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in der DGO e. V.
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Guidelines Breast
Version 2021.10

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FÜR DEN
LEBEN
FÜR DEN

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Brustkrebsrisiko und Prävention



AGO e. V.
in der DGGG e. V.
in der DKG e. V.
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Brustkrebsrisiko und Prävention

- **Versionen 2003–2020:**
Schmutzler mit Albert / Bischoff / Blohmer / Ditsch / Fasching / Fehm / Kiehle / Maass / Müller-Schimpfle / Mundhenke / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen
- **Version 2021:**
Park-Simon / Witzel



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FÜR DEN FORTSCHRITT
DER GYNEKOLOGIE
UND GEBURTSHILFE

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

* Einzelkriterien (EK) des Deutschen Konsortiums: Familiärer Brust- und Eierstockkrebs (DK/FBOC) 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 Einzelkriterien 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: ++

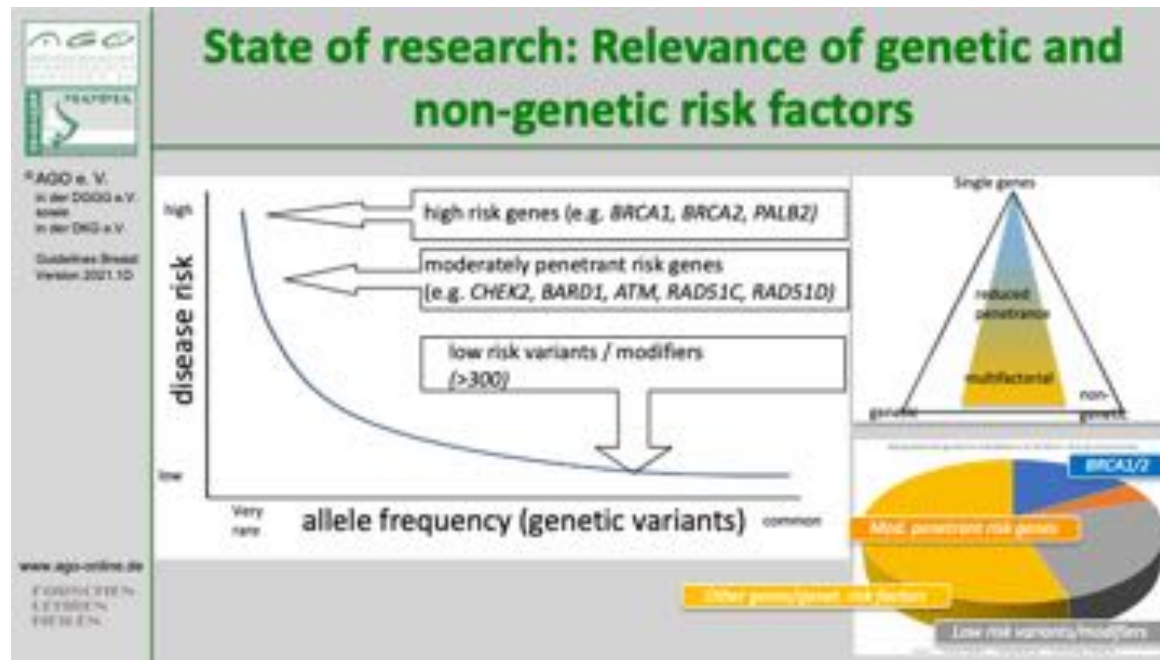
▪ Weitere empfohlene Kriterien

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

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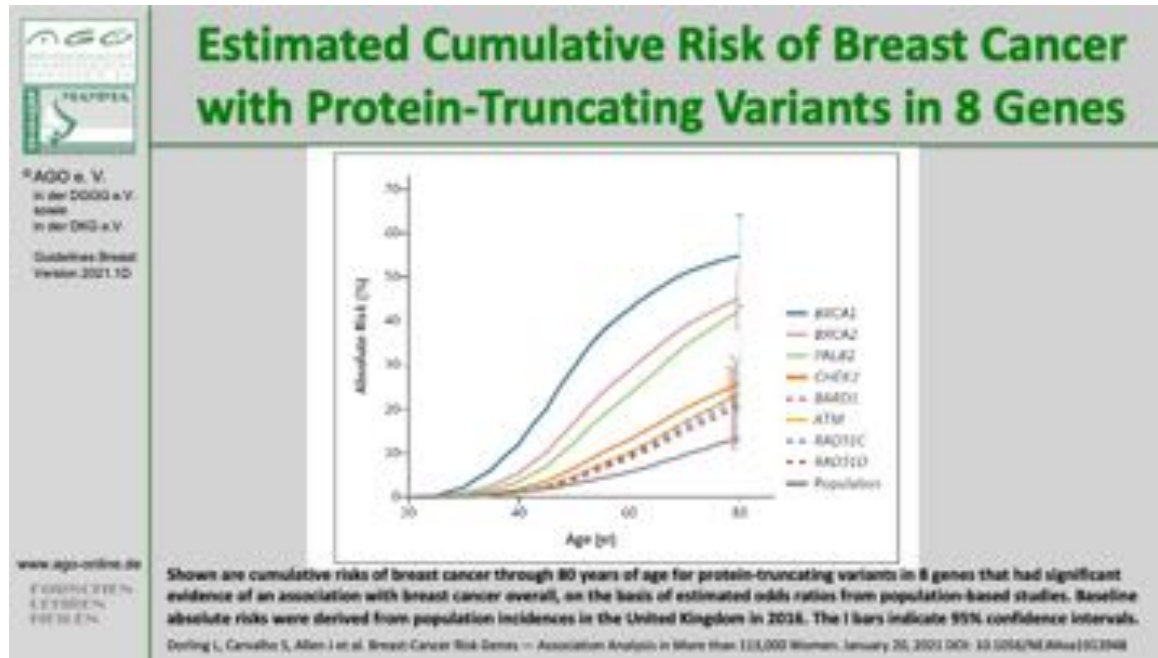
Gene mit moderatem bis hohem Erkrankungsrisiko für Brustkrebs

	Oxford		
	LoE	GR	AGO
Kumulatives Erkrankungsrisiko für Brustkrebs			
▪ hoch: <i>BRCA1, BRCA2, PALB2</i>	1b	A	++
▪ moderat erhöht: <i>ATM, CHEK2, BARD1, RAD51C, RAD51D</i>	1b	B	+
Klinischer Nutzen* einer genetischen Untersuchung			
▪ <i>BRCA1, BRCA2</i>	1b	A	++*
▪ <i>PALB2</i>	3a	B	+*
▪ <i>ATM, BARD1, CHEK2, RAD51C, RAD51D</i>	3a	B	+/-*
* Effektivität präventiver Maßnahmen			
* Eine Teilnahme an prospektiven Studien oder Registern wird dringend empfohlen.			

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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	S	D	+

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

Syndrom	Gene	Risk for malignancy
Li Fraumeni	TP53	Breast, endometrium, colorectal, small intestine, stomach, hepato biliary, skin, osteosarcoma, soft tissue sarcoma, urogenital, CNS, ACC, leukemia, lymphoma, lung
Cowden	PTEN	Breast, endometrium, thyroid, colorectal, kidney, melanoma
Hereditary diffuse gastric cancer syndrome	CDH1	Hereditary diffuse gastric cancer, lobular invasive breast cancer
Peutz-Jeghers Syndrome	JN1/ LKB1	Colorectal, small intestine, stomach, pancreas, testicle, endometrium
Lynch	MLH1, MSH2, MSH6, PMS2, EPCAM	Endometrium, ovary, colorectal, small intestine, stomach, hepato biliary, pancreas, kidney, urogenital, CNS
Alexia telangiectasia (AT Syndrome)	ATM	Breast cancer, leukemia, stomach, melanoma, sarcoma
Fanconi Anämie	BRCA2, BRIP1, RAD51C, PALB2	AML, MDS, SCC, medulloblastoma, neuroblastoma, breast, pancreas, ovary

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 FÜR HEREDITÄRE UND FAMILIÄRE
 KREBLERKENDEGENE
 VERBÄNDE

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

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ATM	BRCA1	BRCA2	BRCA2	BRIP1	CDH1	CHD1	HR23
RAD51	RAD51B	TP53	EPCAM	MMI1	MSH2	MSH6	PMS2
PTEN	STK11	APC	FAM175A	FANCC	FANCM	HORHA1	MEN1
MRE11A	MUTYH	NBN	NF1	POLD1	POLE	RAD50	RECQL1
SMARCA4	KRCC2						

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, 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

- „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 (≤ 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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UND MOLEKULARE MEDIZIN


1. Ernst C, Hahnen E, Engel C, et al. Performance of in silico prediction tools for the classification of rare BRCA1/2 missense variants in clinical diagnostics. *BMC Med Genomics*. 2018;11(1):35. Published 2018 Mar 27. doi:10.1186/s12920-018-0353-y
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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	0,85 – 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.



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).

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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 valide 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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Nicht-direktive Beratung vor der Durchführung präventiver Maßnahmen

- | | Oxford | | |
|---|--------|----|-----|
| | LoE | GR | AGO |
| • Berücksichtigung des Gendiagnostikgesetzes | 5 | D | ++ |
| • Berücksichtigung des Medizinproduktegesetzes (e.g. Risikokalkulation) | | | |
| • Anwendung von Software zur Risikokalkulation erfordert ein professionelles Training und Erfahrung | | | |
| • Kommunikation absoluter Erkrankungsrisiken in einem überschaubaren Zeitraum | | | |
| • Kommunikation von Risiko und Nutzen der intensivierten Früherkennung | | | |
| • Kommunikation von Risiko und Nutzen präventiver Maßnahmen | | | |
| • Kommunikation konkurrierender Risiken, e.g. Rezidiv- und 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 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 metastasenfremien Überlebens	2b	B	+
▪	Überlebende nach kindlichen Tumoren mit therapeutischer Radiatio der Brustwand (z.B. M. Hodgkin)	2a	B	++
* Das multimodale intensiviertes Früherkennungsprogramm sollte im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen.				

1. 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.
2. 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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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.



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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1. Bick U, Engel C, Krug B et al.: German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC). 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 May;175(1):217-228. doi: 10.1007/s10549-019-05152-9. Epub 2019 Feb 6. PMID: 30725383.



Multimodales Nachsorgeprogramm für das kontralaterale Mammakarzinom bei Frauen mit *BRCA1/2* Mutation nach primärer Mammakarzinom-Erkrankung*

		Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Multimodales intensiviertes lebenslanges Früherkennungsprogramm 				
<ul style="list-style-type: none"> ▪ Zum Nachweis früher Tumorstadien 		2a	B	++
<ul style="list-style-type: none"> ▪ Ärztliche Tastuntersuchung 	> = 25 Jahre			halbjährlich
<ul style="list-style-type: none"> ▪ Ultraschall 	> = 25 Jahre			halbjährlich
<ul style="list-style-type: none"> ▪ Mammographie 	> = 40 Jahre			1-2 jährlich
<ul style="list-style-type: none"> ▪ Kernspintomographie 	> = 25 Jahre			jährlich
<ul style="list-style-type: none"> ▪ Zur Mortalitätsreduktion 		3a	C	+/-*
<ul style="list-style-type: none"> ▪ Die Nachsorge sollte im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen. 				

1. 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.
2. Bick U, Engel C, Krug B et al.: German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC). 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 May;175(1):217-228. doi: 10.1007/s10549-019-05152-9. Epub 2019 Feb 6. PMID: 30725383.
3. Carbine NE, Lostumbo L, Wallace J et al.: Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev. 2018 Apr 5;4:CD002748. Review
4. 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.
5. 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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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.

Aktuell kein spezifisches Früherkennungsprogramm

- Für Brustkrebs:
Selbstuntersuchung und Watchful waiting*


- 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
Für Brustkrebs: Selbstuntersuchung und Watchful waiting*	S	D	+
Für Prostatakarzinom: vgl. Empfehlung zum Prostatakarzinom S3-Leitlinie	S	D	+

1. 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.
2. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in *BRCA2* families: estimates for sites other than breast and ovary. *J Med Genet*. 2005;42(9):711-9.
3. Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in *BRCA1* and *BRCA2* mutation carriers: results from the initial screening round of the IMPACT study. *Eur Urol*. 2014;66(3):489-99.
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7. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline *BRCA1* mutations increase prostate cancer risk. *Br J Cancer*. 2012;106(10):1697-701.
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10. S3-Leitlinie Prostatakarzinom (Version 5.1, 2019)



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GBO in der DGO e. V.
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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.
2. Ibrahim EM, Abouelkhair KM, Kazkaz GA, et al. Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. *BMC Cancer.* 2012;12:197.
3. 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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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.
2. 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, DOI: [http://dx.doi.org/10.1016/S1470-2045\(17\)30891-4](http://dx.doi.org/10.1016/S1470-2045(17)30891-4).



Chirurgische Prävention bei gesunden BRCA1/2 Mutationsträgerinnen

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

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

1. 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.
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4. 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.
5. 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.
6. 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.
7. Kotsopoulos J, Huzarski T, Gronwald J, et al: Hereditary Breast Cancer Clinical Study Group. Bilateral Oophorectomy and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. *J Natl Cancer Inst.* 2016 Sep 6;109(1). doi: 10.1093/jnci/djw177. Print 2017 Jan.
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2010(11):CD002748.

9. Mavaddat N, Antoniou AC, Mooij TM et al: Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res* 2020, 22(1):8.
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11. Rebbeck TR, Friebel T, Lynch HAT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol*. 2004;22(6):1055-62.
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
<ul style="list-style-type: none"> • Risikoreduzierende Salpingo-Oophorektomie (RSO) <ul style="list-style-type: none"> • reduziert Eierstockkrebsinzidenz und -mortalität • reduziert die Gesamtmortalität (gegensätzliche Ergebnisse bzgl. kontralateraler Brustkrebsinzidenz) 	2b	B	++*
<ul style="list-style-type: none"> • Risikoreduzierende kontralaterale Mastektomie (RRCM)* reduziert kontralaterale Brustkrebsinzidenz und die Mortalität 	2b	B	++*
<ul style="list-style-type: none"> • Tamoxifen (reduziert kontralaterale Brustkrebsinzidenz) 	2b	B	+/-*
<ul style="list-style-type: none"> • Indikationsstellung für RRCM sollte Alter, Ersterkrankungsalter und betroffenes Gen berücksichtigen. 	2a	B	++*
<ul style="list-style-type: none"> • 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

1. Domchek SM, Jhaveri K, Patil S et al. Risk of metachronous breast cancer after BRCA mutation associated ovarian cancer. *Cancer* 2013;119:1344-8.
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15. Ye-Lei Xiao, Kang Wang, Qiang Liu, et al.: Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review. *Clinical Breast Cancer*, Vol. 19, No. 1, e48-65

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) ^c
(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) ^d 0.49 (0.29-0.82) ^e
(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) ^d 0.55 (0.32-0.95) ^e

^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 CRRM diagnosis, whichever came first. In the additional analysis (b), the observation starts either 2 years after PBC or at the date of CRRM 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 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 CRRM 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 personalized counselling and improved decision making.

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1. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, et al. Improved overall survival after contralateral risk-reducing mastectomy in *BRCA1/2* mutation carriers with a history of unilateral breast cancer: a prospective analysis. *Int J Cancer*. 2015;136(3):668-77.



Therapie des Keimbahnmutations-assoziierten Mammakarzinoms

Es liegen prospektive Kohortenstudien mit begrenzter Nachbeobachtungszeit vor	Oxford		
	LoE	GR	AGO
• Brusterhaltende Operation: Adäquate lokale Tumorkontrolle (~10 Jahre Follow-up)	2a	B	+
• Systemische Therapie nach den allgemeinen Standards	3a	B	+
• gBRCA Mutationsstatus ist ein prädiktiver Faktor für das Ansprechen auf Chemotherapie bei TNBC	2b	B	+
• Carboplatin (vs. Docetaxel) bei metastasiertem Mammakarzinom	2b	B	+
• PARP-Inhibitor bei metastasiertem Mammakarzinom			
• BRCA1/2	1b	B	+
• PALB2	2b	B	+/-

Breast-conserving therapy in BRCA 1/2 mutation carriers

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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Medikamentöse Prävention für Frauen mit erhöhtem Risiko

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Tamoxifen für Frauen > 35 Jahre Reduktion des invasiven MaCa, DCIS und LN 	1a	A	+*
<ul style="list-style-type: none"> Raloxifen für postmenopausale Frauen Reduktion des invasiven MaCa 	1b	A	+*
<ul style="list-style-type: none"> Aromatasehemmer für postmenopausale Frauen 	1b	A	+*

* 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.
 * Risiko definiert wie in der NSABP P1-Studie (1,66% in 5 Jahren) oder nach #Fyrer-Cuzick-Modell (IBIS-II).

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Risikoreduktion für das ipsi- und kontralaterale Mammakarzinom

Frauen nach Brustkrebs haben ein erhöhtes Risiko für ein kontralaterales Zweitkarzinom

- Tamoxifen*
- Aromatasehemmer*
- GnRHa + Tamoxifen*

Oxford		
LoE	GR	AGO
1a	A	+
1a	A	+
1b	B	+

* Nur für das HR positive sporadische MaCa belegt

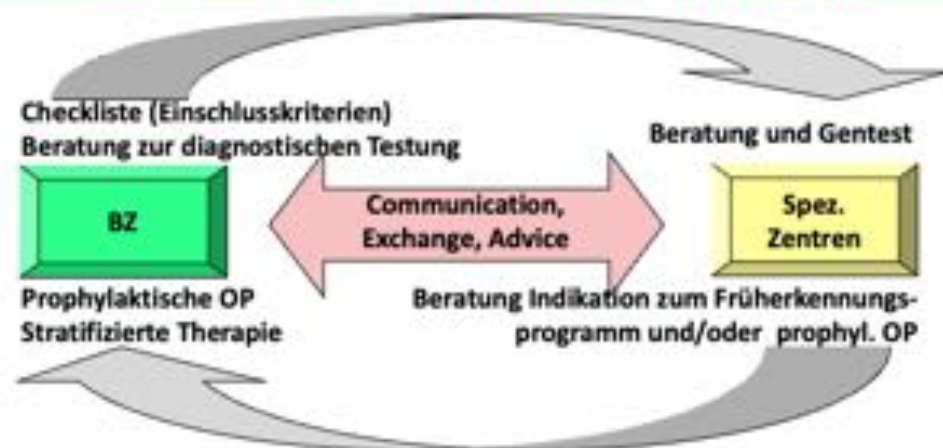
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BRUSTKREISLAUFKREISLÄUF

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



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