Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

- **Versions 2003–2014:**
  Schmutzler with Albert / Blohmer / Fehm / Kiechle / Maass / Mundhenke / Rody / Thomssen

- **Version 2015:**
  Schmutzler / Schmidt
Principles in Prevention

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

- 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 ~17,000 families tested by 2013
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
Recruitment of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)

18,875 in 2014; exp. +3,000 new families in 2015

BRCA1/2 mutation frequency: 24% (OC only: 35%, BC/OC: 42%)

- since 1996, 15 centres
- national database (IMISE*, Leipzig)
- national DNA-biobank (center Cologne)

*Institute for Medical Genetics, Statistics and Epidemiology, Leipzig
Suggested Use of a Screening Checklist *

Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs

<table>
<thead>
<tr>
<th>Name der Patientin:</th>
<th>Geburtsdatum:</th>
</tr>
</thead>
</table>

A. Patientin und deren Geschwister / Kinder

<table>
<thead>
<tr>
<th>Auftreten</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
<td>eines Mamma-Karzinoms bei der Patientin vor dem 36. Lj</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei der Patientin vor dem 51. Lj</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines bilateralen Mamma-Karzinoms bei der Patientin, das erste vor dem 51. Lj</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin nach dem 50. Lj</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei der Patientin</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei Schwester/Töchtern vor dem 36. Lj</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei Schwester/Töchtern vor dem 51. Lj</td>
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<td></td>
<td></td>
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<td>eines bilateralen Mamma-Karzinoms bei Schwester/Töchtern, das erste vor dem 51. Lj</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei Schwester/Töchtern nach dem 50. Lj</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>eines Mamma-Karzinoms bei Brüdern/Söhnen</td>
<td>2</td>
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<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei Schwester/Töchtern</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summe Patientin / Geschwister / Kinder

B. Mütterliche Linie

<table>
<thead>
<tr>
<th>Auftreten</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei einem angehörigen Mann</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen</td>
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</tbody>
</table>

Summe mütterliche Linie

C. väterliche Linie

<table>
<thead>
<tr>
<th>Auftreten</th>
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<tr>
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<td></td>
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</tr>
<tr>
<td>eines Mamma-Karzinoms bei einem angehörigen Mann</td>
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<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen</td>
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<td></td>
</tr>
</tbody>
</table>

Summe väterliche Linie

D. Der höhere Wert aus B und C

E. Summe aus A und D = Risiko-Score

Version: 03. Dezember 2012 (C) Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erbbliche Brust- und Eierstockkrebs

*online tool provided by the Ärztekammer Westfalen-Lippe based on the inclusion criteria of the GC-HBOC
www.aekwl.de/brustzentren-download
State of the Art
Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity

- **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 vs. disease risk graph]

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>
</tr>
<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>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: ~20 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervix: ~10 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterus: ~10 %</td>
</tr>
<tr>
<td>Lynch</td>
<td>mismatch repair MLH1, MSH2, MSH6, PMS2</td>
<td>up to twofold increased risk compared to general population(^5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial: ~ 25-60 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: up to 25 %</td>
</tr>
</tbody>
</table>

**Recommendation:** genetic counselling: GCP
Third Moderate to High Risk Gene Identified within the GC-HBOC

Germ-line mutations in breast and ovarian cancer pedigrees establish *RAD51C* as a human cancer susceptibility gene

**Nature Genetics April 18, 2010**

Alfons Meindl¹, Heide Hellebrand¹, Constanze Wick², Verena Erven², Barbara Wappenschmidt³, Dieter Niederacher⁴, Marcel Freund⁵, Peter Lichtner⁵, Linda Hartmann⁶, Heiner Schaal⁶, Juliane Ramser¹, Ellen Honisch⁴, Christian Kubisch⁷, Hans E. Wichmann⁸, Karin Kast⁹, Helmut Deißler¹⁰, Christoph Engel¹¹, Bertram Müller-Myhsok¹², Kornelia Neveling¹³, Marion Kiechle¹, Christopher G. Mathew¹⁴, Detlev Schindler¹³, Rita K. Schmutzler³, Helmut Hanenberg⁷,¹⁵⁺

- 1.100 BRCA1/2 negative risk families: 670 breast only, 430 breast and ovarian cancer
- 6 deleterious mutations in BC/OC families only (1.5%)
### Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction

<table>
<thead>
<tr>
<th>Panel Name</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BROCA 40 Gene Panel</strong></td>
<td>APC, ATM, BAP1, BARD1, BMPR1A, BRC2, BRI1, CDK4, CDK2, CDKN2A, CHEK1, CHEK2, EPCAM, FAM175A, GALNT12, GEN1, GREM1, HOUX13, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, PRSS1, PTEN, RAD50, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td><strong>AMBRY Genetics BreastNext (16 genes)</strong></td>
<td>ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, MEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td><strong>CEGAT CAN02: Brust- und Ovarialkarzinom (30 genes)</strong></td>
<td>ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td><strong>TruSight™ Cancer (Illumina)</strong></td>
<td>AIP, ALK, ALR, ATM, BAP1, ATM, BLM, BARD1, BRC2, BRCA1, BRCA2, BRIP1, CDH1, CHEK1, CHEK2, CHEK3, CEBPA, CEP57, CHEK2, CYLD, DDB2, DICER1, DIS3L2, EGFR, EPCAM, EPCAM, ERCC2, ERCC3, ERCC4, ERCC5, EXO1, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FH, FLCN, GATA2, GPC3, HNF1A, HRAS, KIT, MAX, MEN1, MET, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td><strong>CENTOGENE BC/OC panel (16 genes)</strong></td>
<td>ATM, BARD1, BRCA1, BRCA2, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
</tr>
<tr>
<td><strong>MYRIAD myRisk Panel (25 genes)</strong></td>
<td>APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, STK11, TP53</td>
</tr>
</tbody>
</table>
TruRisk™ BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC

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)
- **12 BC/OC research genes** (validation in cooperation with the ENIGMA consortium)
- **8 candidate BC/OC genes** (GC-HBOC, unpublished)

**Strategy:**

- Validation in large cohort, constant expansion and improvement
Clinical Implication:
Genotype/Phenotype

- Genotype determines not only disease penetrance but phenotype and clinical disease course

*Meindl et al. Nat. Genet 2010
Gevensleben et al. submitted
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
- VUS classification and clinical decision making are not standardized yet
## Low risk Variants from Genome Wide Association Studies (GWAS)

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Häufigkeit</th>
<th>TOTAL BCAC</th>
<th>FRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio</td>
<td>P-trend</td>
</tr>
<tr>
<td><strong>FGFR2</strong></td>
<td>rs2981582</td>
<td>38%</td>
<td>1.24</td>
<td>5x10^-87</td>
</tr>
<tr>
<td><strong>TOX3</strong></td>
<td>rs3803662</td>
<td>25%</td>
<td>1.21</td>
<td>8x10^-52</td>
</tr>
<tr>
<td>2q35</td>
<td>rs13387042</td>
<td>51%</td>
<td>1.12</td>
<td>3x10^-34</td>
</tr>
<tr>
<td>11q15</td>
<td>rs614367</td>
<td>15%</td>
<td>1.20</td>
<td>5x10^-16</td>
</tr>
<tr>
<td>SLC4A7</td>
<td>rs4973768</td>
<td>46%</td>
<td>1.11</td>
<td>4x10^-23</td>
</tr>
<tr>
<td>5p12</td>
<td>rs10941679</td>
<td>26%</td>
<td>1.12</td>
<td>4x10^-23</td>
</tr>
<tr>
<td>MAP3K1</td>
<td>rs889312</td>
<td>28%</td>
<td>1.11</td>
<td>3x10^-20</td>
</tr>
<tr>
<td>8q24</td>
<td>rs13281615</td>
<td>40%</td>
<td>1.10</td>
<td>8x10^-15</td>
</tr>
<tr>
<td>CASP8</td>
<td>rs1045485</td>
<td>13%</td>
<td>0.9</td>
<td>2x10^-8</td>
</tr>
<tr>
<td>ESR1</td>
<td>rs2046210</td>
<td>33%</td>
<td>1.09</td>
<td>2x10^-15</td>
</tr>
<tr>
<td>LSP1</td>
<td>rs3817198</td>
<td>30%</td>
<td>1.08</td>
<td>5x10^-11</td>
</tr>
<tr>
<td>1p11.2</td>
<td>rs11249433</td>
<td>39%</td>
<td>1.10</td>
<td>7x10^-10</td>
</tr>
<tr>
<td>ZNF365</td>
<td>rs10995190</td>
<td>15%</td>
<td>0.88</td>
<td>4x10^-15</td>
</tr>
<tr>
<td>ZMIZ1</td>
<td>rs704010</td>
<td>39%</td>
<td>0.92</td>
<td>3x10^-8</td>
</tr>
<tr>
<td>CDKN2A/B</td>
<td>rs1011970</td>
<td>17%</td>
<td>1.08</td>
<td>7x10^-8</td>
</tr>
<tr>
<td>COX11</td>
<td>rs6504950</td>
<td>27%</td>
<td>0.95</td>
<td>10^-8</td>
</tr>
<tr>
<td>ANKRD16</td>
<td>rs2380205</td>
<td>43%</td>
<td>0.98</td>
<td>4x10^-7</td>
</tr>
<tr>
<td>RAD51L1</td>
<td>rs999737</td>
<td>24%</td>
<td>0.94</td>
<td>2x10^-7</td>
</tr>
</tbody>
</table>
Low Risk Variants as Modifiers

**Retrospective**

**Gaudet et al., in coop with GC-HBOC 2013:** Combined genotype distribution of **14 variants** in 8,221 BRCA2 mutation carriers (FGFR2, TOX3, 12p11, 5q11, CDKN2A/B, LSP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13)

- **Couch et al. in coop with the GC-HBOC 2013:** Combined genotype distribution of **10 variants** in 11,705 BRCA1 mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, TOX3, 2q35, LSP1, RAD51L1, TERT)
- 5% of BRCA1 carriers at lowest risk (28–50%) compared to the 5% at highest risk (81–100%)

**Prospective**

**Mavaddat et al., 2013:** combined genotype distribution of **7 low-risk SNP** in **909** BRCA2 carriers

BRCA2 carriers at the highest tertile of the score distribution were at significantly higher risk than women at the lowest tertile (HR = 4.1, 95%; CI = 1.2 to 14.5; P = .02)´ first ´proof of principle´

**Associations are breast cancer subtype specific**

Garcia-Closas et al., Clin Cancer Res, 2008
Current Clinical Impact of Other Risk 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

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>3b</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>
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 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 life time risk of $\geq 30\%$ acc. to a validated standard risk prediction model
- Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)

Oxford / AGO
LoE / GR

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<thead>
<tr>
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<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>
Surveillance Program for Women with Deleterious BRCA-mutations*

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) 4 C +

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

Oxford / AGO LoE / GR
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
Surgical Prevention

- Unilateral or bilateral mastectomy is not indicated in the absence of clearly defined genetic risk factors

Oxford / AGO
LoE / GR

2a B +*
Surgical Prevention for Healthy 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

• Risk-reducing bilateral 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 Mutation Carriers Affected by Breast Cancer

• Bilateral salpingo-oophorectomy (RR-BSO) reduces OvCa incidence and mortality
  reduces BrCa mortality
  reduces overall mortality
  (contradictory results for reduction of cl BrCa incidence)

• Bilateral mastectomy + (RR-BM) reduces cl BrCa incidence

• Tamoxifen (reduces cl BrCa incidence)

• Indication for PBM should consider age at onset of first breast cancer and the affected gene

+ Overall prognosis has to be considered

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
<th>B</th>
<th>+/*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study participation recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall prognosis has to be considered</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Risk-reducing Salpingo-oophorectomy and All-cause Mortality

## Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer</th>
<th>Prior Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 2462)</td>
<td>BRCA1 (n = 1367)</td>
<td>BRCA2 (n = 695)</td>
</tr>
<tr>
<td>Risk-reducing salpingo-oophorectomy</td>
<td>Yes</td>
<td>993 (40.0)</td>
<td>706 (44.5)</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>31 (3.1)</td>
<td>25 (3.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1489 (60.0)</td>
<td>881 (55.5)</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>146 (8.8)</td>
<td>93 (10.6)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>At time of risk-reducing salpingo-oophorectomy</td>
<td>45.4 (20.5-79.0)</td>
<td>44.5 (20.5-79.0)</td>
</tr>
<tr>
<td></td>
<td>At start of follow-up for those without salpingo-oophorectomy</td>
<td>39.8 (18.1-90.4)</td>
<td>38.5 (18.1-90.4)</td>
</tr>
<tr>
<td>Follow-up, mean (range), y</td>
<td>To death</td>
<td>6.0 (0.5-23.5)</td>
<td>5.9 (0.5-23.5)</td>
</tr>
<tr>
<td></td>
<td>To censoring</td>
<td>5.0 (0.5-27.8)</td>
<td>5.0 (0.5-27.8)</td>
</tr>
<tr>
<td>All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)</td>
<td></td>
<td>0.40 (0.26-0.61)</td>
<td>0.38 (0.24-0.62)</td>
</tr>
<tr>
<td>Age &lt;50 y</td>
<td></td>
<td>0.41 (0.25-0.67)</td>
<td>0.40 (0.24-0.66)</td>
</tr>
<tr>
<td>Age ≥50 y</td>
<td></td>
<td>0.37 (0.15-0.94)</td>
<td>0.22 (0.06-0.85)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

a Values are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.

b Breast cancer cases prior to risk-reducing salpingo-oophorectomy in those who underwent salpingo-oophorectomy prior to the start of follow-up.

c Prior breast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.

Domchek et al. JAMA 2010; Table 4.
Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive)

Table 2 Cumulative risks (in %) and 95% confidence intervals (in parentheses) for contralateral breast cancer depending on age at first breast cancer observed in relatives of index patients.

<table>
<thead>
<tr>
<th>Age at first breast cancer</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>14.1 (10.1-18.0)</td>
<td>2.9 (0.0-6.3)</td>
<td>4.8 (2.6-6.9)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>30.1 (24.0-36.2)</td>
<td>18.2 (7.9-28.5)</td>
<td>10.6 (6.8-14.4)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>40.8 (33.2-48.3)</td>
<td>20.9 (9.7-32.1)</td>
<td>15.3 (10.4-20.3)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>55.1 (45.4-64.9)</td>
<td>38.4 (18.5-58.2)</td>
<td>28.4 (20.5-36.3)</td>
</tr>
<tr>
<td>≥ 40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>9.2 (5.8-12.5)</td>
<td>6.9 (2.7-11.1)</td>
<td>4.2 (2.9-5.5)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>16.7 (11.7-21.7)</td>
<td>13.4 (7.0-19.8)</td>
<td>8.4 (6.3-10.5)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>23.2 (16.9-29.6)</td>
<td>22.0 (12.1-31.9)</td>
<td>10.7 (8.1-13.3)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>44.5 (33.2-55.7)</td>
<td>40.5 (22.4-58.6)</td>
<td>18.1 (13.9-22.3)</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>7.1 (3.8-10.5)</td>
<td>3.5 (0.9-6.1)</td>
<td>3.6 (2.7-4.5)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>11.4 (6.5-16.3)</td>
<td>10.4 (4.9-16.0)</td>
<td>5.5 (4.3-6.7)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>18.7 (11.0-26.3)</td>
<td>15.5 (7.8-23.3)</td>
<td>8.1 (6.3-9.9)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>21.6 (12.3-30.8)</td>
<td>15.5 (7.8-23.3)</td>
<td>12.9 (8.9-17.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>10.4 (8.3-12.5)</td>
<td>4.5 (2.5-6.5)</td>
<td>3.9 (3.2-4.6)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>20.4 (17.1-23.7)</td>
<td>13.2 (9.2-17.2)</td>
<td>7.1 (6.0-8.2)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>28.7 (24.4-32.9)</td>
<td>19.0 (13.5-24.4)</td>
<td>9.9 (8.5-11.4)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>44.1 (37.6-50.6)</td>
<td>33.5 (22.4-44.7)</td>
<td>17.2 (14.5-19.9)</td>
</tr>
</tbody>
</table>
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 mutation status is predictive for chemotherapy response 3b B +
- Carboplatin (vs. Docetaxel) in MBC 2b\(^a\) B +
- PARP inhibitor in breast cancer 2b D +/−*

+ Overall prognosis has to be considered

*Study participation recommended
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC

Check list (inclusion criteria)

Communication, Exchange, Advice

Prophylactic surgery

Indication for prophylactic surgery

Counselling and testing

BC

Spec. BC
Medical Prevention for Women at Increased Risk

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

• Raloxifene 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

- Tamoxifen*
  - Oxford / AGO LoE / GR: 1a A +

- Aromatase inhibitors*
  - Oxford / AGO LoE / GR: 1a A +

- Suppression of ovarian function* + Tamoxifen
  - Oxford / AGO LoE / GR: 1b B +

*Only proven for ER/PgR-positive primary sporadic BrCa
Breast Cancer Risk and Prevention (2/32)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references
**Principles in Prevention (3/32)**

*No further information*

*No references*
Who Should be Tested for BRCA1/2 Mutations? (4/32)

No further information

References:


2. German Consortium for Hereditary Breast and Ovarian Cancer, personal communication of up-dated numbers. Molecular genetic testing is recommended for the above listed families in which the mutation probability exceeds 10%. 
**BRCA1/2 Testing in Patients with TNBC (irrespective of family history) (5/32)**

*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.*

Recruitment of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) up to 2013 (6/32)

No further information

No references
Suggested Use of a Screening Checklist (7/32)

No further information

No references
State of the Art: Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity (8/32)

No further information

No references
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (9/32)

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
Third Moderate to High Risk Gene Identified within the GC-HBOC (10/32)

No further information

References:


Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction (11/32)

No further information

No references
TruRisk™ BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC (12/32)

No further information

No references
Clinical Implication: Genotype/Phenotype (13/32)

No further information

No references
Genetically Defined Subtypes are Distinct Tumor Entities (14/32)

No further information

References:


VUS: Problems and Questions (15/32)

No further information

No references
Low Risk Variants from Genome Wide Association Studies (GWAS) (16/32)

No further information

References:

**Low Risk Variants as Modifier (17/32)**

*No further information*

**References:**


Current Clinical Impact of Other Risk Genes (18/32)

No further information

References:

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing (19/32)

No further information

References:

Non Directive Counseling for the Uptake of Preventive Measures (20/32)

No further information

No references
Definition of Women at Moderate to High Risk (21/32)

No further information

References:

**Surveillance Program for Women with deleterious BRCA-mutations (22/32)**

*Further information and references:*

7. 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.

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

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 (24/32)

No further information

References:

**Surgical Prevention for Healthy BRCA1/2 Mutation Carriers (25/32)**

*Further information and references:*

2. Kauff et al NEJM 2002
3. Rebbeck et al. NEJM 2002
4. Domcheck et al. 2006
5. Meijers-Heijboer et al. 2001
6. Rebbeck et al. 2004
7. Hoogerbrugge et al. 2006
8. Domcheck et al. 2010
9. Sitzmann et al., JAMA Surg 2013

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 preceded 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 (26/32)**

No further information

**References:**


Risk-reducing Salpingo-oophorectomy and All-cause Mortality (27/32)

No further information

References:

Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive) (28/32)

No further information

No references
Therapy of BRCA1/2-associated Breast Cancer+ (29/32)

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

References:
1. Metcalfe et al. JCO 2004
2. Pierce L. et al. JCO 2006
4. Tassone et al. BJC 2003
8. Rottenberg et al. 2008
9. Ashworth et al. JCO 2008
10. Rottenberg et al. PNAS 2008
11. Fong et al. NEJM 2009
12. Tutt et al, ASCO abst. 2009, 27(15S) CRA501
15. Robson et al. BCR 2004
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (30/32)

No further information

No references
Medical Prevention for Women at Increased Risk (31/32)

No further information

References:

1. NSABP-P1 (Tamoxifen): Fischer B et al JNCI 1998
2. Star (Raloxifen): Vogel VG et al. JAMA 2006
Risk Reduction for Ipsi- and Contralateral Breast Cancer (32/32)

Further information:

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

No references