Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

- **Versions 2003–2015:** Schmutzler with Albert / Blohmer / Fehm / Kiechle / Maass / Mundhenke / Rody / Thomssen / Schmidt

- **Version 2016:** Schmutzler / Stickeler
Principles in 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?

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

Families with
at least three women with breast cancer independent of age or
at least two women with breast cancer, one < 51 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 < 51 yrs. or
at least one woman affected by breast cancer < 36 yrs. or
at least one man affected by breast cancer and one additional relative
affected by breast or ovarian cancer*

* in one side of the family

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate ≥ 10% in ~25,000 families tested by 2015
## Suggested Use of a Screening Checklist *

<table>
<thead>
<tr>
<th>A. Patientin oder Patient und demnächsten Eltern/Geschwister/Kinder</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
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<tbody>
<tr>
<td>Aufreben eines Mammaplastomns bei der Patientin vor dem 30. LJ</td>
<td>1</td>
<td>3</td>
<td>2</td>
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<tr>
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<td>1</td>
<td>3</td>
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<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>B. Weitere mütterliche Linie</td>
<td>Anzahl</td>
<td>Gewichtung</td>
<td>Ergebnis</td>
</tr>
<tr>
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<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
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<td>1</td>
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</tr>
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<td>eines bilateralen Mammaplastomns bei einem angehöriigen Mann</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>C. Weitere väterliche Linie</td>
<td>Anzahl</td>
<td>Gewichtung</td>
<td>Ergebnis</td>
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<tr>
<td>Aufreben eines Mammaplastomns bei einer Angehörigen vor dem 30. LJ</td>
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<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

### *online tool provided by the Ärztekammer Westfalen-Lippe in cooperation with the GC-HBOC based on the inclusion criteria of the GC-HBOC, http://www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/FB-erbliche Belastung_V2016-01-06.pdf*
BRCA1/2 Testing in Patients with TNBC (irrespective of family history)

BRCA1/2 testing in patients with TNBC if an impact on treatment decisions is anticipated

Regardless of age *

* Study participation recommended
* The rate of BRCA 1/2 mutation is decreasing with increasing age
# Mutation Prevalences in TNBC

<table>
<thead>
<tr>
<th></th>
<th>&lt;35 y</th>
<th>35-39 y</th>
<th>40-49 y</th>
<th>50-59 y</th>
<th>&gt;=60 y</th>
<th>Total</th>
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<tbody>
<tr>
<td>No BC, no OC</td>
<td>18/91 (23%)</td>
<td>23/149 (15.4%)</td>
<td>18/209 (8.6%)</td>
<td>18/241 (7.5%)</td>
<td>6/279 (1.4%)</td>
<td>83/969 (8.5%)</td>
</tr>
<tr>
<td>1 BC, no OC</td>
<td>7/48 (14.6%)</td>
<td>7/50 (14%)</td>
<td>14/103 (13.6%)</td>
<td>5/80 (6.3%)</td>
<td>4/79 (5.1%)</td>
<td>37/360 (10.3%)</td>
</tr>
<tr>
<td>&gt;=2 BC, no OC</td>
<td>6/12 (50%)</td>
<td>6/16 (37.5%)</td>
<td>8/38 (21%)</td>
<td>2/28 (7.1%)</td>
<td>1/23 (0%)</td>
<td>23/117 (19.7%)</td>
</tr>
<tr>
<td>&gt;= 1 OC</td>
<td>3/5 (60%)</td>
<td>8/15 (53.3%)</td>
<td>7/18 (38.9%)</td>
<td>10/17 (58.8%)</td>
<td>1/7 (14.3%)</td>
<td>29/62 (46.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>34/156 (21.8%)</td>
<td>44/230 (19.1%)</td>
<td>47/368 (12.8%)</td>
<td>35/366 (9.6%)</td>
<td>12/388 (3.1%)</td>
<td>173/1508 (11%)</td>
</tr>
</tbody>
</table>

Couch et al. JCO DOI 10.1200/JCO.2014.57.1414
State of the Art

Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity

**disease risk**

- **high risk genes (OR >5.0)**
  - (BRCA1/2)

- **moderately penetrant risk genes (OR 1.5 - 5.0)**
  - (RAD51C, ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, …)

- **low risk variants / modifiers (OR/HR <1.5)**
  - (FGFR2, TOX3, 2q35, 11q15, SLC4A7, 5p12, MAP3K1, …)

**minor allele frequency**

**Contribution of known genes to familial aggregation of breast cancer**

- BRCA1
- BRCA2
- TP53
- PTEN
- ATM
- CHEK2, BRIP1, PALB2

Other genes, familial risk factors

79 common SNPs
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene alteration</th>
<th>Lifetime Risk BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li Fraumeni</td>
<td>p53</td>
<td>~50%(^1)</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>~25%(^2)</td>
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<tr>
<td>Hereditary diffuse gastric cancer syndrome</td>
<td>CDH1</td>
<td>~40-50% (lobular)(^3)</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/ LKB1</td>
<td>~45-50%(^4)</td>
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<tr>
<td>Lynch</td>
<td>mismatch repair MLH1, MSH2, MSH6, PMS2</td>
<td>up to twofold increased risk compared to general population(^5)</td>
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<td></td>
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<tr>
<td>Ataxia telangiectasia (AT-Syndrome)</td>
<td>ATM</td>
<td>20-40%(^6)</td>
</tr>
<tr>
<td>Franconi Anämie</td>
<td>RAD51C / D PALB2</td>
<td>&gt;30%(^7,8)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nijmegen-Breakage Syndrome</td>
<td>NBN</td>
<td>20-30%(^10,11)</td>
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</table>

Recommendation: genetic counselling: GCP
## Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction

### BROCA 40 gene panel
- **BROCA 40 gene panel**
  - [cross-cancer](http://web.labmed.washington.edu/tests/genetics/BROCA)
- **CENCOGENE BC/OC panel (16 genes)**
  - [Centogene](https://www.centogene.com/centogene)
- **AMBRY Genetics BreastNext (16 genes)**
  - [AMBRY Genetics](http://www.ambrygen.com/tests/breastnext)
- **CEGAT CAN02: Brust- und Ovarialkarzinom (30 genes)**
  - [CEGAT](http://www.cegat.de/Tumorerkrankungen_171.html)

### TruSight™ Cancer (Illumina)
- **TruSight™ Cancer (Illumina)**
- [TruSight™ Cancer (Illumina)](http://res.illumina.com/documents/products%5Cdatasheets%5Cdatasheet_trusight_cancer.pdf)

### MYRIAD myRISK Panel (25 genes)
- **MYRIAD myRISK Panel (25 genes)**

### Further Information
- [www.ago-online.de](http://www.ago-online.de)

### References
- FORSCHEN
- LEHREN
- HEILEN

### Guidelines Breast
- [Guidelines Breast](https://www.ago-online.de)
TruRisk® BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATM</td>
<td>core gene</td>
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<tr>
<td>BRCA1</td>
<td>core gene</td>
</tr>
<tr>
<td>BRCA2</td>
<td>core gene</td>
</tr>
<tr>
<td>CDH1</td>
<td>core gene</td>
</tr>
<tr>
<td>CHEK2</td>
<td>core gene</td>
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<tr>
<td>NBN</td>
<td>core gene</td>
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<tr>
<td>PALB2</td>
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<td>RAD51C</td>
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</tr>
<tr>
<td>RAD51D</td>
<td>core gene</td>
</tr>
<tr>
<td>TP53</td>
<td>core gene</td>
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<td>MLH1</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MSH2</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MSH6</td>
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<tr>
<td>PMS2</td>
<td>Lynch syndrome</td>
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<tr>
<td>ATM</td>
<td>candidate</td>
</tr>
<tr>
<td>TP53</td>
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<tr>
<td>MLH1</td>
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<tr>
<td>MSH2</td>
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<tr>
<td>MSH6</td>
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</tr>
<tr>
<td>PMS2</td>
<td>candidate</td>
</tr>
<tr>
<td>ATM #3</td>
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</tr>
<tr>
<td>TP53 #4</td>
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<tr>
<td>MLH1 Lynch</td>
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<td>MSH6 Lynch</td>
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<tr>
<td>PMS2 Lynch</td>
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<td>candidate #17</td>
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<tr>
<td>candidate #18</td>
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Gene selection:  
- **10 BC/OC ´core genes´** (sufficient data for genetic counseling)  
- **4 HNPCC genes** (~1% of unselected OC cases show truncating mutations; Song et al., 2014)  
- **20 BC/OC ´research genes**

**Strategy:**

- Validation in large cohort, constant expansion and improvement
Genotype determines not only disease penetrance but phenotype and clinical disease course.

*Meindl et al. Nat. Genet 2010
Gevensleben et al. 2013
Genetically Defined Subtypes are Distinct Tumor Entities

- Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer of prophylactic measures the following questions should be addressed:
  - Disease penetrance?
  - Typical histopathological features?
  - Sensitivity to current screening modalities?
  - Better survival of early detected tumors?
  - Natural disease course?
  - Response to anti-tumor therapy?

Genotype-phenotype-correlations must be employed
VUS: Problems and Questions

- Most VUS are **private** (>60%) or **extremely rare** (≤3, >80%)
- Additional analyses required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurrence analysis, large case / control studies
- *In silico* prediction tools (PolyPhen2, SIFT) are not adequate for clinical decision making
- Classification of sequence variants should be performed according to the IARC classification system
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet
Variant classification proposed by IARC (Plon et al., Human Mutation, 2008)

Only class 4 and 5 variants are considered clinically relevant.
Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.
- Co-occurrence data from large data banks
- Segregation analysis
- Functional analysis etc.

To be accumulated by large study groups such as ENIGMA

Improvement of IARC class 3 classification in the German population by GC-HBOC
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

Acc. to the position paper on risk-adjusted early detection of cancer of the German National Cancer Plan developed under the Federal Ministry of Health
http://www.bmg.bund.de/themen/praevention/nationaler-krebsplan/was-haben-wir-bisher-erreicht/querschnittsthema-risiko-adaptierte-krebsfrueherkennung.html
Current Clinical Impact of non-BRCA1/2 Breast Cancer Risk (NBBC) Genes

The remaining cancer susceptibility is most likely be transmitted by an oligo- or polygenic trait of moderate and low risk genes and alleles.

Moderate risk genes such as *RAD51C* exhibit very low mutation detection rates and may be associated with specific tumor subtypes.

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 the provision of clinical prevention strategies remain to be elucidated.

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.

- Clinical genetic testing for *RAD51C; CHEK2* and/or other moderate risk genes, e.g. gene panels
- Clinical genetic testing for low risk variants
- Referral to centres of the GC-HBOC or cooperating centres

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Category</th>
<th>Level of Evidence</th>
<th>Grade</th>
<th>Comments</th>
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<tbody>
<tr>
<td>2b</td>
<td>B</td>
<td></td>
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</tr>
<tr>
<td>3b</td>
<td>D</td>
<td>--</td>
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</tr>
<tr>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
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</tbody>
</table>
Non Directive Counseling for the Uptake of Preventive Measures

- According to the Genetic Diagnostic Law
- According to the Medical Devices Act, e.g. risk assessment requires professional training and expertise
- Communicate absolute risks within a manageable timeframe
- Communicate competing risks, e.g. risk of progressive disease in relation to the risk of a secondary primary in case women have already been affected by primary breast cancer
- Allow for appropriate time for consideration
Definition of Women at Moderate to High Risk

- Deleterious mutation in the BRCA1, BRCA2
- Heterozygous risk of $\geq 20\%$ or remaining lifetime risk of $\geq 30\%$ according to a validated standard risk prediction model
- Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
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<tbody>
<tr>
<td>1a A</td>
<td>++</td>
</tr>
<tr>
<td>2b B</td>
<td>+</td>
</tr>
<tr>
<td>2a B</td>
<td>++</td>
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</table>
Surveillance Program for Female Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC*

Multimodal intensive surveillance program lifelong

For the detection of early stage breast cancers

- Clinical breast exam >=25 years semi-annually
- Sonography >=25 years semi-annually
- Mammography >=40 years biannual
- Breast MRI (until ACR1) >=25 years annual

For mortality reduction (10 year survival)

- Oxford / AGO LoE / GR

*Referral to centres of the GC-HBOC or cooperating centres is recommended

See Table 4: Five- and 10-year overall survival in BRCA women and
Figure 1: overall survival in BRCA women
Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer acc. to GC-HBOC*

Multimodal intensive surveillance program lifelong

For the detection of early stage breast cancers

- Clinical breast exam  
  >=25 years  
  semi-annually
- Sonography  
  >=25 years  
  semi-annually
- Mammography  
  >=40 years  
  biannual
- Breast MRI (until ACR1)  
  >=25 years  
  annual

For mortality reduction (10 year survival)

- Oxford / AGO
- LoE / GR

2a  B  ++

For mortality reduction (10 year survival)

4  C  +

*Referral to centres of the GC-HBOC or cooperating centres is recommended
Surveillance for Male Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC*

BRCA1 mutation carrier have a near average life time risk to develop breast cancer and a 1.8-4.5-fold risk to develop prostate cancer by <=65y.

BRCA2 mutation carrier have a 5-7% life time risk to develop breast cancer and a 2.5-8.6-fold risk to develop prostate cancer by <=65y.

Currently no specific surveillance is recommended

- For breast cancer prevention:
  self examination and watchful waiting

- For prostate cancer prevention:
  study participation if available

Oxford / AGO LoE / GR

5 D +

3b C +
Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

- Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (8-18 years)
- Increased risk of breast or ovarian cancer in women from BRCA1/2 negative families at risk that is, however, lower than in women from BRCA1/2 positive families
- Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up
Unilateral or bilateral mastectomy is not indicated in the absence of clearly defined genetic risk factors
Surgical Prevention for Healthy Female BRCA1/2 Mutation Carriers

- Risk-reducing bilateral salpingo-oophorectomy (RR-BSO, PBSO) around 40 years of age
  - reduces OvCa incidence and mortality
  - reduces BrCa incidence and mortality
  - reduces overall mortality

- Contralateral mastectomy (RR-BM, PBM)
  - reduces BrCa incidence and mortality

RR-BSO is performed after completion of family planning
RR-BM revealed a high incidence of premalignant lesions

*Study participation recommended
Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

- **Bilateral salpingo-oophorectomy (RR-BSO)**
  - 2b B +*
  - reduces OvCa incidence and mortality
  - reduces BrCa mortality
  - reduces overall mortality
  - (contradictory results for reduction of cl BrCa incidence)

- **Contralateral mastectomy + (RR-BM)**
  - 2b B +/-*
  - reduces cl BrCa incidence

- **Tamoxifen** (reduces cl BrCa incidence)
  - 2b B +/-*

- **Indication for PBM should consider age at onset of first breast cancer and the affected gene**
  - 2a B ++*
  - Overall prognosis has to be considered

*Study participation recommended

See table 3: Efficacy of contralateral risk-reducing mastectomy on overall survival

We conclude that CRRM is associated with improved overall survival in BRCA1/2 mutation carriers with a history of PBC. Further research is warranted to develop a model based on age at diagnosis and tumour and treatment characteristics that can predict survival benefit for specific subgroups of patients, aiming at further personalized counselling and improved decision making.
Therapy of BRCA1/2-associated Breast Cancer+

Limited prospective cohort studies with short follow-up time

- Breast conserving therapy:
  - Adequate local tumor control (10 years observation) 2a B +

- Systemic therapy according to sporadic breast cancer 3a B +

- BRCA1/2 mutation status is predictive for chemotherapy response 3b B +

- Carboplatin (vs. Docetaxel) in MBC 2b B +

- PARP inhibitor in breast cancer 2b D +/-*

+ Overall prognosis has to be considered

*Study participation recommended
BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto


for the GBG/AGO-B study groups
Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)

Gunter von Minckwitz, Sibylle Loibl, Andreas Schneeweiss, Christoph Salat, Eric Hahnen, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens Uwe Blohmer, Hans Tesch, Fariba Khandan, Peter Fasching, Christian Jackisch, Rita Schmutzler, Valentina Nekljudova, Michael Untch

for the GBG/AGO-B study groups
Medical Prevention for Women at Increased Risk

- Tamoxifen for women > 35 years
  Reduction of invasive BrCA, DCIS, and LN

- Raloxifen for postmenopausal women
  Reduction of invasive BrCa only

- AI for postmenopausal women

#Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers.

Chemopreventive regimes 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)
## Risk Reduction for Ipsi- and Contralateral Breast Cancer

**Rationale:** Women with breast cancer have an increased risk for a second primary.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen*</td>
<td>1a A +</td>
</tr>
<tr>
<td>Aromatase inhibitors*</td>
<td>1a A +</td>
</tr>
<tr>
<td>Suppression of ovarian function* + Tamoxifen</td>
<td>1b B +</td>
</tr>
</tbody>
</table>

*Only proven for ER/PgR-positive primary sporadic BrCa
Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*

Check list (inclusion criteria)
Counselling for diagnostic genetic testing

Certified BC Ctr

Genetic testing

Familial BC Ctr

Communication, Exchange, Advice

Prophylactic surgery
Stratified therapy

Counselling: Indication for surveillance and/or prophylactic surgery

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015
Breast Cancer Risk and Prevention (2/35)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references
Principles in Prevention (3/35)

No further information

No references
Who Should be Tested for BRCA1/2 Mutations? (4/35)

No further information

References:

2. German Consortium for Hereditary Breast and Ovarian Cancer, personal communication of updated numbers. Molecular genetic testing is recommended for the above listed families in which the mutation probability exceeds 10%.
Suggested Use of a Screening Checklist (5/35)

No further information

No references
BRCA1/2 Testing in Patients with TNBC (irrespective of family history) (6/35)

Further information:

TED poll:
N=5 „as predictive marker“
N=21 „impact“
N=3, omit
N=9 ++
N=21 +

References:

*Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer.*


**Mutation prevalences in TNBC (7/35)**

*Further information:*
W/o fam. history and cumulative up to 50 y: 13%

**References:**

State of the Art: Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity (8/35)

No further information

No references
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (9/35)

No further information

References:

2. Tan et al., Lifetime cancer risks in individuals with germline PTEN mutations, Clin Cancer Res. 2012 Jan 15;18(2):400-7

Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction (10/35)

No further information

No references
TruRisk™ BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC (11/35)

No further information

No references
Clinical Implication: Genotype/Phenotype (12/35)

No further information

References


Genetically Defined Subtypes are Distinct Tumor Entities (13/35)

No further information

References:


VUS: Problems and Questions (14/35)

No further information

References

Variant classification proposed by IARC (15/35)

No further information

References:

Classification of IARC class 3 variant (16/35)

No further information

References:

1. ENIGMA – evidence-based network for the interpretation of germline mutant alleles: an international interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Human Mutat 33: 2-7, 2012
Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing (17/35)

No further information

References:

Current Clinical Impact of of non-BRCA1/2 Breast Cancer Risk (NBBC) (18/35)

No further information

References:

Non Directive Counseling for the Uptake of Preventive Measures (19/35)

No further information

No references
Definition of Women at Moderate to High Risk (20/35)

No further information

References:


Surveillance Program for Female for Women with deleterious BRCA-mutations (21/35)

Further information and references:


The German Consortium for Hereditary Breast and Ovarian Cancer has established an intensive surveillance program that is offered to mutation carriers and women at high risk within the 12 centres of familial breast and ovarian cancer in

These guidelines are in close agreement with the NICE-guidelines on Great Britain (McIntosh A et al.: Clinical Guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: national Collaborating Centre for Primary Care/University of Sheffield, 2004).

The surveillance program allows the detection of early stage breast carcinomas (MARIBS study group Lancet 2005, Kriege et al. NEJM 2004, Warner et al. JAMA 2004, Kuhl, Schmutzler et al. 2000 ). However, no data exist so far on long term follow-up and mortality reduction.

MRI Breast Screening in high-risk women (22/35)

No further information

References:

Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer acc. to GC-HBOC (23/35)

No further information

References:

**Surveillance for Male Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC (24/35)**

No further information

**References:**

Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

(25/35)

Further information and references:

5. Leach MO et al. Lancet 2005


These guidelines are in close agreement with the NICE-guidelines on Great Britain (McIntosh A et al.: Clinical Guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: national Collaborating Centre for Primary Care/University of Sheffield, 2004).
The surveillance program allows the detection of early stage breast carcinomas (MARIBS study group Lancet 2005, Kriege et al. NEJM 2004, Warner et al. JAMA 2004, Kuhl, Schmutzler et al. 2000 ). However, no data exist so far on long term follow-up and mortality reduction.

Surgical Prevention (26/35)

No further information

References:

**Surgical Prevention for Healthy BRCA1/2 Mutation Carriers (27/35)**

*Further information and references:*

Prophylactic bilateral salpingo-oophorectomy (PBSO) reduces the risk for ovarian cancer in BRCA1/2 mutation carriers to >95% and the risk for breast cancer to 50% (Kauff et al NEJM 2002, Rebbeck et al. NEJM 2002). Short term HRT does not negate the protective effect of PBSO on subsequent breast cancer risk (Rebbeck et al. 2005). The residual risk for peritoneal cancer after PBSO accumulates to 3.5% after 20 years of follow up (Casey et al. Gynecol Oncol 2005). Moreover, PBSO improves overall survival of mutation carriers (Domchek et al. The Lancet 2006). These studies support the current strategy of the German consortium to recommend PBSO in mutation carriers after completion of childbearing around the age of 40.

Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer in BRCA1/2 mutation carriers by >95% (Meijers-Heijboer et al. NEJM 2001, Rebbeck et al. JCO 2004) and may be performed in these women after the age of 25. However, only few women opt for this intervention.

For women at high risk defined as having a heterozygote risk of >20% or a life time risk of >30% and in whom genetic analysis is not possible or not informative the beneficial effect of preventive surgery is not clear and requires an individualized strategy. Premalignant lesions of the breast develop especially over the age of 40 (Hoogerbrugge N et al. Eur J Cancer 2006). A recent cohort study proved a breast cancer specific, ovarian cancer specific and overall survival benefit for PBSO (Domchek et al. Lancet Oncology 2006).

The German Consortium for Hereditary Breast and Ovarian Cancer has developed guidelines for prophylactic surgery. Prophylactic surgery should be proceeded by interdisciplinary counselling and, if possible, genetic testing within a familial breast cancer centre (addresses are deposited at www.deutsche-krebshilfe.de)
Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer (28/35)

No further information

References


Improved survival after contralateral risk-reducing mastectomy (29/35)

No further information

References:

Therapy of BRCA1/2-associated Breast Cancer+ (30/35)

Further information and references:

TED poll:
Caboplatin (vs Docetaxel): 3 ++, 17 +

3. L. et al. JCO 2006
At present, the German consortium for hereditary breast and ovarian cancer recommends surgical and adjuvant therapy of hereditary breast cancer according to standard guidelines. As the risk of contra-lateral breast cancer is 30-40% in 10 years while the risk of ipsi-lateral breast cancer is not significantly elevated (Metcalfe et al. JCO 2004, Pierce L. et al. JCO 2006), cl-MXT may be considered. PBSO significantly reduces the risk of ovarian cancer from 12.7% to 6.8% in 10 years (p=0.03) in breast cancer affected women. Therefore, PBSO is recommended in case of a good prognosis i.e. stage I breast cancer (Metcalfe K. et al. Gynecol Oncol 2005).

BRCA1 associated breast cancers have a poor prognosis that is mitigated by adjuvant chemotherapy (Robson et al. Breast Cancer Res 2003). Moreover, in vitro studies suggest a distinct chemosensitivity profile of BRCA associated breast carcinomas (Lafarge et al. Oncogene 2001, Quinn et al. Cancer Res 2003). Recent data suggest the benefit of new
therapeutic strategies that need to be further proven by RCTs. Therefore, affected BRCA mutation carriers and women at high risk should be referred to the centres for familial breast and ovarian cancer
BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto Study (31/35)

No further information

No references
Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto) (32/35)

No further information

No references
Medical Prevention for Women at Increased Risk (33/35)

No further information

References:


Risk Reduction for Ipsi- and Contralateral Breast Cancer (34/35)

Further information:

Large RCTs have proven a risk reduction of breast cancer by Tamoxifen, aromatase inhibitors and the combination of GnRHα plus Tamoxifen

No references
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (35/35)

No further information

No references