Guidelines Breast
Version 2023.1D

Brustkrebsrisiko, Genetik und Prävention

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Brustkrebsrisiko und Prävention

- **Versionen 2003–2022:**
  Albert / Bischoff / Blohmer / Dall / Ditsch / Fasching / Fehm / Gerber / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Stickeler / Thomssen / Witzel

- **Version 2023:**
  Schütz / Thomssen

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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)

1. Beitsch PD, Whitworth PW, Hughes K. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? Journal of Clinical Oncology 2019 37:6, 453-460
2. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-11.
3. Meindl A, German Consortium for Hereditary B, Ovarian C. Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. Int J Cancer. 2002;97(4):472-80.
4. Kast K, Rhiem K, Wappenschmidt B, et al., Prevalence of BRCA1/2 germline mutations in 21.401 families with breast and ovarian cancer. J Med Genet 2016;53:465-71.
5. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review.Cancers (Basel). 2018 Nov 5;10(11).
6. Rolfes M, Borde J, Möllenhoff K et al, Prevalence of Cancer Predisposition Germline Variants in Male Breast Cancer Patients: Results of the German Consortium for Hereditary Breast and Ovarian Cancer, Cancers, 2022, 14(13): 3292

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Indikation für eine genetische Testung in den Genen *BRCA 1/2* und ggf. weiteren Risikogenen

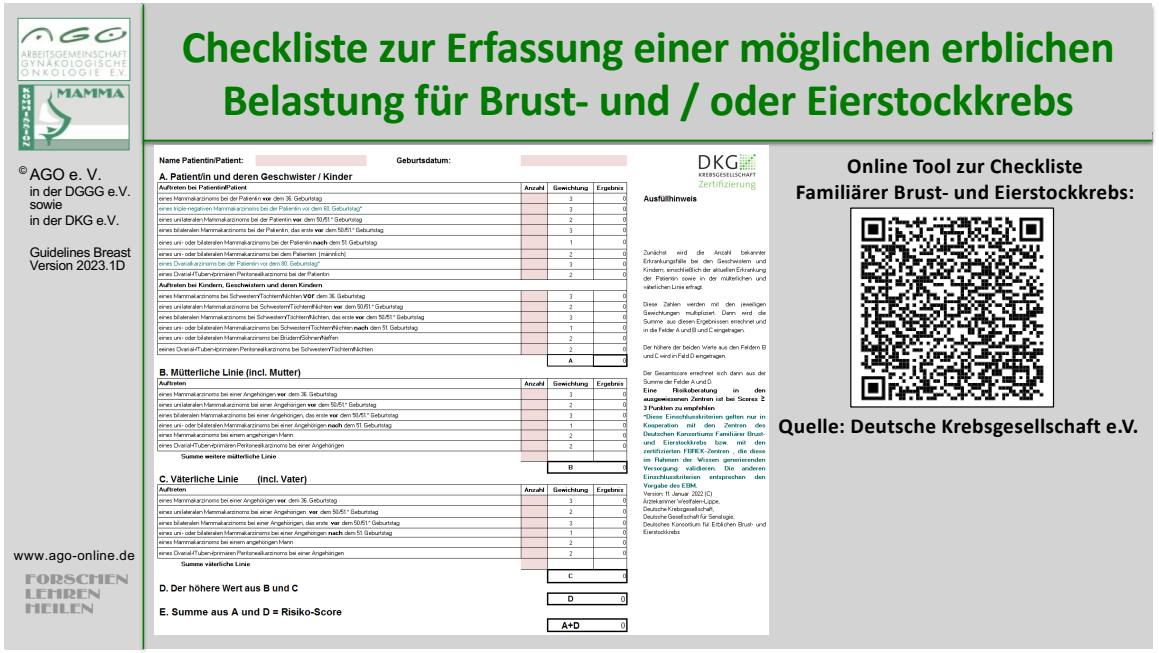
(Teil 2 von 2 – Testung nach Erkrankung)

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

- **Weitere empfohlene Kriterien**
  - **Eigene Erkrankung mit triplenegativem Brustkrebs mit Erkrankungsalter vor dem 60. Geburtstag**
  - **Eigene Erkrankung mit Eierstockkrebs vor dem 80. Geburtstag**
  - **Bei therapeutischer Relevanz (z. B. PARPi; nur BRCA1 und BRCA2; ggf. PALB2)**

1. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-11.
2. Engel C, Rhiem K, Hahnen E, et al. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. *BMC Cancer*. 2018;18(1):265. Published 2018 Mar 7. doi:10.1186/s12885-018-4029-y
3. Hahnen E, Lederer B, Hauke J et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol. 2017 Oct 1;3(10):1378-1385. doi: 10.1001/jamaoncol.2017.1007. PMID: 28715532; PMCID: PMC5710508.
4. Harter P, Hauke J, Heitz F, et al. Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR1). PLoS One 2017;12:e0186043.
5. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Nov;31(11):1526-1535. doi: 10.1016/j.annonc.2020.08.2098. Epub 2020 Aug 20. PMID: 32828825.
6. Manchanda R, Gaba F. Population Based Testing for Primary Prevention: A Systematic Review. Cancers (Basel). 2018 Nov 5;10(11).
7. Meindl A, German Consortium for Hereditary B, Ovarian C. Comprehensive analysis of 989 patients with breast or ovarian cancer

provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. Int J Cancer. 2002;97(4):472-80.
8. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation N Engl J Med 2017;377:523-533



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

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Name Patientin/Patient: **Geburtsdatum:**

DKG KREBSGESELLSCHAFT Zertifizierung

A. Patientin und deren Geschwister / Kinder

Auftreten bei Patientin/Patient	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei der Patientin **vor** dem 36. Geburtstag		3	0
eines triple-negativen Mammakarzinoms bei der Patientin vor dem 60. Geburtstag*		3	0
eines unilateralen Mammakarzinoms bei der Patientin **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei der Patientin, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei der Patientin **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei dem Patienten (männlich)		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei der Patientin vor dem 80. Geburtstag*		3	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei der Patientin		2	0
Auftreten bei Kindern, Geschwistern und deren Kindern			
eines Mammakarzinoms bei Schwestern/Töchtern/Nichten **VOR** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei Brüdern/Söhnen/Neffen		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei Schwestern/Töchtern/Nichten		2	0
		A	0

B. Mütterliche Linie (incl. Mutter)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe weitere mütterliche Linie			
		B	0

C. Väterliche Linie (incl. Vater)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe väterliche Linie			
		C	0

D. Der höhere Wert aus B und C D 0

E. Summe aus A und D = Risiko-Score A+D 0

Ausfüllhinweis

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D angetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.

Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen.

*Diese Einschlusskriterien gelten nur in Kooperation mit den Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs bzw. mit den zertifizierten FBREK-Zentren, die diese im Rahmen der Wissen generierenden Versorgung validieren. Die anderen Einschlusskriterien entsprechen den Vorgabe des EBM.

Version: 11. Januar 2022 (C)
Ärztekammer Westfalen-Lippe,
Deutsche Krebsgesellschaft,
Deutsche Gesellschaft für Senologie,
Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

Online Tool zur Checkliste Familiärer Brust- und Eierstockkrebs:

Quelle: Deutsche Krebsgesellschaft e.V.

Hier ist das Online Tool zur Checkliste „Familiärer Brust- und Eierstockkrebs“ hinterlegt:
https://www.krebsgesellschaft.de/zertdokumente.html?file=files/dkg/deutsche-krebsgesellschaft/content/pdf/Zertifizierung/Checklisten-und-Algorithmen/checkliste_erbliche_belastung_brust_gyn-220118.xlsx&cid=98969

Referenzen:

1. Kast K, Rhiem K, Wappenschmidt B, et al., Prevalence of BRCA1/2 germline mutations in 21.401 families with breast and ovarian cancer. J Med Genet 2016;53:465-71.
2. Rhiem K, Bücker-Nott HJ, Hellmich M, et al. Benchmarking of a checklist for the identification of familial risk for breast and ovarian cancers in a prospective cohort. Breast J. 2019;25(3):455–460. doi:10.1111/tbj.13257

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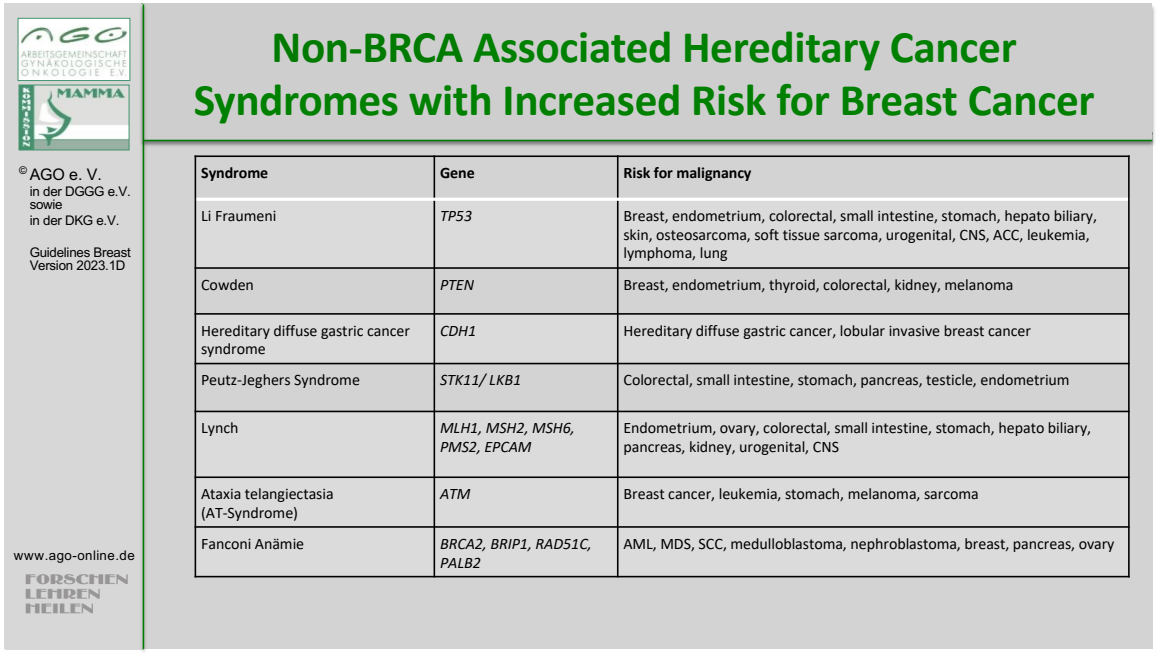
Risikoabschätzung für syndromassoziierte Mammakarzinome (non-BRCA)

	Oxford		
	LoE	GR	AGO
Eigen- und Familienanamnese über mindestens drei Generationen (mit Angabe des Ersterkrankungsalters)	**2b**	**B**	**++**

- Typische Erkrankungen:
  - Mamma- und Ovarialkarzinom
- Weitere Erkrankungen, insbesondere:
  - Pankreas-, Schilddrüsen-, Kolorektal-, Magenkarzinom, hepato-biliäres und urogenitales Karzinom, Melanom, Osteosarkom, Leukämie, Lymphom, Lungenkarzinom
  - Nierenzellkarzinom
  - Hodenkarzinom
  - Endometriumkarzinom
  - Prostatakarzinom

1. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-506.
2. Benusiglio PR, Malka D, Rouleau E, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013;50(7):486-9
3. Couch FJ et al.: Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncology 2017, DOI: 10.1001/jamaoncol.2017.042
4. di Masi A, Antoccia A. NBS1 Heterozygosity and Cancer Risk. Curr Genomics. 2008;9(4):275-81.
5. Gao P, Ma N, Li M, et al. Functional variants in NBS1 and cancer risk: evidence from a meta-analysis of 60 publications with 111 individual studies. Mutagenesis. 2013;28(6):683-97.
6. Goldgar DE, Healey S, Dowty JG, et al. Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res. 2011;13(4):R73.
7. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012;30(35):4409-15.
8. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. 2018 Mar 9. doi: 10.1002/cam4.1376.
9. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209-15.

10. Masciari S, Dillon DA, Rath M, et al. Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012;133(3):1125-30.
11. Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010;42(5):410-4.
12. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015;33(26):2901-7.
13. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400-7.
14. Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. 2018 Jan 24;20(1):7. doi: 10.1186/s13058-018-0935-9.



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

Syndrome	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	*STK11/ 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
Ataxia telangiectasia (AT-Syndrome)	*ATM*	Breast cancer, leukemia, stomach, melanoma, sarcoma
Fanconi Anämie	*BRCA2, BRIP1, RAD51C, PALB2*	AML, MDS, SCC, medulloblastoma, nephroblastoma, breast, pancreas, ovary

1. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-506.
2. Benusiglio PR, Malka D, Rouleau E, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013;50(7):486-9
3. Couch FJ et al.: Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncology 2017, DOI: 10.1001/jamaoncol.2017.042
4. di Masi A, Antoccia A. NBS1 Heterozygosity and Cancer Risk. Curr Genomics. 2008;9(4):275-81.
5. Gao P, Ma N, Li M, et al. Functional variants in NBS1 and cancer risk: evidence from a meta-analysis of 60 publications with 111 individual studies. Mutagenesis. 2013;28(6):683-97.
6. Goldgar DE, Healey S, Dowty JG, et al. Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res. 2011;13(4):R73.
7. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012;30(35):4409-15.
8. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. 2018 Mar 9. doi: 10.1002/cam4.1376.
9. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209-15.

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11. Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010;42(5):410-4.
12. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015;33(26):2901-7.
13. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400-7.
14. Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. 2018 Jan 24;20(1):7. doi: 10.1186/s13058-018-0935-9.

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**

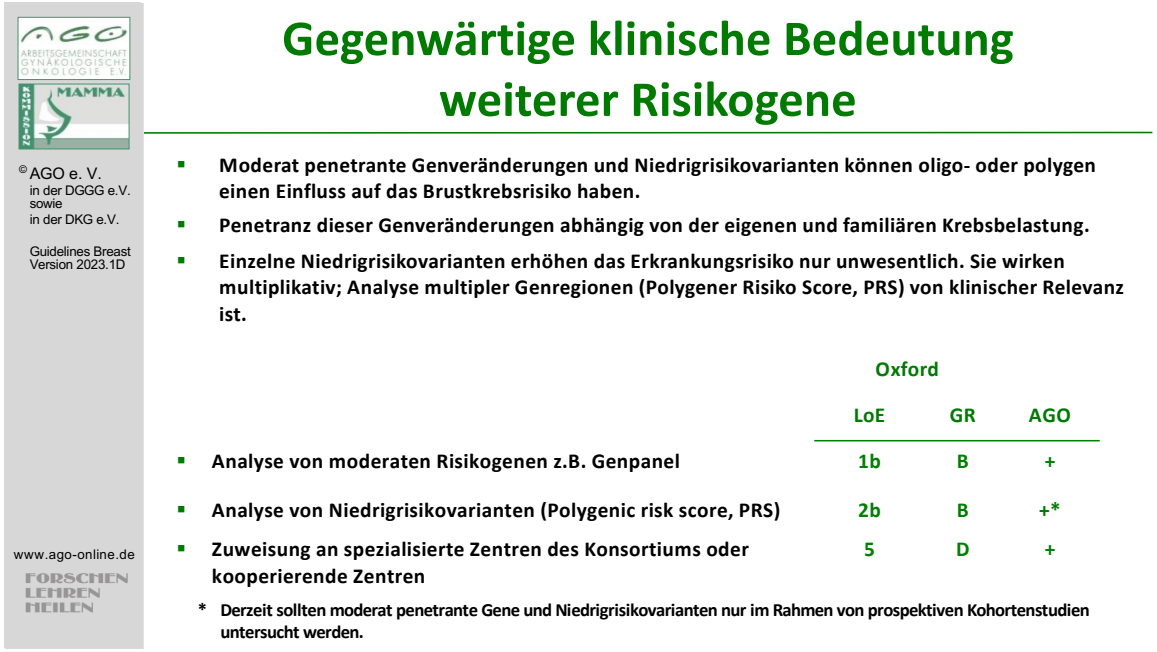
Angemessene Bedenkzeit vor prophylaktischen Operationen

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

SOFTWARE (BOADICEA, IBIS)

1. Lee A, Mavaddat N, Wilcox AN et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. 2019 Aug;21(8):1708-1718. Erratum in: Genet Med. 2019 Feb 21;:

1. Terry MB, Liao Y, Whittemore AS et al. 10-year performance of four models of breast cancer risk: a validation study. Lancet Oncol. 2019 Apr;20(4):504-517.



Gegenwärtige klinische Bedeutung weiterer Risikogene

- **Moderat penetrante Genveränderungen und Niedrigrisikovarianten können oligo- oder polygen einen Einfluss auf das Brustkrebsrisiko haben.**
- **Penetranz dieser Genveränderungen abhängig von der eigenen und familiären Krebsbelastung.**
- **Einzelne Niedrigrisikovarianten erhöhen das Erkrankungsrisiko nur unwesentlich. Sie wirken multiplikativ; Analyse multipler Genregionen (Polygener Risiko Score, PRS) von klinischer Relevanz ist.**

	Oxford		
	LoE	GR	AGO
▪ Analyse von moderaten Risikogenen z.B. Genpanel	1b	B	+
▪ Analyse von Niedrigrisikovarianten (Polygenic risk score, PRS)	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 untersucht werden.

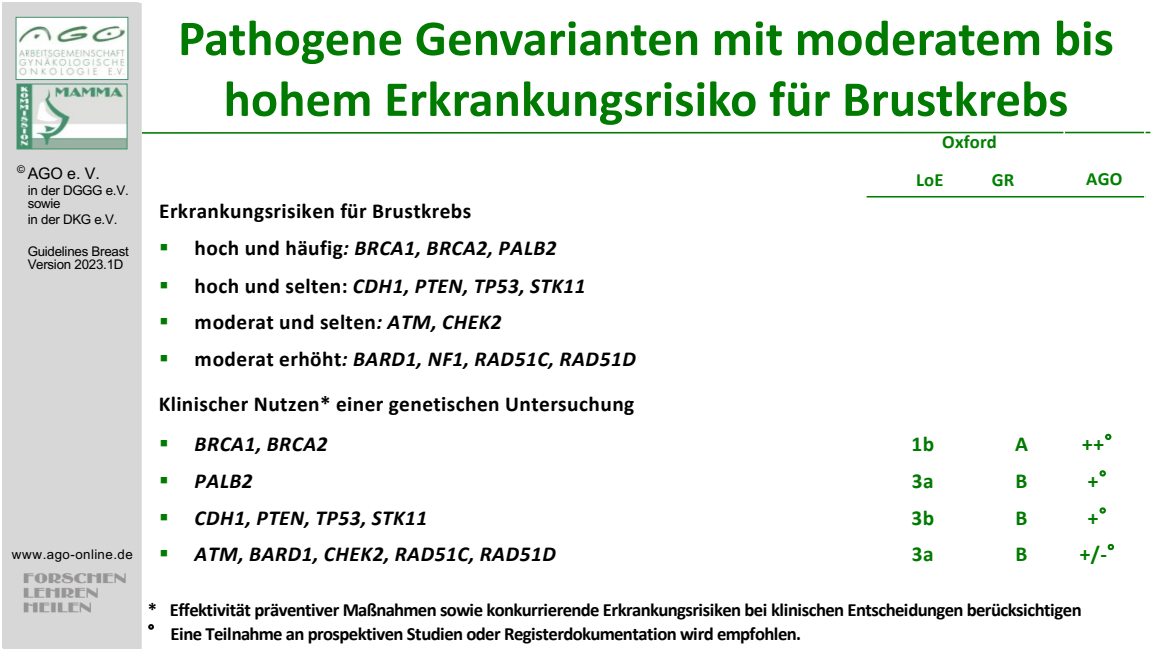
Analyse von moderaten Risikogenen e.g. Genpanel

1. Borde J, Ernst C, Wappenschmidt B et al. Performance of breast cancer polygenic risk scores in 760 female CHEK2 germline mutation carriers. J Natl Cancer Inst. 2020 Dec 29:djaa203. doi: 10.1093/jnci/djaa203. Epub ahead of print. PMID: 33372680.
2. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer JAMA Oncol 2017;3:1190-1196.
3. Cuzick J, Brentnall AR, Segal C, et al. Impact of a Panel of 88 Single Nucleotide Polymorphisms on the Risk of Breast Cancer in High-Risk Women: Results From Two Randomized Tamoxifen Prevention Trials. J Clin Oncol. 2016:JCO2016698944.
4. Dunning AM, Michailidou K, Kuchenbaecker KB, et al. Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170. Nat Genet. 2016;48(4):374-86.
5. 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
6. Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. *Cancer Med 2018 Apr;7(4):1349-1358. doi: 10.1002/cam4.1376. Epub 2018 Mar 10.*
7. Mavaddat N, Pharoah PD, Michailidou K, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015;107(5).

8. Mavaddat N, Michailidou K, Dennis J et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet. 2019 Jan 3;104(1):21-34..
9. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet. 2015;47(4):373-80.
10. Lakeman IMM, van den Broek AJ, Vos JAM, et al. The predictive ability of the 313 variant-based polygenic risk score for contralateral breast cancer risk prediction in women of European ancestry with a heterozygous BRCA1 or BRCA2 pathogenic variant. *Genet Med*. 2021;23(9):1726-1737.
11. Brooks JD, Nabi HH, Andrulis IL, et al. Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I). *J Pers Med*. 2021;11(6):511.

Analyse von Niedrigrisikovarianten (Polygenic risk score, PRS)

1. Jiao Y, Truong T, Eon-Marchais S, et al. Association and performance of polygenic risk scores for breast cancer among French women presenting or not a familial predisposition to the disease. Eur J Cancer. 2023 Jan;179:76-86.
2. Ohbe H, Hachiya T, Yamaji T et al..; Japan Public Health Center-based Prospective Study Group. Development and validation of genome-wide polygenic risk scores for predicting breast cancer incidence in Japanese females: a population-based case-cohort study. Breast Cancer Res Treat. 2022 Dec 20.
3. Jiao Y, Truong T, Eon-Marchais S et al. Association and performance of polygenic risk scores for breast cancer among French women presenting or not a familial predisposition to the disease. Eur J Cancer. 2023 Jan;179:76-86.
4. Lopes Cardozo JMN, Andrulis IL, Bojesen SE et al. ; Breast Cancer Association Consortium and MINDACT Collaborators. Associations of a Breast Cancer Polygenic Risk Score With Tumor Characteristics and Survival. J Clin Oncol. 2023 Jan 23:JCO2201978.



Pathogene Genvarianten mit moderatem bis hohem Erkrankungsrisiko für Brustkrebs

	Oxford		
	LoE	GR	AGO
Erkrankungsrisiken für Brustkrebs			
▪ **hoch und häufig*: BRCA1, BRCA2, PALB2***			
▪ **hoch und selten: *CDH1, PTEN, TP53, STK11***			
▪ **moderat und selten*: ATM, CHEK2***			
▪ **moderat erhöht*: BARD1, NF1, RAD51C, RAD51D***			
Klinischer Nutzen* einer genetischen Untersuchung			
▪ ***BRCA1, BRCA2***	1b	A	++°
▪ ***PALB2***	3a	B	+°
▪ ***CDH1, PTEN, TP53, STK11***	3b	B	+°
▪ ***ATM, BARD1, CHEK2, RAD51C, RAD51D***	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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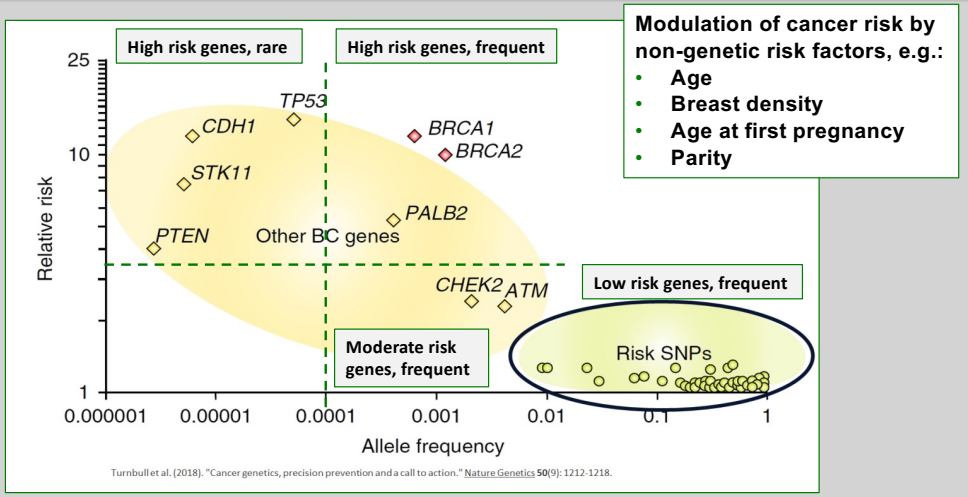
State of research: Relevance of Genetic and non-Genetic Risk Factors

Guidelines Breast
Version 2023.1D



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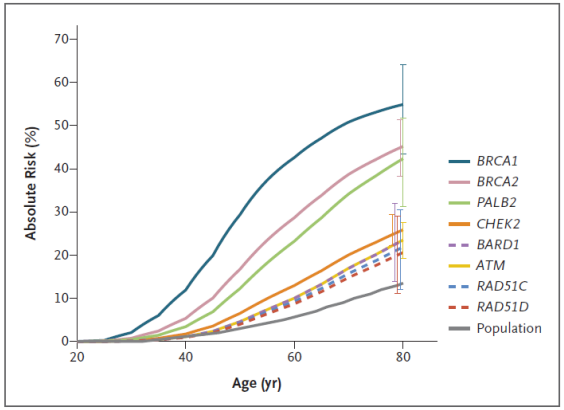
Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

Guidelines Breast
Version 2023.1D



Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016. The I bars indicate 95 % confidence intervals.

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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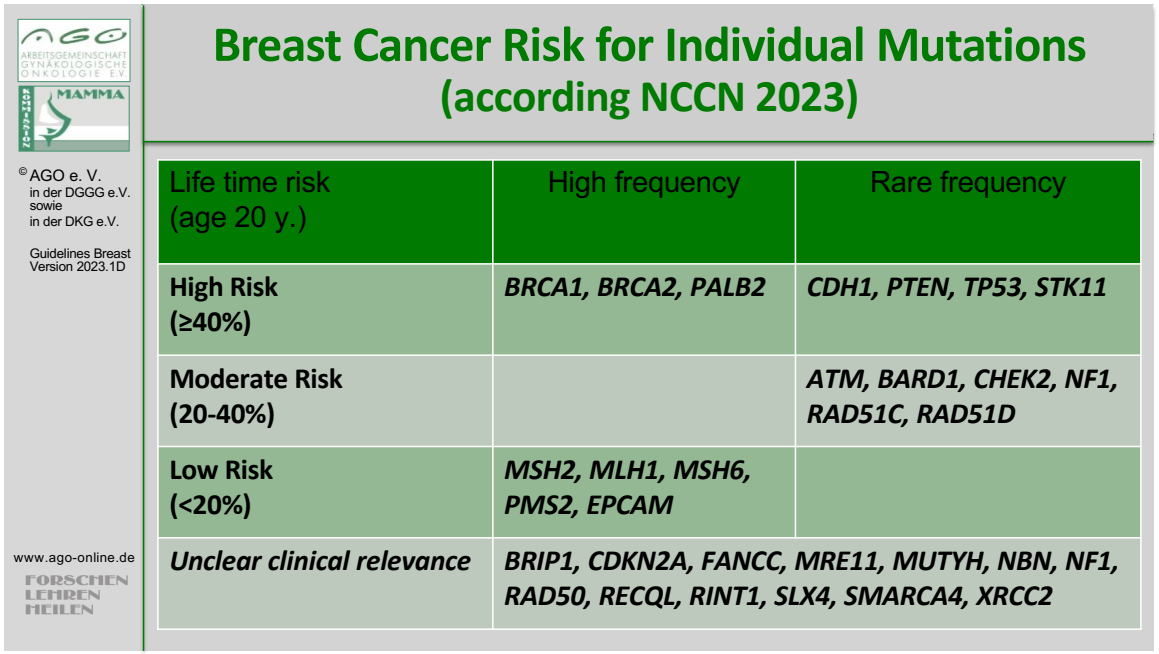

Breast Cancer Risk for Individual Mutations (according NCCN 2023)

Life time risk (age 20 y.)	High frequency	Rare frequency
High Risk (≥40%)	***BRCA1, BRCA2, PALB2***	***CDH1, PTEN, TP53, STK11***
Moderate Risk (20-40%)		***ATM, BARD1, CHEK2, NF1, RAD51C, RAD51D***
Low Risk (<20%)	***MSH2, MLH1, MSH6, PMS2, EPCAM***	
Unclear clinical relevance	***BRIP1, CDKN2A, FANCC, MRE11, MUTYH, NBN, NF1, RAD50, RECQL, RINT1, SLX4, SMARCA4, XRCC2***	

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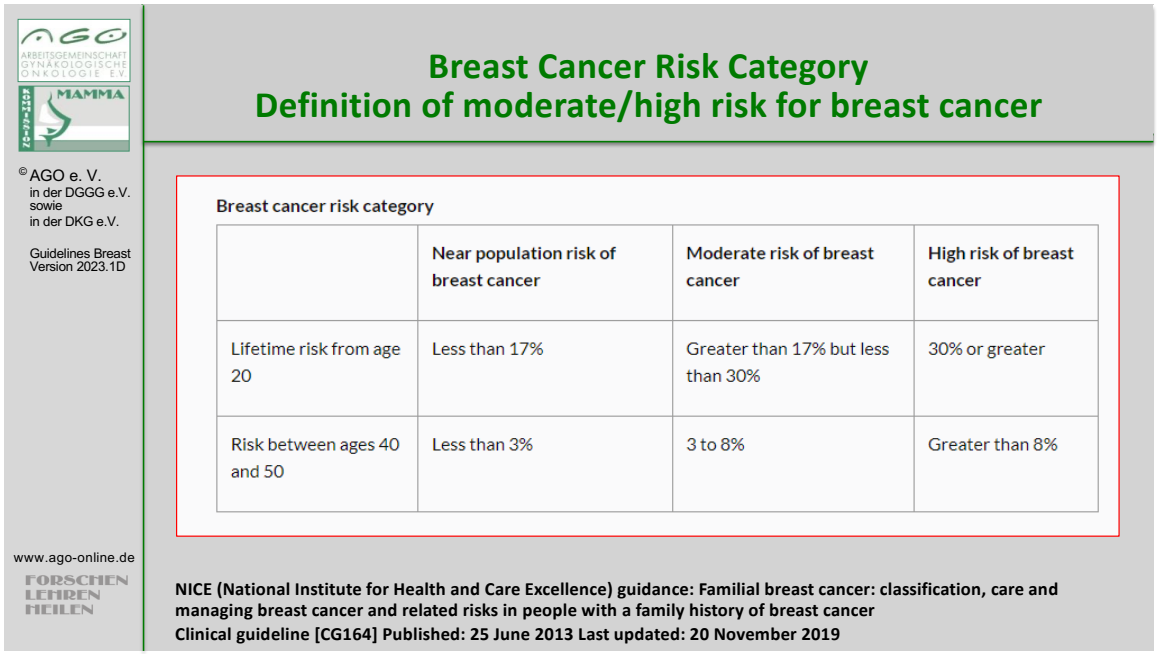

Breast Cancer Risk Category
Definition of moderate/high risk for breast cancer

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

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IARC - classification of sequence variants (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

Only class 4 and class 5 variants are considered clinically relevant.
Class 3 are considered as Variants of Unknown Significance (VUS).

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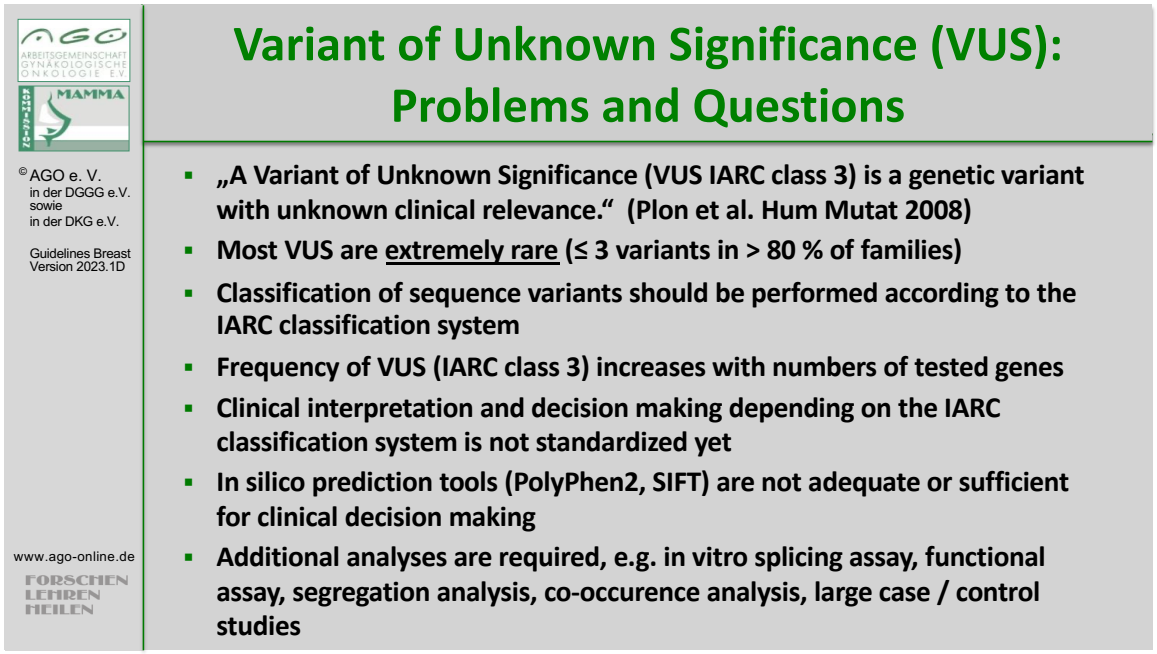

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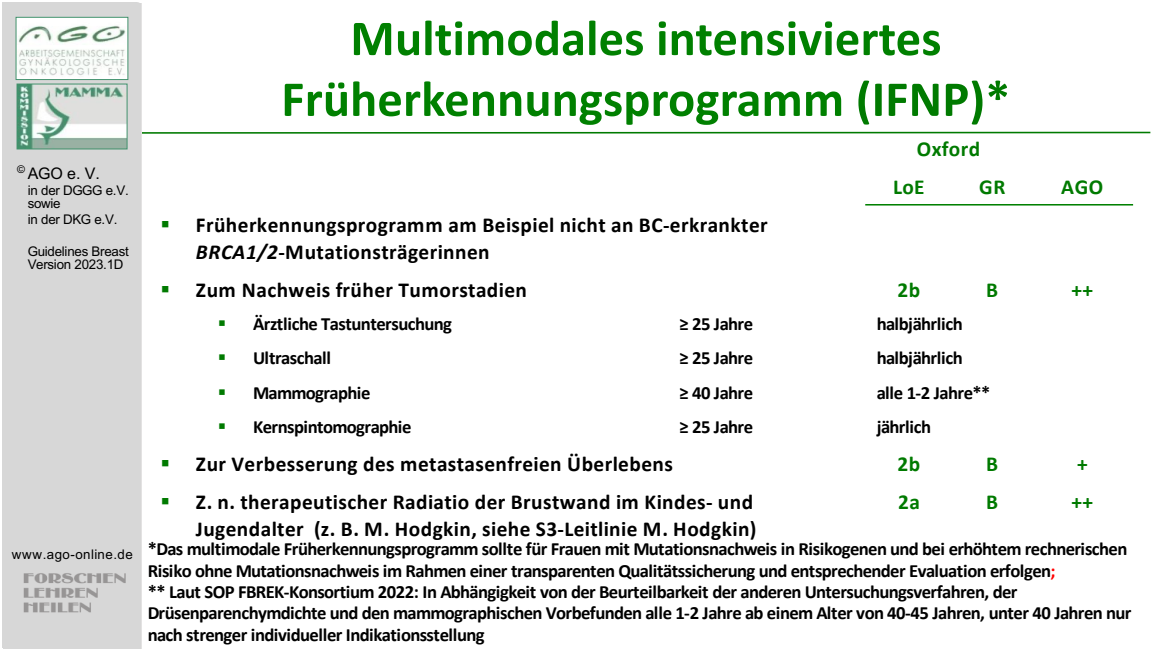

Multimodales intensiviertes Früherkennungsprogramm (IFNP)*

		Oxford LoE	GR	AGO
▪ Früherkennungsprogramm am Beispiel nicht an BC-erkrankter *BRCA1/2*-Mutationsträgerinnen				
▪ Zum Nachweis früher Tumorstadien		2b	B	++
▪ Ärztliche Tastuntersuchung	≥ 25 Jahre	halbjährlich		
▪ Ultraschall	≥ 25 Jahre	halbjährlich		
▪ Mammographie	≥ 40 Jahre	alle 1-2 Jahre**		
▪ Kernspintomographie	≥ 25 Jahre	jährlich		
▪ Zur Verbesserung des metastasenfreien Überlebens		2b	B	+
▪ Z. n. therapeutischer Radiatio der Brustwand im Kindes- und Jugendalter (z. B. M. Hodgkin, siehe S3-Leitlinie 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;
** Laut SOP FBREK-Konsortium 2022: In Abhängigkeit von der Beurteilbarkeit der anderen Untersuchungsverfahren, der Drüsenparenchymdichte und den mammographischen Vorbefunden alle 1-2 Jahre ab einem Alter von 40-45 Jahren, unter 40 Jahren nur nach strenger individueller Indikationsstellung

1. E-Learning DKG/FBREK, 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.
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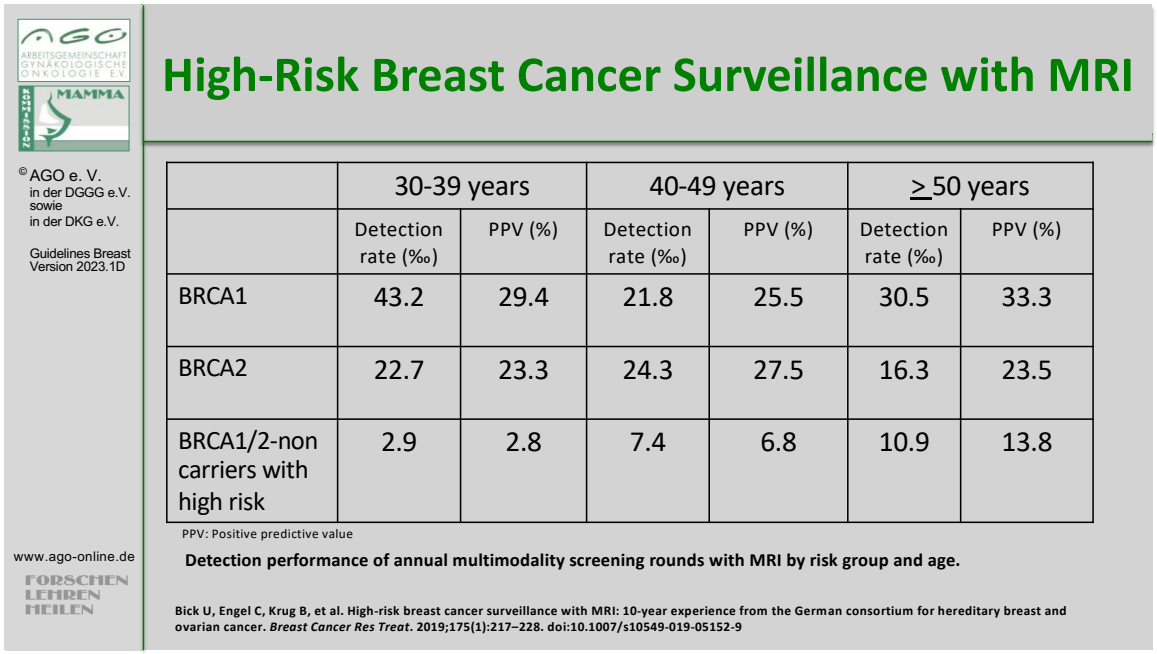
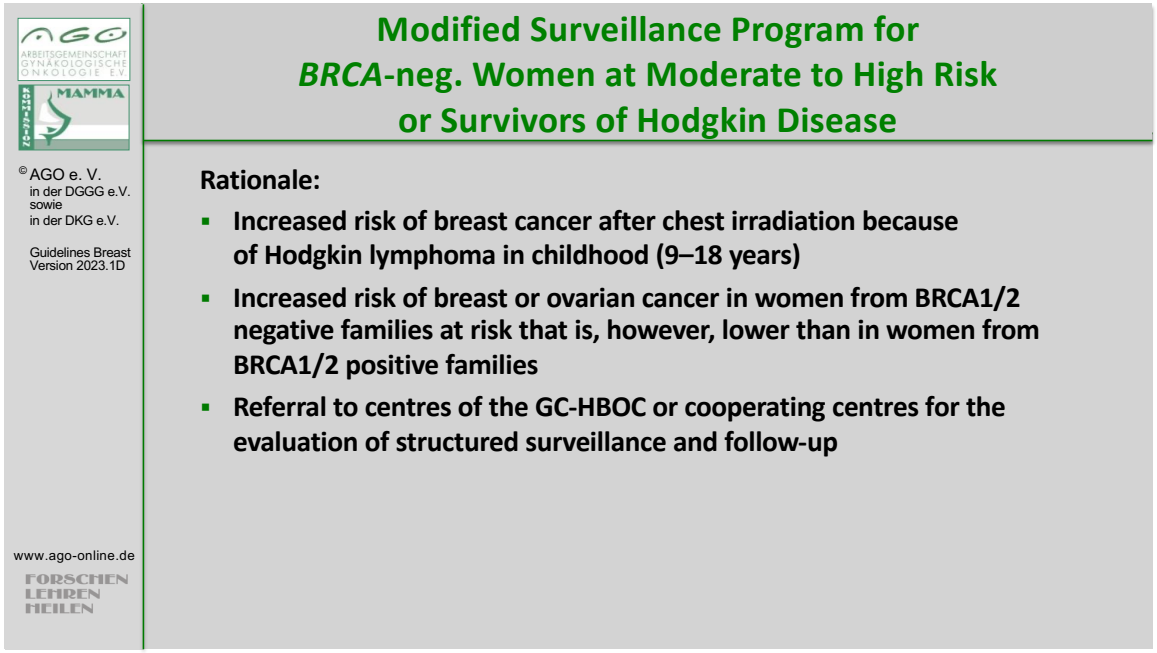


	30-39 years		40-49 years		≥ 50 years	
	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)	Detection rate (‰)	PPV (%)
BRCA1	43.2	29.4	21.8	25.5	30.5	33.3
BRCA2	22.7	23.3	24.3	27.5	16.3	23.5
BRCA1/2-non carriers with high risk	2.9	2.8	7.4	6.8	10.9	13.8

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.



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Multimodales Nachsorgeprogramm (IFNP) für Frauen mit *BRCA1/2* Mutation nach primärer einseitiger Mammakarzinom-Erkrankung

	Oxford LoE	GR	AGO
▪ **Multimodales intensiviertes Nachsorgeprogramm***			
▪ **Zum Nachweis früher Tumorstadien**	**2a**	**B**	**++**
▪ **Ärztliche Tastuntersuchung**	**halbjährlich**		
▪ **Ultraschall**	**halbjährlich**		
▪ **Mammographie**	**alle 1-2 Jahre****		
▪ **Kernspintomographie**	**jährlich**		
▪ **Zur Mortalitätsreduktion**	**3a**	**C**	**+/-**

*** Die Nachsorge sollte im Rahmen einer transparenten Qualitätssicherung und entsprechender Evaluation erfolgen.**

**** Laut SOP FBREK-Konsortium 2022: In Abhängigkeit von der Beurteilbarkeit der anderen Untersuchungsverfahren, der Drüsenparenchymdichte und den mammographischen Vorbefunden alle 1-2 Jahre ab einem Alter von 40-45 Jahren, unter 40 Jahren nur nach strenger individueller Indikationsstellung.**

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FORSCHEN
LEHREN
HEILEN

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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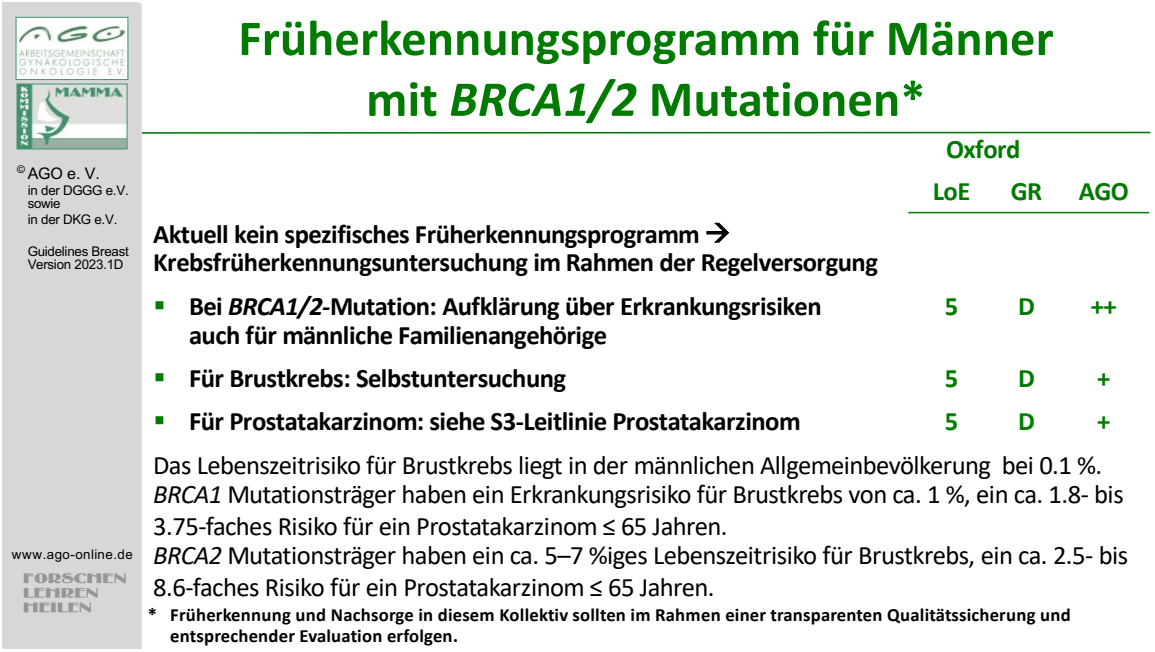

Früherkennungsprogramm für Männer mit *BRCA1/2* Mutationen*

	Oxford LoE	GR	AGO
Aktuell kein spezifisches Früherkennungsprogramm → Krebsfrüherkennungsuntersuchung im Rahmen der Regelversorgung			
▪ **Bei *BRCA1/2*-Mutation: Aufklärung über Erkrankungsrisiken auch für männliche Familienangehörige**	5	D	++
▪ **Für Brustkrebs: Selbstuntersuchung**	5	D	+
▪ **Für Prostatakarzinom: siehe S3-Leitlinie Prostatakarzinom**	5	D	+

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.

* **Früherkennung und Nachsorge in diesem Kollektiv sollten 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.
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Chirurgische Prävention

	Oxford		
	LoE	GR	AGO
▪ **Risiko-reduzierende, unilaterale oder bilaterale Mastektomie (RRME) ohne Vorliegen von genetischen Risikofaktoren (führt nicht zu einer Mortalitätsreduktion)**	2a	B	-*
▪ **Axilladissektion oder Sentinel-Lymphknoten Exzision bei RRME**	2a	B	--

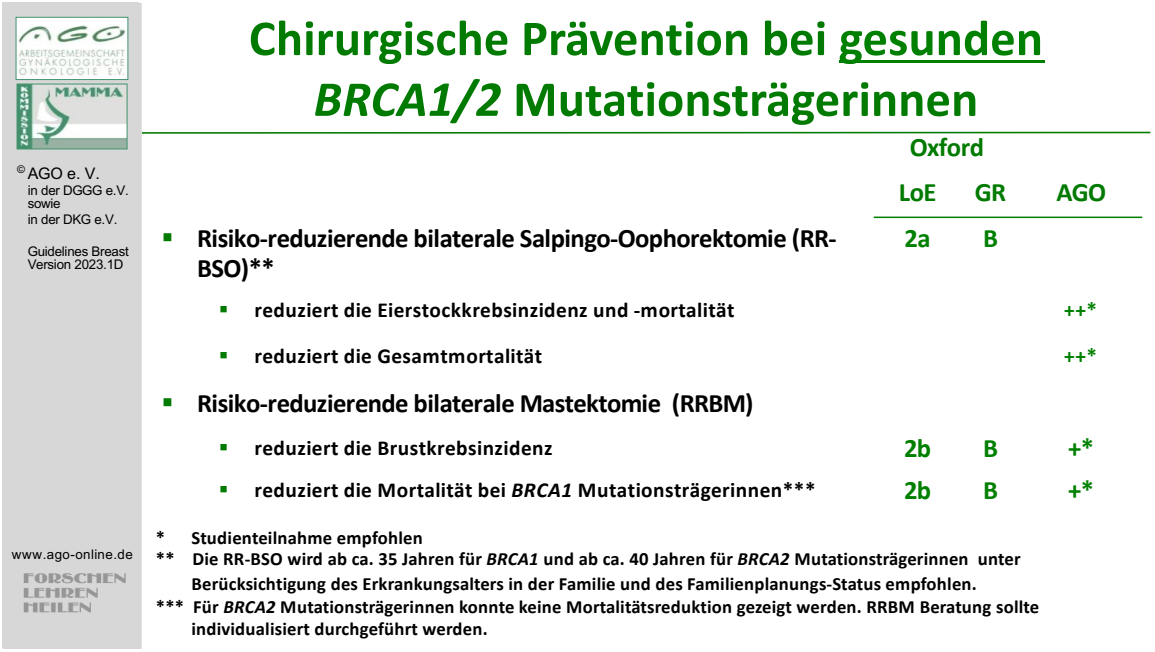
* **Studienteilnahme empfohlen**

RRME ohne gentisches Risiko

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.

Sentinel-Lymphknoten Exzision bei RRME

1. Wong SM, Ferroum A, Apostolova C et al. Incidence of Occult Breast Cancer in Carriers of BRCA1/2 or Other High-Penetrance Pathogenic Variants Undergoing Prophylactic Mastectomy: When is Sentinel Lymph Node Biopsy Indicated? Ann Surg Oncol. 2022 Oct;29(11):6660-6668.



Chirurgische Prävention bei gesunden *BRCA1/2* Mutationsträgerinnen

	Oxford LoE	Oxford GR	AGO
▪ **Risiko-reduzierende bilaterale Salpingo-Oophorektomie (RR-BSO)****	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 RR-BSO 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.**

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.
2. 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.
3. Heemskerk-Gerritsen BAM, Seynaeve C, van Asperen CJ, et al.: Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction. JNCI J Natl Cancer Inst (2015) 107(5): djv033
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.
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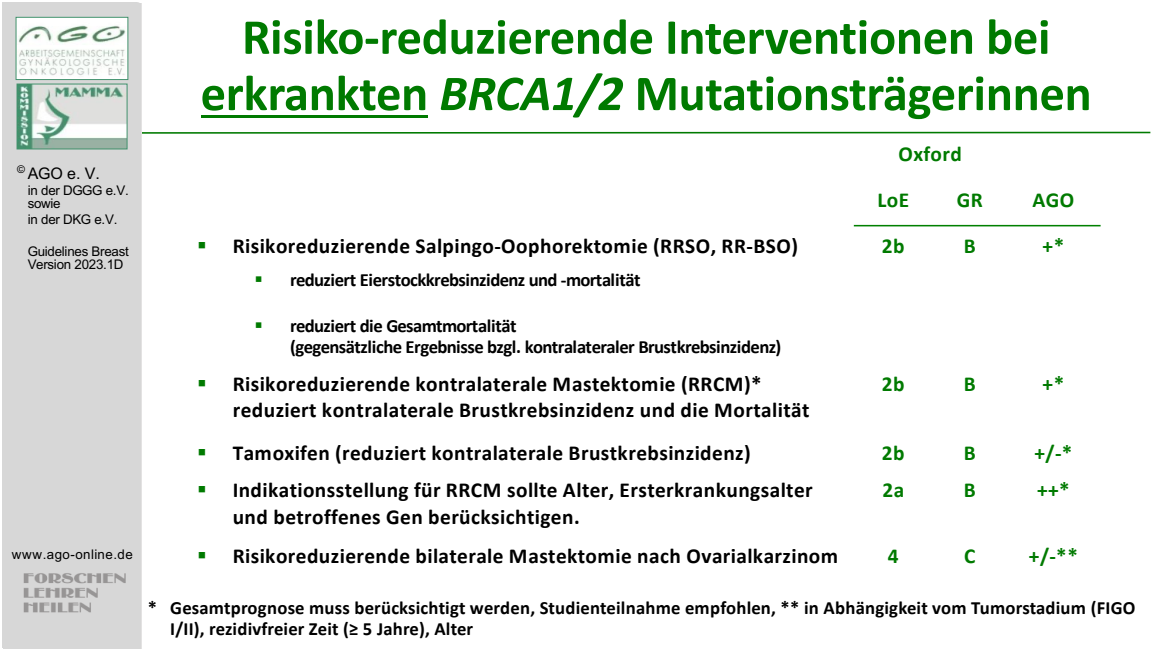

Risiko-reduzierende Interventionen bei erkrankten *BRCA1/2* Mutationsträgerinnen

	Oxford		
	LoE	GR	AGO
▪ Risikoreduzierende Salpingo-Oophorektomie (RRSO, RR-BSO)	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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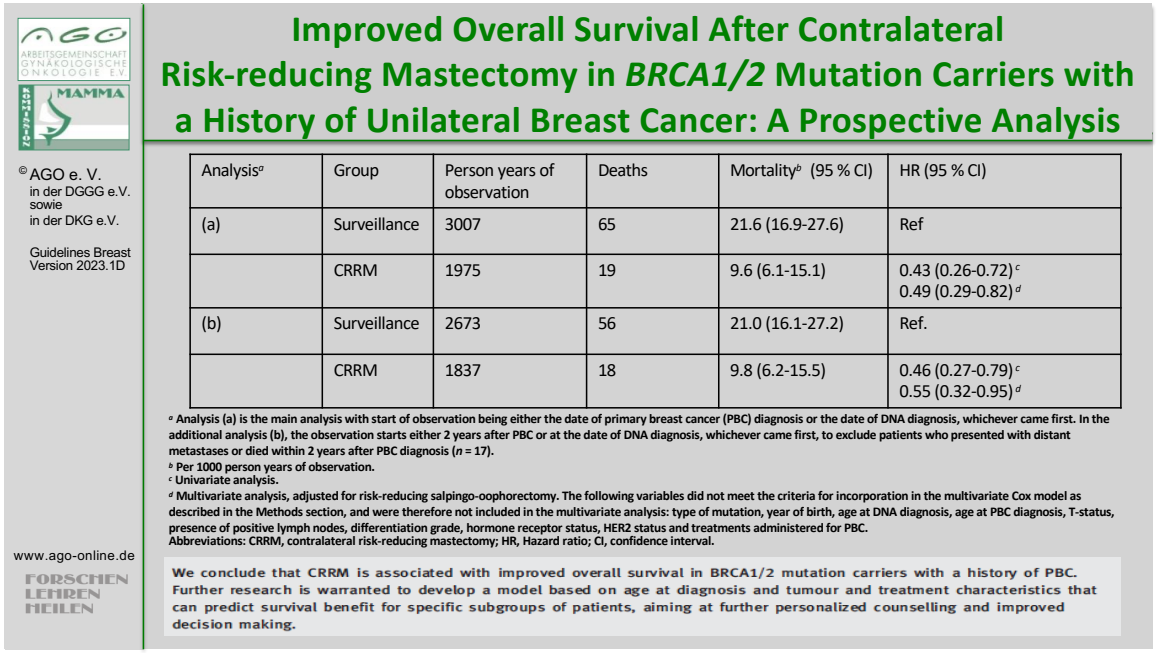

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

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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] 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] 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 personalized counselling and improved decision making.

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FORSCHEN
LEHREN
HEILEN

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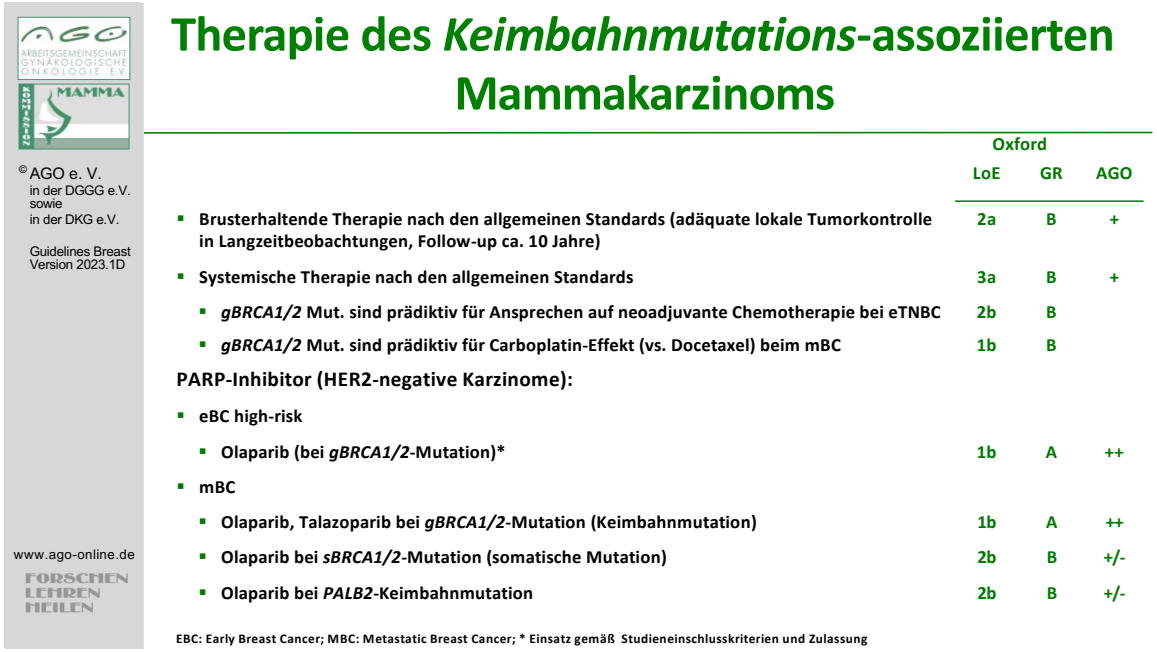

Therapie des *Keimbahnmutations*-assoziierten Mammakarzinoms

	Oxford LoE	Oxford GR	AGO
▪ Brusterhaltende Therapie nach den allgemeinen Standards (adäquate lokale Tumorkontrolle in Langzeitbeobachtungen, Follow-up ca. 10 Jahre)	2a	B	+
▪ Systemische Therapie nach den allgemeinen Standards	3a	B	+
▪ *gBRCA1/2* Mut. sind prädiktiv für Ansprechen auf neoadjuvante Chemotherapie bei eTNBC	2b	B	
▪ *gBRCA1/2* Mut. sind prädiktiv für Carboplatin-Effekt (vs. Docetaxel) beim mBC	1b	B	
PARP-Inhibitor (HER2-negative Karzinome):			
▪ eBC high-risk			
▪ Olaparib (bei *gBRCA1/2*-Mutation)*	1b	A	++
▪ mBC			
▪ Olaparib, Talazoparib bei *gBRCA1/2*-Mutation (Keimbahnmutation)	1b	A	++
▪ Olaparib bei *sBRCA1/2*-Mutation (somatische Mutation)	2b	B	+/-
▪ Olaparib bei *PALB2*-Keimbahnmutation	2b	B	+/-

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

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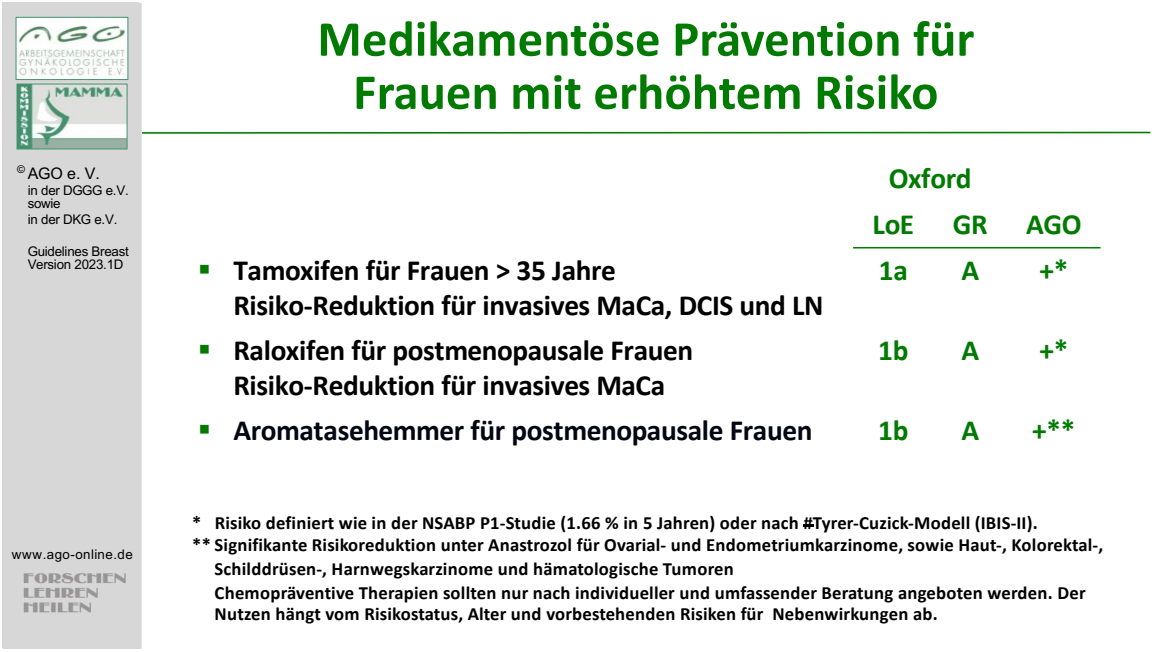

Medikamentöse Prävention für Frauen mit erhöhtem Risiko

	Oxford		
	LoE	GR	AGO
▪ **Tamoxifen für Frauen > 35 Jahre** **Risiko-Reduktion für invasives MaCa, DCIS und LN**	1a	A	+*
▪ **Raloxifen für postmenopausale Frauen** **Risiko-Reduktion für invasives 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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