate-risk genes, e.g. gene panels</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Clinical genetic testing for low-risk variants</td>
<td>3b</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td>Referral to centers of the GC-HBOC or cooperating centers</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>


Current version of the TruRisk® BC/OC* Gene Panel by the German Consortium (GC-HBOC)

<table>
<thead>
<tr>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
</tr>
<tr>
<td>BARD1</td>
</tr>
<tr>
<td>BRCA1</td>
</tr>
<tr>
<td>BRCA2</td>
</tr>
<tr>
<td>BRIP1</td>
</tr>
<tr>
<td>CDH1</td>
</tr>
<tr>
<td>CHEK2</td>
</tr>
<tr>
<td>PALB2</td>
</tr>
<tr>
<td>RAD51C</td>
</tr>
<tr>
<td>RAD51D</td>
</tr>
<tr>
<td>TPS3</td>
</tr>
<tr>
<td>EPCAM</td>
</tr>
<tr>
<td>MLH1</td>
</tr>
<tr>
<td>MSH2</td>
</tr>
<tr>
<td>MSH6</td>
</tr>
<tr>
<td>PMS2</td>
</tr>
<tr>
<td>PTEN</td>
</tr>
<tr>
<td>STK11</td>
</tr>
<tr>
<td>APC</td>
</tr>
<tr>
<td>FAM175A</td>
</tr>
<tr>
<td>FANCC</td>
</tr>
<tr>
<td>FANCM</td>
</tr>
<tr>
<td>HOXB13</td>
</tr>
<tr>
<td>MEN1</td>
</tr>
<tr>
<td>MRE11A</td>
</tr>
<tr>
<td>MUTYH</td>
</tr>
<tr>
<td>NBN</td>
</tr>
<tr>
<td>NF1</td>
</tr>
<tr>
<td>POLD1</td>
</tr>
<tr>
<td>POLE</td>
</tr>
<tr>
<td>RAD50</td>
</tr>
<tr>
<td>RECL</td>
</tr>
<tr>
<td>SMARCA4</td>
</tr>
<tr>
<td>XRCC2</td>
</tr>
</tbody>
</table>

**Selection of genes:**
- 11 BC/OC ‘core genes’ (Data on risk increase)
- 7 other syndrome-associated genes (Lynch, Cowden, Peutz-Jeghers) with suspected BC/OC association
- 16 BC/OC candidate genes from scientific projects (validation in the GC-HBOC)

**Strategy:** Validation in prospective cohort, continuous expansion and improvement

*BC=breast cancer, OC=ovarian cancer


<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>0.95 – 0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05 – 0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely not pathogenic or of little clinical significance</td>
<td>0.001 – 0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not pathogenic or no of clinical significance</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Only class 4 and 5 variants are considered clinically relevant.
Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing*

- The risk collective is clearly defined by risk criteria.
- The positive predictive value of risk criteria with respect to the identification of the genetic risk factor is known.
- The cut-off values for genetic testing evolved through a transparent consensus process.
- The genetic test is valid and reliable.
- A spectrum bias is excluded or defined.
- A clinical prevention strategy exists that leads to early detection or prevention and mortality reduction of the genetically defined subset of the disease.


Non-Directive Counseling regarding Preventive Measures

- According to the Genetic Diagnostic Law
- According to the Medical Devices Act, e.g. risk assessment requires professional training and expertise
- Application of software for risk calculation requires professional training and experience
- Communicate absolute risks within a manageable timeframe
- Communicate risk and benefit of a multimodal intensive surveillance program
- Communicate risk and benefit of preventive clinical methods
- Communicate competing risks, e.g. risk of disease progression in relation to risk of a secondary primary in case women already affected by primary breast cancer
- Allow appropriate time for consideration

2. Aktualisierte Empfehlungen nach Bewertung von Gdablagerungen im Gehirn und anderen Geweben (08.01.2018) durch EMA und BfArM


### High risk screening including MRI

- A cohort of 4,573 high-risk, previously unaffected women (954 BRCA1 carriers, 598 BRCA2 carriers, 3,021 BRCA1/2 non-carriers) participated.
- Screening outcomes for 14,142 screening rounds with MRI between 2006 and 2015 were analyzed and stratified by risk group, type of screening round, and age.
- A total of 221 primary breast cancers (185 invasive, 36 in situ) was detected.
- 84.5% (174/206, 15 unknown) were stage 0 or I.
- Program sensitivity was 89.6% (95% CI 84.9-93.0) with no significant differences in sensitivity between risk groups or by age.
- Of all cancers, only 1.4% were symptomatic interval cancers.
- The rate of MRI-only detected cancers was 15/71 in BRCA 1 carriers (21%), 17/47 in BRCA 2 carriers (36%), and 29/80 high risk BRCA 1,2 non carriers (36%).
- The rate of MG-only detected cancers was 7/198 cases, the rate of US-only cancers 2/198 cases (BRCA 1 carriers in the 6 month interval of first round).


Breast Cancer Risk Genes with moderate to high Lifetime Risk


Breast cancer in young women after treatment for Hodgkin's disease during childhood or adolescence--an observational study with up to 33-year follow-up.

Schellong G¹, Riepenhausen M, German Consortium for Hereditary Breast and Ovarian Cancer et al.


### Surgical Prevention

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>B</td>
<td>*</td>
</tr>
</tbody>
</table>

* study participation recommended

- A secondary risk-reducing unilateral or bilateral mastectomy is not indicated without the presence of clearly defined genetic risk factors because it does not lead to a reduction in mortality.


Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)</td>
<td>2b B</td>
<td></td>
<td>+*</td>
</tr>
<tr>
<td>■ Reduces OvCa incidence and mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>■ Reduces overall mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(contradictory results for reduction of cl BC incidence)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic contralateral mastectomy (RR-CM)</td>
<td>2b B</td>
<td></td>
<td>+*</td>
</tr>
<tr>
<td>■ Reduces BC incidence and mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen (reduces contralateral BC incidence)</td>
<td>2b B</td>
<td>+/-*</td>
<td></td>
</tr>
<tr>
<td>■ Indication for RR-M should consider age at onset of first breast cancer in affected gene</td>
<td>2a B</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>RR-M after ovarian cancer</td>
<td>4 C</td>
<td></td>
<td>+/-**</td>
</tr>
</tbody>
</table>

* study participation recommended
** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5y), age


19. Meisner E, Rollins R, Ensr J et al.: Efficacy of olaparib monotherapy in patients (pts) with HER2-negative metastatic breast cancer (MBC) with germline BRCA mutation (gBRCAm) or lesional BRCA mutation (lBRCAm). J Clin Oncol 2018, 36 (suppl; abstr 1074)


### Medical Prevention for Women at Increased Risk

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>+*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>+&quot;</td>
</tr>
</tbody>
</table>

- **Tamoxifen for women >35 years: reduction of invasive BC, DCIS, and LN**
- **Raloxifene for postmenopausal women: reduction of invasive BC only**
- **AI for postmenopausal women**

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Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*

Check list (inclusion criteria)
Counseling for diagnostic genetic testing

Certified BC Center

Communication, Exchange, Advice

Genetic testing

Familial BC Center

Prophylactic surgery
Stratified therapy

Counseling: Indication for surveillance and/or prophylactic surgery

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015