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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Brustkrebsrisiko, Genetik und Prävention



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# Brustkrebsrisiko und Prävention

- **Versionen 2003–2021:**

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- **Version 2022:**

Dall / Ditsch / Gerber / Rhiem



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## 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)*

## Indikation für eine genetische Testung in den Genen *BRCA 1/2* und ggf. weiteren Risikogenen (Teil 1 von 2 – Testung nach Familienanamnese )

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

### Familien mit (je aus einer Familienseite) mindestens\*

- drei an Brustkrebs erkrankten Frauen unabh. vom Alter
- zwei an Brustkrebs erkrankten Frauen, von denen eine im Alter unter 50 Jahren (vor dem 51. Geburtstag) erkrankt ist
- einer an Brust- und einer an Eierstockkrebs erkrankten Frau
- einer an Brust- und Eierstockkrebs erkrankten Frau
- zwei an Eierstockkrebs erkrankten Frauen
- einer an beidseitigem Brustkrebs erkrankten Frau mit einem Ersterkrankungsalter vor dem 51. Geburtstag
- einer an Brustkrebs erkrankten Frau vor dem 36. Geburtstag
- einem an Brustkrebs erkrankten Mann und mindestens einem / einer weiteren Erkrankten an Brust- oder Eierstockkrebs

\* Einschlusskriterien (EK) des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs (DK-FBEK) basierend auf der genetischen Analyse von 21 401 Familien; bei Vorliegen eines dieser EK liegt die Wahrscheinlichkeit für den Nachweis einer *BRCA1/2*-Mutation bei  $\geq 10\%$ . Eine Erfassung möglichst aller Mutationsträgerinnen ist anzustreben. Hierzu sollten geeignete Einschlusskriterien weiter validiert werden und Nutzen und Schaden in Studien erarbeitet werden (inklusive populations-basierter Untersuchungen).

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## Indikation für eine genetische Testung in den Genen **BRCA 1/2 und ggf. weiteren Risikogenen** (Teil 2 von 2 – Testung nach Erkrankung)

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

### ■ Weitere empfohlene Kriterien

- Eigene Erkrankung mit triple-negativem Mammakarzinom mit Erkrankungsalter ≤ 60 Jahre
- Eigene Erkrankung mit Ovarialkarzinom
- Bei therapeutischer Relevanz (z. B. PARPi)

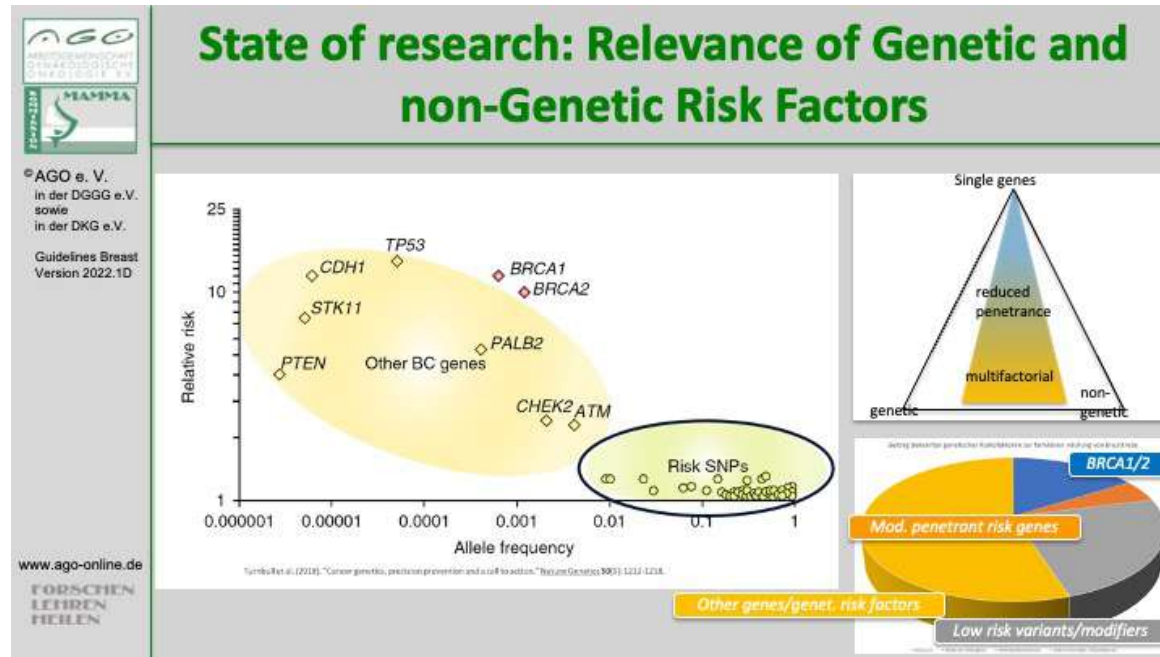
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- 6





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## Pathogene Genvarianten mit moderatem bis hohem Erkrankungsrisiko für Brustkrebs

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### Altersabhängige Erkrankungsrisiken für Brustkrebs

- hoch: *BRCA1, BRCA2, PALB2*
- hoch: *CDH1, PTEN, TP53, STK11*
- moderat erhöht: *ATM, CHEK2*
- moderat erhöht: *BARD1, RAD51C, RAD51D*

### Klinischer Nutzen\* einer genetischen Untersuchung

- *BRCA1, BRCA2*
- *PALB2*
- *CDH1, PTEN, TP53, STK11*
- *ATM, BARD1, CHEK2, RAD51C, RAD51D*

1b	A	++°
3a	B	+°
3b	B	+°
3a	B	+/-°

- \* Effektivität präventiver Maßnahmen sowie konkurrierende Erkrankungsrisiken bei klinischen Entscheidungen berücksichtigen
- \* Eine Teilnahme an prospektiven Studien oder Registerdokumentation wird empfohlen.

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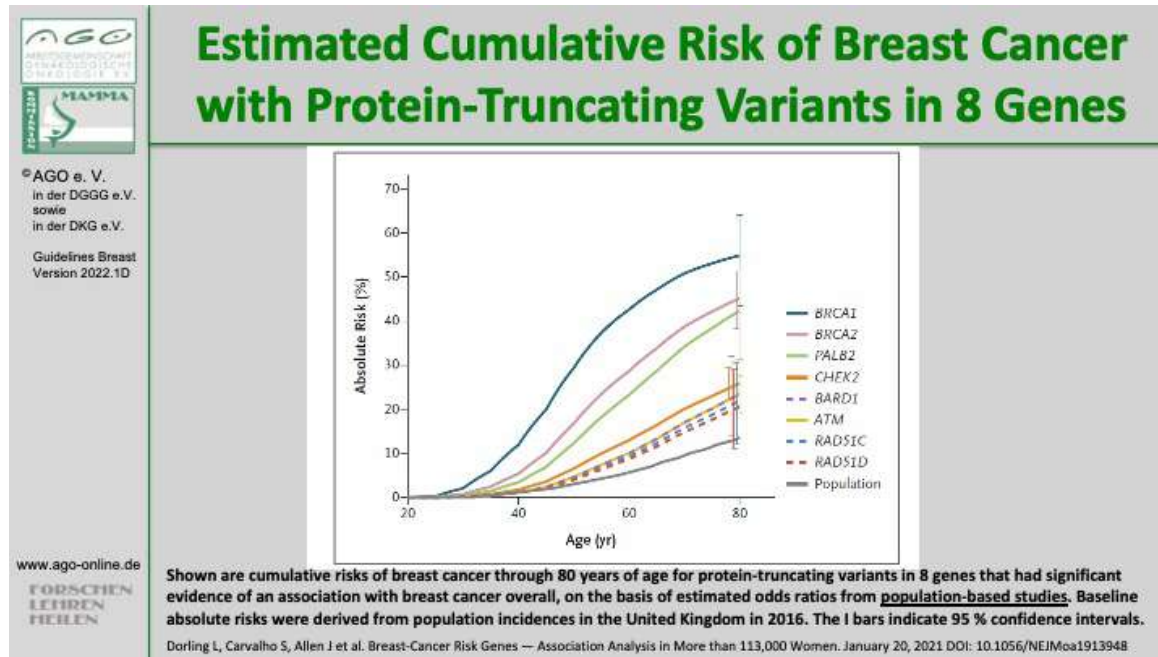


## Breast Cancer Risk Category


Breast cancer risk category

	Near population risk of breast cancer	Moderate risk of breast cancer	High risk of breast cancer
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3 to 8%	Greater than 8%

**NICE (National Institute for Health and Care Excellence) guidance: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer**  
Clinical guideline [CG164] Published: 25 June 2013 Last updated: 20 November 2019



1. Dorling L, Carvalho S, Allen J et al. Breast-Cancer Risk Genes — Association Analysis in More than 113,000 Women. January 20, 2021 DOI: 10.1056/NEJMoa1913948



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## Management of Individuals with Germline Variants in PALB2: A Clinical Practice Resource of the American College of Medical Genetics and Genomics (ACMG)

**Conclusion:**

The recommendations made here have been based on expert opinion using comprehensive literature ascertainment approach, but not systematic review. There is strong evidence that P/LP *PALB2* variants confer a range of breast cancer risks across what is considered moderate to high; consequently, enhanced surveillance and the option of risk-reducing interventions are warranted.

**The risk range for this gene underlies the need to move away from compartmentalizing PALB2 and consider risk to be a continuous variable from high to moderate, influenced by family history, polygenic risk score, and other factors.** The same applies to other breast cancer genes.

**Changing this paradigm will allow us to move to personalized risk estimates by placing the risk from the P/LP variant in the context of other risk factors and develop strategies to translate this information to enhance medical management.** There is reasonable evidence that *PALB2* P/LP variants confer a small to moderately increased risk for ovarian cancer that may warrant risk-reducing interventions, albeit their clinical benefit is not sufficiently proven yet with respect to the efficacy of preventive measures to reduce morbidity and mortality. ...

**Given the many uncertainties, those at risk for *PALB2*-related cancers, and the health professionals who care for them are encouraged to contribute follow-up data to long term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures...**

Tischkowitz M, Balmaña J, Foulkes WD, et al. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1416-1423. doi:10.1038/s41436-021-01151-8

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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 wirken multiplikativ, so dass die Analyse multipler Genregionen (Polygener Risiko Score, PRS) zukünftig von klinischer Relevanz ist.


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	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	+

\* Derzeit sollten moderat penetrante Gene und Niedrigrisikovarianten nur im Rahmen von prospektiven Kohortenstudien, wie der des Deutschen Konsortiums, untersucht werden, um den klinischen Nutzen zu bewerten.

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	<h2 style="text-align: center;">Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer</h2>		
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HELEN</p>	Syndrome	Gene	Risk for malignancy
	Li Fraumeni	<i>TP53</i>	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
	Cowden	<i>PTEN</i>	Breast, endometrium, thyroid, colorectal, kidney, melanoma
	Hereditary diffuse gastric cancer syndrome	<i>CDH1</i>	Hereditary diffuse gastric cancer, lobular invasive breast cancer
	Peutz-Jeghers Syndrome	<i>STK11/LKB1</i>	Colorectal, small intestine, stomach, pancreas, testicle, endometrium
	Lynch	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	Endometrium, ovary, colorectal, small intestine, stomach, hepato biliary, pancreas, kidney, urogenital, CNS
	Ataxia telangiectasia (AT-Syndrom)	<i>ATM</i>	Breast cancer, leukemia, stomach, melanoma, sarcoma
	Fanconi Anämie	<i>BRCA2, BRIP1, RAD51C, PALB2</i>	AML, MDS, SCC, medulloblastoma, nephroblastoma, breast, pancreas, ovary

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

ATM	BARD1	BRCA1	BRCA2	BRIP1	CDH1	CHEK2	PALB2
RAD51C	RAD51D	TP53	EPCAM	MLH1	MSH2	MSH6	PMS2
PTEN	SMARCA4	STK11	APC	FAM175A	FANCC	FANCM	HOXB13
MEN1	MRE11A	MUTYH	NBN	NF1	POLD1	POLE	RAD50
RECQL	XRCC2						

Selection of genes:	11 BC (breast cancer) / OC (ovarian cancer) '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

TruRisk® V3.1.1. \* BC = breast cancer, OC = ovarian cancer



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## Distinct Genetically Subtypes Defines Distinct Tumor Entities

Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer risk reducing clinical procedures the following facts and data should be addressed:

- Age related 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 known before performing preventive clinical measures**

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## VUS: Problems and Questions

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- „A Variant of Unknown Significance (VUS IARC class 3) is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are extremely rare ( $\leq 3$  variants in  $> 80\%$  of families)
- Classification of sequence variants should be performed according to the IARC classification system
- Frequency of VUS (IARC class 3) increases with numbers of tested genes
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet
- In silico prediction tools (PolyPhen2, SIFT) are not adequate or sufficient for clinical decision making
- Additional analyses are required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurrence analysis, large case / control studies

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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	Description	Probability of being pathogenic
5	Definitely 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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## 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.
- Data should be pooled in large study groups (e.g. ENIGMA)

▪ Most class 3 variants can be downgraded to clinically irrelevant classes 1 or 2 by these analyses. Few are upgraded to the clinically relevant classes 4 or 5. Any re-evaluation of the IARC class should be communicated to the tested persons (see for example the concept of supervision in centres of the German Consortium / GC-HBOC).

1. Spurdle AB, Healey S, Devoreau A, et al. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Human mutation. 2012;33(1):2-7.

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## 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, e.g. "Präventive Gendiagnostik - Hoffnung und Fluch der Genanalyse", Heft 26 des Deutschen Ärzteblattes vom 29.06.2012; Dtsch. Ärztebl. 2012; 109(26): A-1371 / B-1183 / C-1163)

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2. "Präventive Gendiagnostik - Hoffnung und Fluch der Genanalyse", Heft 26 des Deutschen Ärzteblattes vom 29.06.2012; Dtsch. Ärztebl. 2012; 109(26): A-1371 / B-1183 / C-1163),



## Nicht-direktive Beratung vor der Durchführung präventiver Maßnahmen

### AGO ++

- Berücksichtigung des:
  - Gendiagnostikgesetzes
  - Medizinproduktegesetzes (z. B. Risikokalkulation)
- Anwendung von Software zur Risikokalkulation erfordert ein professionelles Training und Erfahrung
- Kommunikation von:
  - absoluten Erkrankungsrisiken in einem überschaubaren Zeitraum
  - Risiken und Nutzen der intensivierten Früherkennung
  - Risiken und Nutzen präventiver Maßnahmen
  - konkurrierenden Risiken, z. B. Rezidiv- / Metastasierungsrisiko im Vergleich zum Zweitkarzinomrisiko bei bereits erkrankten Frauen
- Angemessene Bedenkzeit vor prophylaktischen Operationen

1. Phi XA, Houssami N, Hooning MJ et al., Accuracy of screening women at familial risk of breast cancer without a known gene mutation.. Eur J of Cancer 2017;85:31-38




## Multimodales intensiviertes Früherkennungsprogramm\*

		Oxford		
		LoE	GR	AGO
■ Früherkennungsprogramm am Beispiel nicht an BC-erkrankter <i>BRCA1/2</i> -Mutationsträgerinnen				
■ 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 metastasenfren Überlebens		2b	B	+
■ Überlebende nach kindlichen Tumoren mit therapeutischer Radiatio der Brustwand (z. B. M. Hodgkin)		2a	B	++
* Das multimodale Früherkennungsprogramm sollte für Frauen mit Mutationsnachweis in Risikogenen und bei erhöhtem rechnerischen Risiko ohne Mutationsnachweis im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen				

1. E-Learning DKG/FBREC, 2022
2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.4, 2021, AWMF Registernummer: 032-045OL, <http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/> (abgerufen am: 24.1.2022) 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
3. Ellen Warner: Screening BRCA1 and BRCA2 Mutation Carriers for Breast Cancer. Review. *Cancers* 2018, 10, 477; doi:10.3390/cancers10120477
4. Evans, D.G.; Kesavan, N.; Lim, Y. et al.: MRI breast screening in high-risk women: Cancer detection and survival analysis. *Breast Cancer Res. Treat.* 2014, 145: 663–672
5. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet.* 2005;365(9473):1769-78.
6. Meindl A, Ditsch N, Kast K, et al. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. *Dtsch Arztebl Int.* 2011;108(19):323-30.
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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 predictive 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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## Multimodales Nachsorgeprogramm für Frauen mit *BRCA1/2* Mutation nach primärer einseitiger Mammakarzinom-Erkrankung

		Oxford		
		LoE	GR	AGO
■ Multimodales intensiviertes Nachsorgeprogramm <sup>o</sup>				
■ Zum Nachweis früher Tumorstadien		2a	B	++
■ Ärztliche Tastuntersuchung	≥ 25 Jahre*	halbjährlich		
■ Ultraschall	≥ 25 Jahre*	halbjährlich		
■ Mammographie	≥ 40 Jahre*	1–2 jährlich		
■ Kernspintomographie	≥ 25 Jahre*	jährlich		
■ Zur Mortalitätsreduktion		3a	C	+/-*

\* bzw. ab Alter bei Erstdiagnose  
 \* die Nachsorge sollte im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen.

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.4, 2021, AWMF Registernummer: 032-045OL, <http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/> (abgerufen am: 24.1.2022) 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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## Früherkennungsprogramm für Männer mit *BRCA1/2* Mutationen\*

Das Lebenszeitrisiko für Brustkrebs liegt in der männlichen Allgemeinbevölkerung bei 0.1 %.  
*BRCA1* Mutationsträger haben ein Erkrankungsrisiko für Brustkrebs von 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.

Aktuell kein spezifisches Früherkennungsprogramm →  
 Krebsfrüherkennungsuntersuchung im Rahmen der Regelversorgung

- Für Brustkrebs:  
Selbstuntersuchung
- Für Prostatakarzinom:  
vgl. Empfehlung zum Prostatakarzinom S3-Leitlinie


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

Oxford		
LoE	GR	AGO
5	D	+
5	D	+

- Albert US, Schreer I; Arbeitsgruppe der Stufe-3-Leitlinie Mammakarzinom. S3 guideline breast cancer: update on early detection, and mammography screening. Radiologe. 2019 Jan;59(1):13-18. doi: 10.1007/s00117-018-0473-6.
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16. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Prostatakarzinom, Kurzversion 6.0, Mai 2021, AWMF Registernummer: 043/022OL, <https://www.leitlinienprogrammonkologie.de/leitlinien/prostatakarzinom/> (abgerufen am: 10.01.2022)





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LEHREN  
HEILEN

## 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 (9–18 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**

1. Darrington DL, Vose JM. Appropriate surveillance for late complications in patients in remission from Hodgkin lymphoma. *Curr Hematol Malig Rep.* 2012;7(3):200-7.
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## Chirurgische Prävention

- Eine sekundär Risiko-reduzierende, unilaterale oder bilaterale Mastektomie ist ohne das Vorliegen von genetischen Risikofaktoren nicht indiziert weil sie zu keiner Mortalitätsreduktion führt.

Oxford		
LoE	GR	AGO
2a	B	+

- Studienteilnahme empfohlen

1. Kurian AW, Lichtensztajn DY, Keegan TH, et al. Use of and mortality after bilateral mastectomy compared with other surgical treatments for breast cancer in California, 1998-2011. JAMA. 2014;312(9):902-14.
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## Chirurgische Prävention bei gesunden **BRCA1/2 Mutationsträgerinnen**

	Oxford		
	LoE	GR	AGO
<b>■ Risiko-reduzierende bilaterale Salpingo-Oophorektomie (RRSO)**</b>	<b>2a</b>	<b>B</b>	
<ul style="list-style-type: none"> <li>reduziert die Eierstockkrebsinzidenz und -mortalität</li> </ul>			++*
<ul style="list-style-type: none"> <li>reduziert die Gesamt mortalität</li> </ul>			++*
<b>■ Risiko-reduzierende bilaterale Mastektomie (RRBM)</b>			
<ul style="list-style-type: none"> <li>reduziert die Brustkrebsinzidenz</li> </ul>	<b>2b</b>	<b>B</b>	+*
<ul style="list-style-type: none"> <li>reduziert die Mortalität bei <i>BRCA1</i> Mutationsträgerinnen***</li> </ul>	<b>2b</b>	<b>B</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.

- Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Lancet Oncol.* 2006;7(3):223-9.
- Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA.* 2010;304(9):967-75.
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- Heemskerk-Gerritsen BAM, Jager A, Koppert LB et al: Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat* 2019, 177(3):723-733.
- Hoogerbrugge N, Bult P, Bonenkamp JJ, et al. Numerous high-risk epithelial lesions in familial breast cancer. *Eur J Cancer.* 2006;42(15):2492-8.
- Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med.* 2002;346(21):1609-15.
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12. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002;346(21):1616-22.
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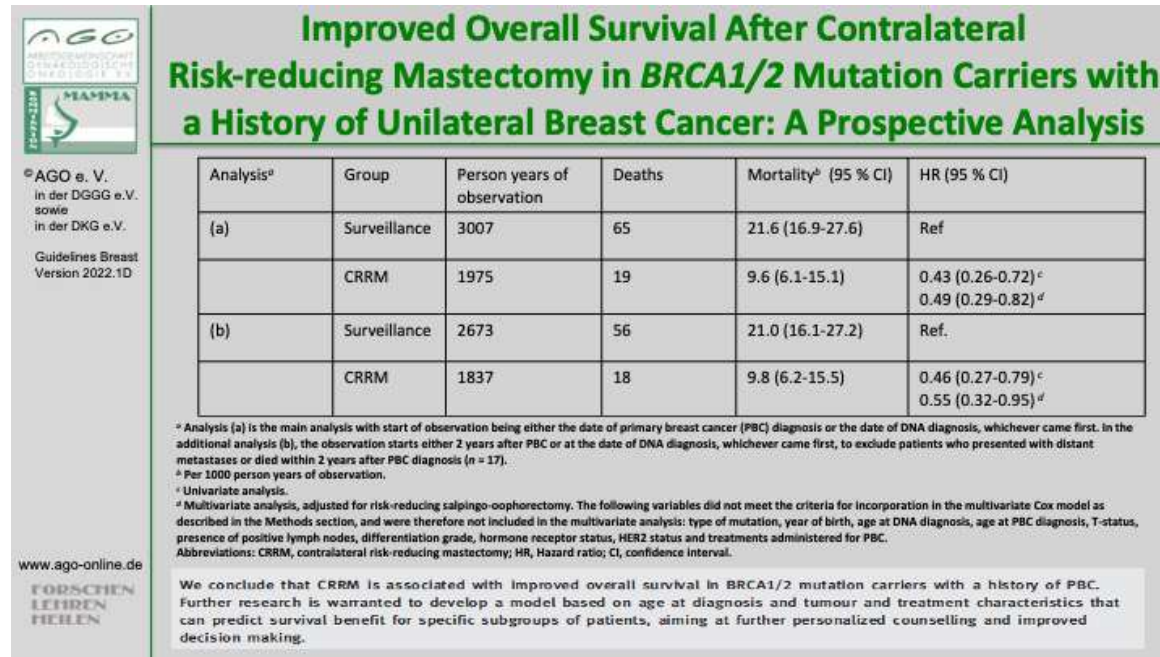
## Risiko-reduzierende Interventionen bei erkrankten **BRCA1/2** Mutationsträgerinnen

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

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

- Domchek SM, Jhaveri K, Patil S et al. Risk of metachronous breast cancer after BRCA mutation associated ovarian cancer. Cancer 2013;119:1344-8.
- Evans DG, Ingham SL, Baildam A, et al. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2013;140(1):135-42.
- Fong A, Cass I, John C, Gillen J, Moore KM, Gangi A, Walsh C, Li AJ, Rimel BJ, Karlan BY, Amersi F. Breast Cancer Surveillance Following Ovarian Cancer in BRCA Mutation Carriers. Am Surg. 2020 Oct;86(10):1243-1247. doi: 10.1177/0003134820964208. Epub 2020 Oct 26. PMID: 33106023.
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## Therapie des Keimbahnmutations-assoziierten Mammakarzinoms

Es liegen prospektive Kohortenstudien mit begrenzter Nachbeobachtungszeit vor

- Brusterhaltende Operation: Adäquate lokale Tumorkontrolle (~ 10 Jahre Follow-up)
- Systemische Therapie nach den allgemeinen Standards
- gBRCA Mutationsstatus ist ein prädiktiver Faktor für das Ansprechen auf Chemotherapie bei TNBC
- Carboplatin (vs. Docetaxel) beim metast. MaCa

PARP-Inhibitor (Her2-negative Karzinome):

- EBC : Olaparib (bei gBRCA1/2-Mutation)\*
- MBC:
  - gBRCA1/2-Mutation
    - Olaparib
    - Talazoparib
  - Somatische BRCA1/2-Mutation (Keimbahntestung gBRCA ist Standard)
    - Olaparib
  - PALB2-Keimbahnmutation
    - Olaparib

Oxford

LoE	GR	AGO
2a	B	+
3a	B	+
2b	B	+
2b	B	+
1b	B	+
1b	A	++
1b	A	++
2b	B	+/-
2b	B	+/-

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; \* Einsatz gemäß Studieneinschlusskriterien und Zulassung

### BCS bei BRCA 1/2 Mutationsträgern

1. Co M, Liu T, Leung J et al. Breast Conserving Surgery for BRCA Mutation Carriers-A Systematic Review. Clin Breast Cancer. 2020 Jun;20(3):e244-e250. doi: 10.1016/j.clbc.2019.07.014. Epub 2019 Aug 22. PMID: 32144082.
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7. Ye F, Huang L, Lang G, et al. Cancer Med. 2020 Mar;9(5):1903-1910. doi: 10.1002/cam4.2836. Epub 2020 Jan 7. PMID: 31912664; PMCID: PMC7050073.
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1. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018 Feb;19(2):169-180. doi: 10.1016/S1470-2045(17)30891-4. Epub 2018 Jan 11. PMID: 29337092; PMCID: PMC5805863.
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4. Loibl S, Weber KE, Timms KM et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018 Dec 1;29(12):2341-2347. doi: 10.1093/annonc/mdy460. PMID: 30335131.
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### **Carboplatin:**

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5. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation [published correction appears in *N Engl J Med*. 2017 Oct 26;377(17 ):1700]. *N Engl J Med*. 2017;377(6):523–533.
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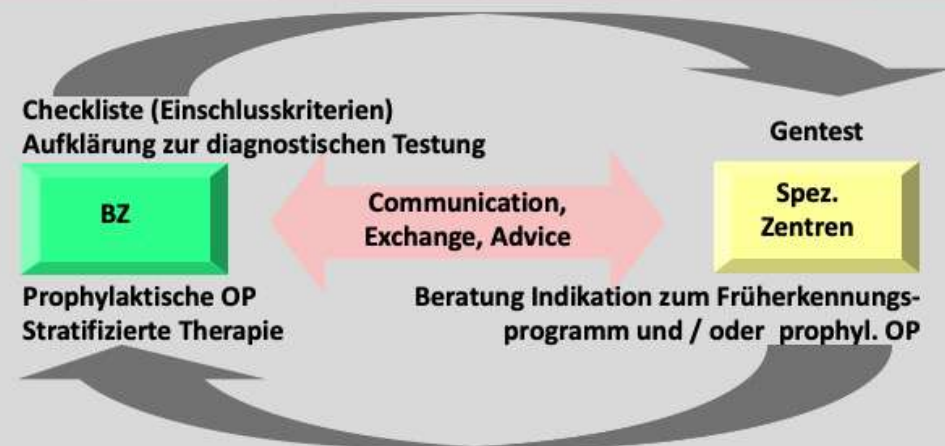
## Medikamentöse Prävention für Frauen mit erhöhtem Risiko

	Oxford		
	LoE	GR	AGO
■ Tamoxifen für Frauen > 35 Jahre Reduktion des invasiven MaCa, DCIS und LN	1a	A	+*
■ Raloxifen für postmenopausale Frauen Reduktion des invasiven MaCa	1b	A	+*
■ Aromatasehemmer für postmenopausale Frauen	1b	A	+**

- \* Risiko definiert wie in der NSABP P1-Studie (1.66 % in 5 Jahren) oder nach #Tyrer-Cuzick-Modell (IBIS-II).
  - \*\* Signifikante Risikoreduktion unter Anastrozol für Ovarial- und Endometriumkarzinome, sowie Haut-, Kolorektal-, Schilddrüsen-, Harnwegskarzinome und hämatologische Tumoren
- Chemopräventive Therapien sollten nur nach individueller und umfassender Beratung angeboten werden. Der Nutzen hängt vom Risikostatus, Alter und vorbestehenden Risiken für Nebenwirkungen ab.

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



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