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Guidelines Breast
Version 2021.1D

# Brustkrebsrisiko und Prävention

# Brustkrebsrisiko und Prävention

- **Versionen 2003–2020:**
  **Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen**

- **Version 2021:**
  **Park-Simon / Witzel**

# Allgemeine Prinzipien in der Prävention

- **Frauen mit einem erhöhten Erkrankungsrisiko für Brustkrebs sind Ratsuchende und nicht Patientinnen.**
- **Dem Angebot präventiver Maßnahmen geht eine umfassende und ausführliche Beratung mit Nutzen/Risikoabwägung voraus.**
- **Das Nichtschadensprinzip steht dabei im Vordergrund.**

***(Primum nil nocere)***



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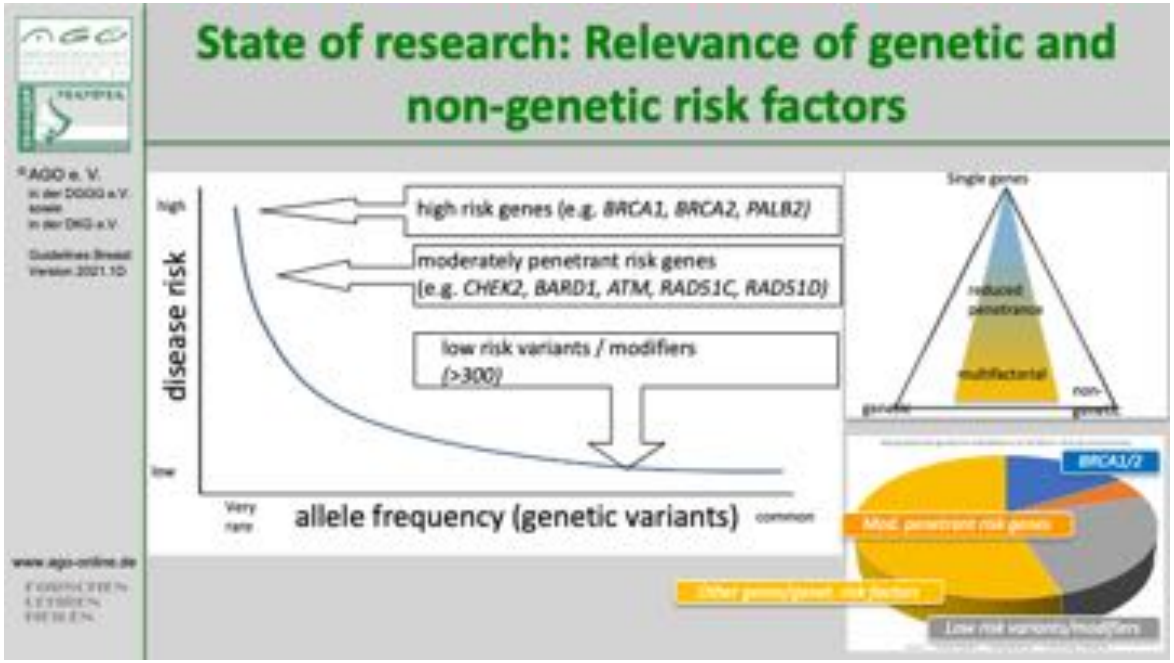



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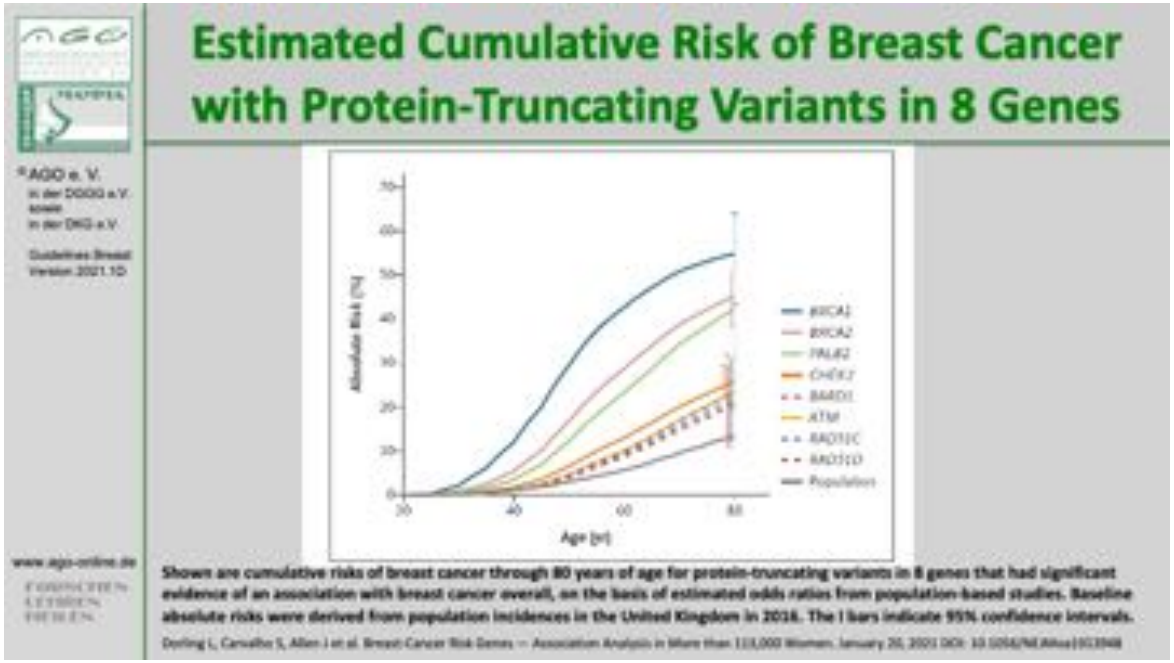


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# Gegenwärtige klinische Bedeutung weiterer Risikogene

- Weitere moderat penetrante Genveränderungen und Niedrigrisikovarianten können oligo- oder polygen einen Einfluss auf das Brustkrebsrisiko haben.
- Die Penetranz dieser Genveränderungen ist abhängig von der eigenen und familiären Krebsbelastung
- Einzelne Niedrigrisikovarianten erhöhen das Erkrankungsrisiko nur unwesentlich. Sie scheinen aber multiplikativ zu wirken, so dass die Analyse multipler Genregionen zukünftig von klinischer Relevanz sein kann.
- *Derzeit sollten moderat penetrante Gene und Niedrigrisikovarianten daher nur im Rahmen von prospektiven Kohortenstudien wie der des Deutschen Konsortiums untersucht werden.

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| Genetische Analyse von moderaten Risikogenen e.g. Genpanel | 1b | B | + |
| Genetische Analyse von Niedrigrisikovarianten (Polygenic risk score) | 2b | B | +/-* |
| Zuweisung an spezialisierte Zentren des Konsortiums oder kooperierende Zentren | 5 | D | + |


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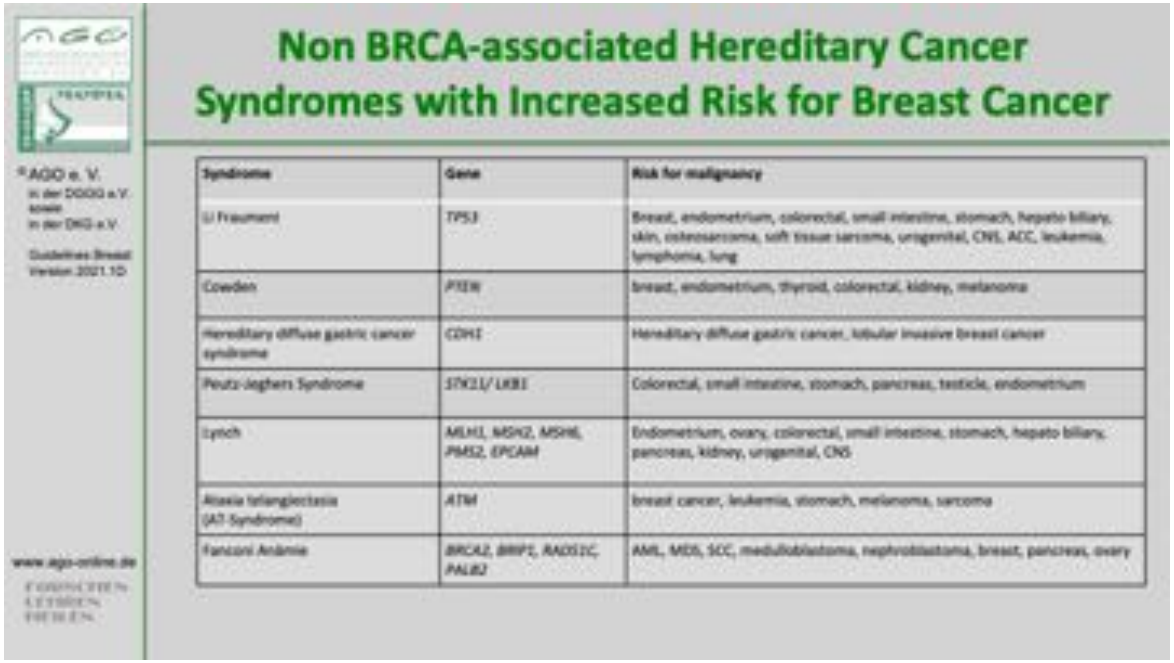



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Current version of the TruRisk® BC/OC* Gene Panel by the German Consortium (GC-HBOC)
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Version 2021.1D
ATM
BRCA1
BRCA2
CDH1
CHEK2
HOXB13
EPCAM
MLH1
MSH2
MSH6
PMS2
PTEN
STK11
APC
FAM175A
FANCC
FANCM
MRE11A
MUTYH
NBN
NF1
POLD1
POLE
RAD50
RECQL
SMARCA4
XRCC2
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
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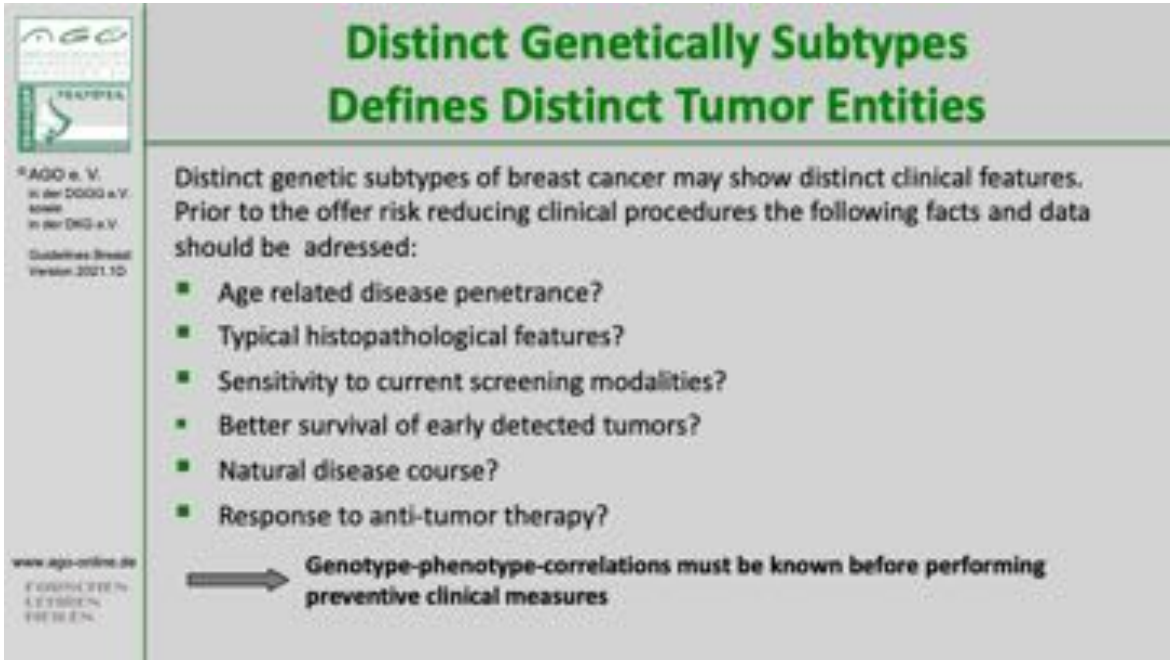



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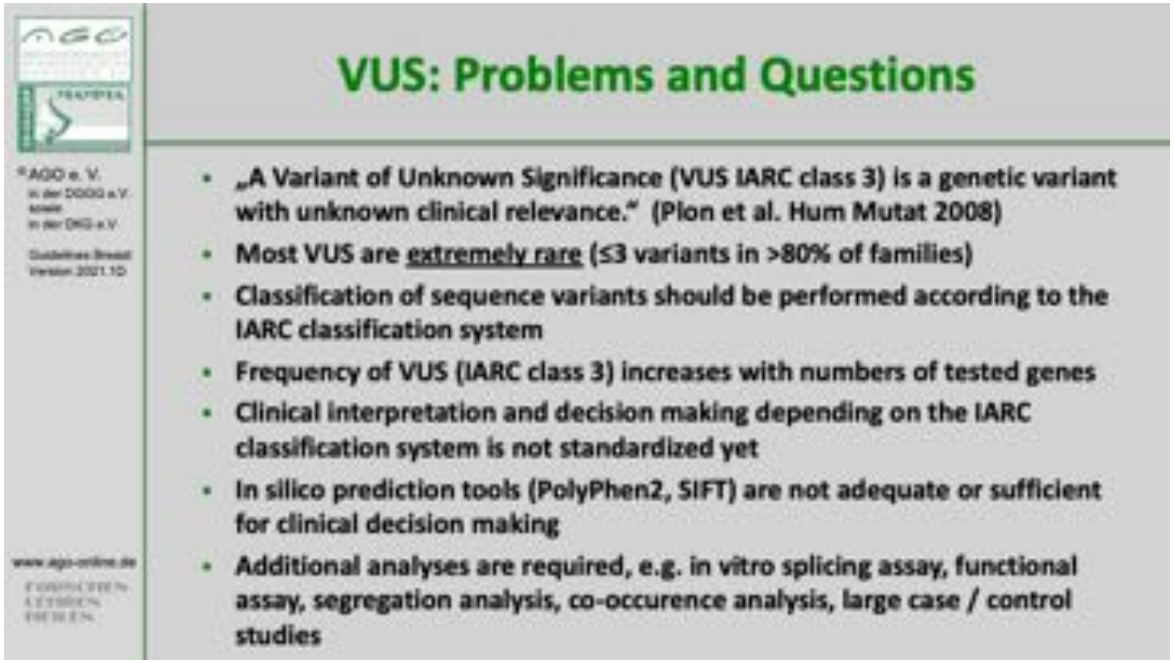



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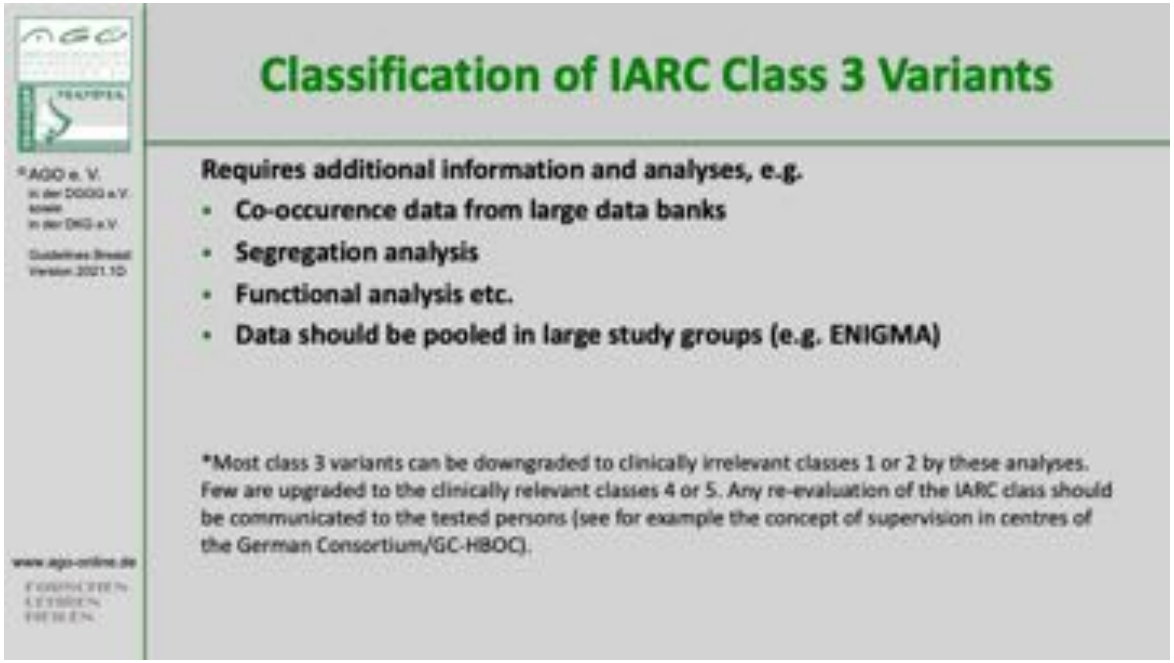
## Klassifikation der Varianten nach IARC (Plon et al., Human Mutation, 2008)

| Proposed Classification System for Sequence Variants Identified by Genetic Testing | | |
|---|---|---|
| **Class** | **Discription** | **Probability of being pathogenic** |
| 5 | Definitly pathogenic | > 0,99 |
| 4 | Likely pathogenic | 0,95 – 0,99 |
| 3 | Uncertain | 0,05 – 0,949 |
| 2 | Likely not pathogenic or of little clinical significance | 0,001 – 0,049 |
| 1 | Not pathogenic or no of clinical significance | < 0,001 |

**Nur Klasse 4 und 5 Varianten gelten als klinisch relevant.**

1. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Human mutation. 2008;29(11):1282-91.

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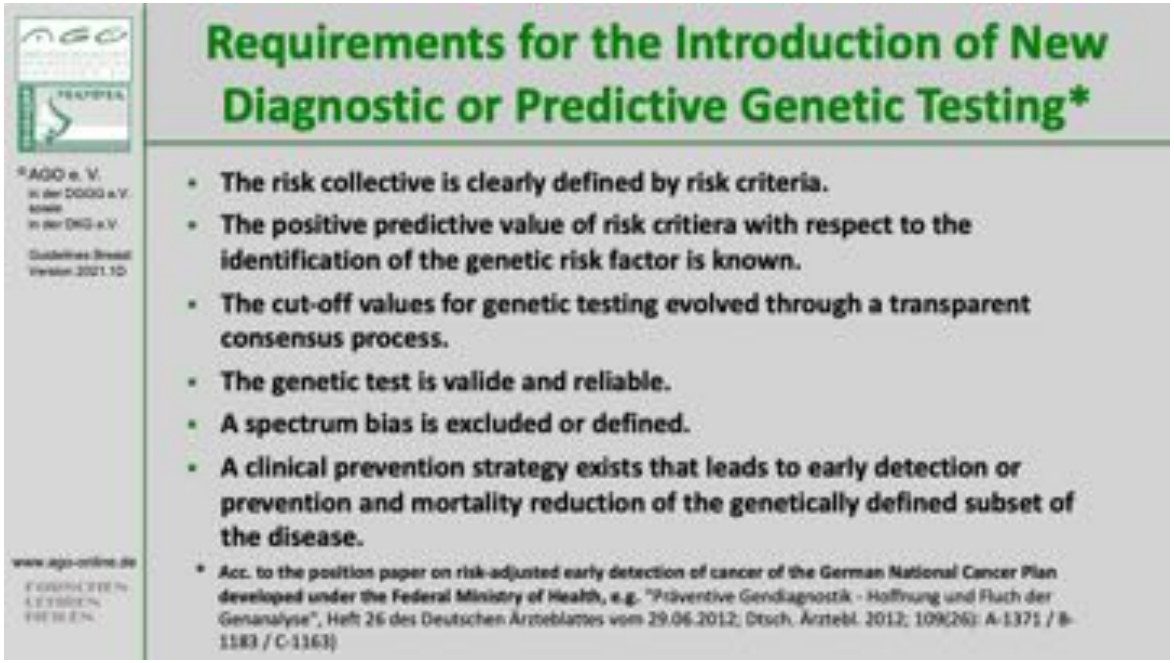



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## Multimodales intensiviertes Früherkennungsprogramm*

| | | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|---|
| • Früherkennungsprogramm bei *BRCA*-Mutation | | | | |
| • Zum Nachweis früher Tumorstadien | | 2b | B | ++ |
| ◦ Ärztliche Tastuntersuchung | >= 25 Jahre | halbjährlich | | |
| ◦ Ultraschall | >= 25 Jahre | halbjährlich | | |
| ◦ Mammographie | >= 40 Jahre | 1-2 jährlich | | |
| ◦ Kernspintomographie | >= 25 Jahre | jährlich | | |
| • Zur Verbesserung des metastasenfreien Überlebens | | 2b | B | + |
| • Überlebende nach kindlichen Tumoren mit therapeutischer Radiatio der Brustwand (z.B. M. Hodgkin) | | 2a | B | ++ |

* Das multimodale intensivierte Früherkennungsprogramm sollte im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen.


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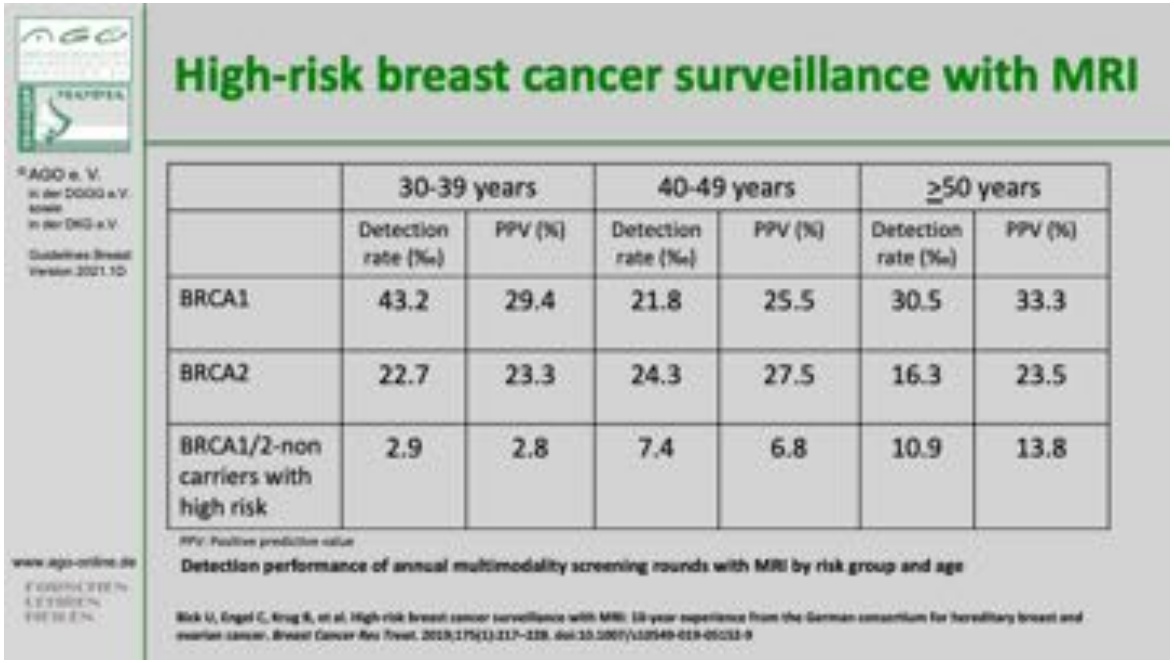


## High-risk breast cancer surveillance with MRI

| | 30-39 years | | 40-49 years | | ≥50 years | |
|---|---|---|---|---|---|---|
| | Detection rate (‰) | PPV (%) | Detection rate (‰) | PPV (%) | Detection rate (‰) | PPV (%) |
| BRCA1 | 43.2 | 29.4 | 21.8 | 25.5 | 30.5 | 33.3 |
| BRCA2 | 22.7 | 23.3 | 24.3 | 27.5 | 16.3 | 23.5 |
| BRCA1/2-non carriers with high risk | 2.9 | 2.8 | 7.4 | 6.8 | 10.9 | 13.8 |

PPV: Positive prediction value

**Detection performance of annual multimodality screening rounds with MRI by risk group and age**

Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat.* 2019;175(1):217–228. doi:10.1007/s10549-019-05152-9

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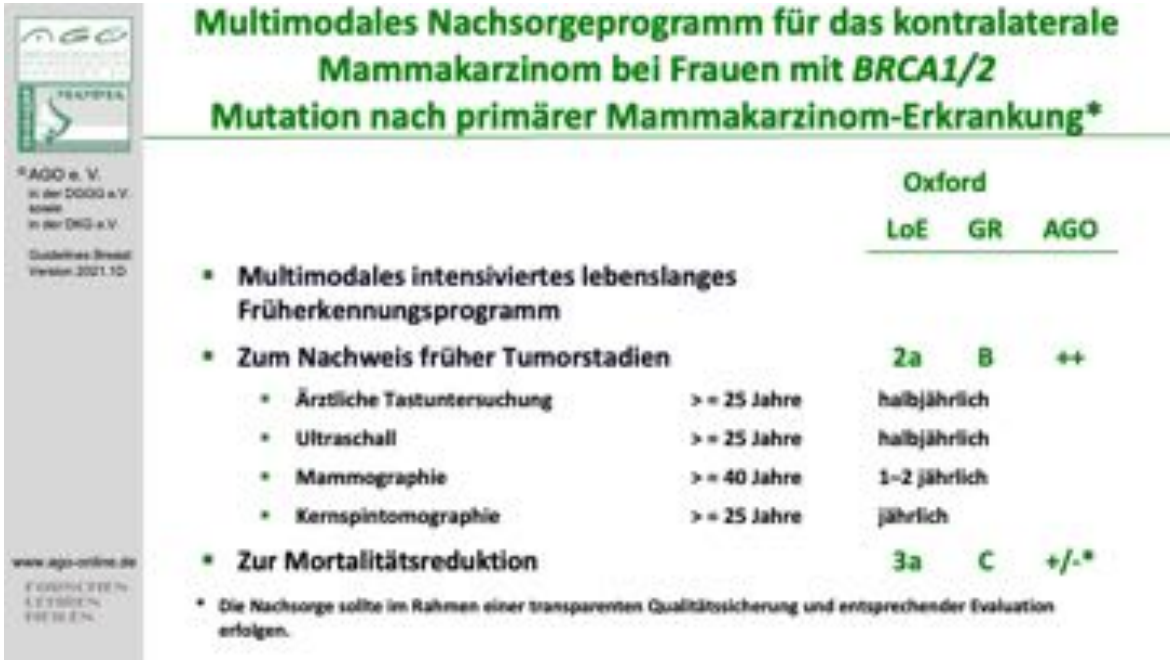



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## Früherkennungsprogramm für Männer mit *BRCA1/2* Mutationen*

**Für *BRCA1* Mutationsträger gilt ein der Allgemeinbevölkerung entsprechendes Erkrankungsrisiko für Brustkrebs (ca. 1%), ein ca. 1.8- bis 3.75-faches Risiko für ein Prostatakarzinom ≤ 65 Jahren.**
***BRCA2* Mutationsträger haben ein ca. 5–7%iges Lebenszeitrisiko für Brustkrebs, ein ca. 2.5- bis 8.6-faches Risiko für ein Prostatakarzinom ≤ 65 Jahren.**

| | Oxford LoE | GR | AGO |
|---|---|---|---|
| **Aktuell kein spezifisches Früherkennungsprogramm** | | | |
| • **Für Brustkrebs: Selbstuntersuchung und Watchful waiting*** | 5 | D | + |
| • **Für Prostatakarzinom: vgl. Empfehlung zum Prostatakarzinom S3-Leitlinie** | 5 | D | + |

* Früherkennung wie Nachsorge in diesem Kollektiv sollten im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen.


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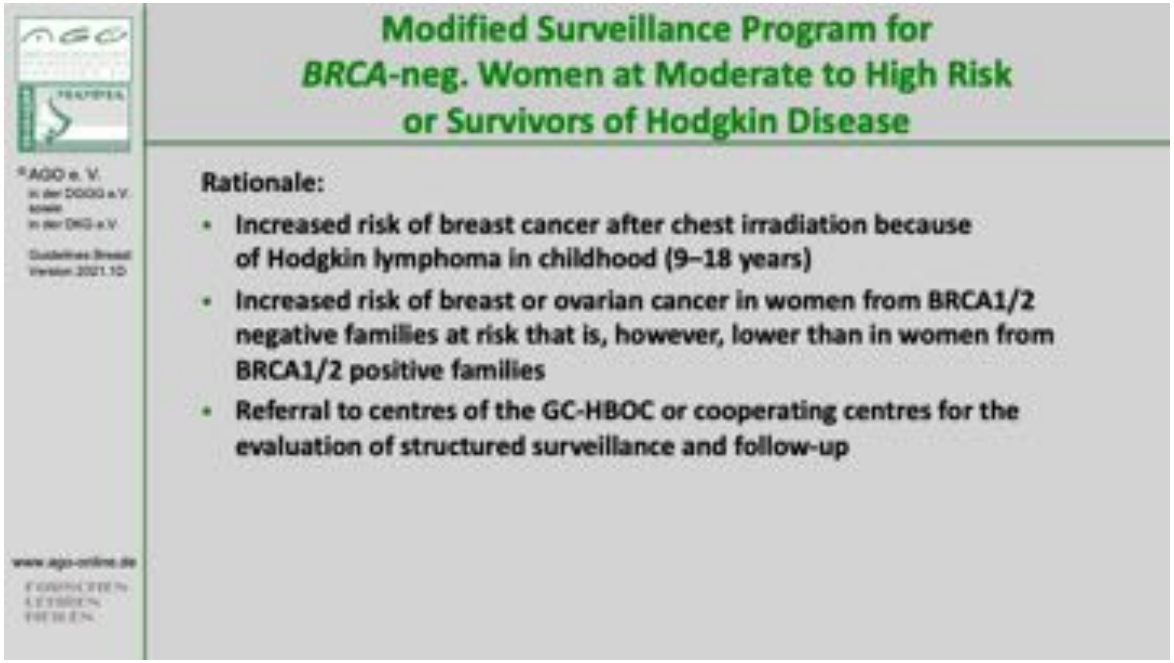
10. S3-Leitlinie Prostatakarzinom (Version 5.1, 2019)





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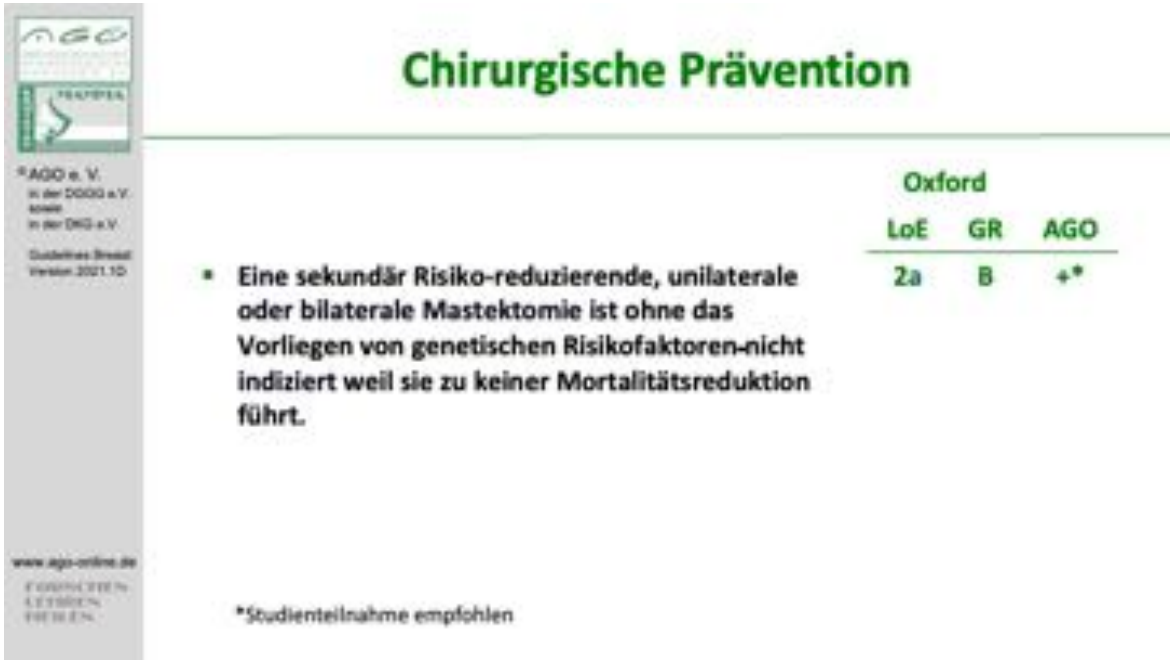



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## Chirurgische Prävention bei gesunden *BRCA1/2* Mutationsträgerinnen

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| • Risiko-reduzierende bilaterale Salpingo-Oophorektomie (RRSO)** | 2a | B | * |
| ◦ reduziert die Eierstockkrebsinzidenz und -mortalität | | | ++* |
| ◦ reduziert die Gesamtmortalität | | | ++* |
| • Risiko-reduzierende bilaterale Mastektomie (RRBM) | | | |
| ◦ reduziert die Brustkrebsinzidenz | 2b | B | +* |
| ◦ reduziert die Mortalität bei *BRCA1* Mutationsträgerinnen*** | 2b | B | +* |

* Studienteilnahme empfohlen
** Die RRSO wird ab ca. 35 Jahren für *BRCA1* und ab ca. 40 Jahren für *BRCA2* Mutationsträgerinnen unter Berücksichtigung des Erkrankungsalters in der Familie und des Familienplanungs-Status empfohlen.
*** Für *BRCA2* Mutationsträgerinnen konnte keine Mortalitätsreduktion gezeigt werden. RRBM Beratung sollte individualisiert durchgeführt werden.


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## Risiko-reduzierende Interventionen bei erkrankten *BRCA1/2* Mutationsträgerinnen

| | Oxford LoE | GR | AGO |
|---|---|---|---|
| • Risikoreduzierende Salpingo-Oophorektomie (RRSO) | 2b | B | +* |
| ◦ reduziert Eierstockkrebsinzidenz und -mortalität | | | |
| ◦ reduziert die Gesamtmortalität (gegensätzliche Ergebnisse bzgl. kontralateraler Brustkrebsinzidenz) | | | |
| • Risikoreduzierende kontralaterale Mastektomie (RRCM)* reduziert kontralaterale Brustkrebsinzidenz und die Mortalität | 2b | B | +* |
| • Tamoxifen (reduziert kontralaterale Brustkrebsinzidenz) | 2b | B | +/-* |
| • Indikationsstellung für RRCM sollte Alter, Ersterkrankungsalter und betroffenes Gen berücksichtigen. | 2a | B | ++* |
| • Risikoreduzierende bilaterale Mastektomie nach Ovarialkarzinom | 4 | C | +/-** |

* Gesamtprognose muss berücksichtigt werden, Studienteilnahme empfohlen
** in Abhängigkeit vom Tumorstadium (FIGO I/II), rezidivfreier Zeit (≥ 5 Jahre), Alter


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## Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a history of unilateral breast cancer: a prospective analysis.

| Analysis[a] | Group | Person years of observation | Deaths | Mortality[b] (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|
| (a) | Surveillance | 3007 | 65 | 21.6 (16.9-27.6) | Ref |
| | CRRM | 1975 | 19 | 9.6 (6.1-15.1) | 0.43 (0.26-0.72)[c]<br>0.49 (0.29-0.82)[d] |
| (b) | Surveillance | 2673 | 56 | 21.0 (16.1-27.2) | Ref. |
| | CRRM | 1837 | 18 | 9.8 (6.2-15.5) | 0.46 (0.27-0.79)[c]<br>0.55 (0.32-0.95)[d] |

[a] Analysis (a) is the main analysis with start of observation being either the date of primary breast cancer (PBC)-diagnosis or the date of DNA diagnosis, whichever came first. In the additional analysis (b), the observation starts either 2 years after PBC or at the date of DNA diagnosis, whichever came first, to exclude patients who presented with distant metastases or died within 2 years after PBC diagnosis (n = 17).
[b] Per 1000 person years of observation.
[c] Univariate analysis.
[d] Multivariate analysis, adjusted for risk-reducing salpingo-oophorectomy. The following variables did not meet the criteria for incorporation in the multivariate Cox model as described in the Methods section, and were therefore not included in the multivariate analysis: type of mutation, year of birth, age at DNA diagnosis, age at PBC diagnosis, T status, presence of positive lymph nodes, differentiation grade, hormone receptor status, HER2 status and treatments administered for PBC.
Abbreviations: CRRM, contralateral risk-reducing mastectomy; HR, Hazard ratio; CI, confidence interval.

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 personalised counselling and improved decision making.

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# Kooperation von Brustzentren (BZ) mit spezialisierten Zentren des DK-FBEK*


* Transsektoraler Vertrag zur integrierten Versorgung nach § 140a SGB V seit 2015