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Guidelines Breast
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FORSCHEN
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HEILEN

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Brustkrebsrisiko, Genetik und Prävention



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Brustkrebsrisiko und Prävention

- **Versionen 2003–2024:**

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- **Version 2025:**

Albert / Rhiem



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Keimbahn-Diagnostik mit therapeutischer Konsequenz

Unabh. von der familiären Risikokonstellation

gBRCA1/2 pV
gPALB2 pV

	Oxford		
	LoE	GR	AGO
	1a	A	++
	2b	B	+

Therapie des Mammakarzinoms bei wahrscheinlich pathogenen / pathogenen Keimbahnvarianten

	Oxford		
	LoE	GR	AGO
▪ Brusterhaltende Therapie nach den allgemeinen Standards (adäquate lokale Tumorkontrolle in Langzeitbeobachtungen, IBTR RR 1,6, kein verschlechtertes Gesamtüberleben, Follow-up ≥ 10 Jahre)	2a	B	+
▪ Systemische Therapie nach den allgemeinen Standards	3a	B	+
▪ <i>gBRCA1/2</i> pathogene Variante (pV) sind prädiktiv für Ansprechen auf neoadjuvante Chemotherapie bei eTNBC	2b	B	
▪ <i>gBRCA1/2</i> pV sind prädiktiv für Carboplatin-Effekt (vs. Docetaxel) beim mBC	1b	B	
PARP-Inhibitor (HER2-negative Karzinome):			
▪ eBC high-risk:			
▪ Olaparib (bei <i>gBRCA1/2</i> pV)*	1b	A	++
▪ mBC:			
▪ Olaparib, Talazoparib bei <i>gBRCA1/2</i> pV	1b	A	++
▪ Olaparib bei <i>sBRCA1/2</i> pV (somatisch)	2b	B	+
▪ Olaparib bei <i>gPALB2</i> pV	2b	B	+

eBC: Early Breast Cancer; mBC: Metastatic Breast Cancer; pV: wahrscheinlich pathogene / pathogene Variante (Klasse 4/5) = Mutation; IBTR: ipsilateral breast tumor recurrence; * Einsatz gemäß Studieneinschlusskriterien und Zulassung

BCS bei BRCA 1/2 Mutationsträgern

1. Nara M, Ishihara S, Kitano A, et al. Does breast-conserving surgery with radiotherapy in BRCA-mutation carriers significantly increase ipsilateral breast tumor recurrence? A systematic review and meta-analysis Breast Cancer 2022 May;29(3):394-401.doi: 10.1007/s12282-022-01343-3. Epub 2022 PMID: 35212965
2. 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.
3. Huang X, Cai XY, Liu JQ, et al. Breast-conserving therapy is safe both within BRCA1/2 mutation carriers and noncarriers with breast cancer in the Chinese population. Gland Surg. 2020 Jun;9(3):775-787.
4. Ye F, Huang L, Lang G et al. Outcomes and risk of subsequent breast events in breast-conserving surgery patients with BRCA1 and BRCA2 mutation. Cancer Med. 2020 Mar;9(5):1903-1910.
5. Golshan M, Loibl S, Wong SM, et al. Breast Conservation After Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer: Surgical Results From the BrightNess Randomized Clinical Trial. JAMA Surg. 2020 Mar 1;155(3):e195410.
6. Pogoda K, Niwińska A, Sarnowska E, et al. Effects of BRCA Germline Mutations on Triple-Negative Breast Cancer Prognosis. J Oncol. 2020 Jan 27;2020:8545643.
7. Yoon KH, Chae S, Kang E, et al. Contralateral Breast Cancer and Ipsilateral Breast Tumor Recurrence in BRCA1/2 Carriers and Non-Carriers at High-Risk of Hereditary Breast Cancer. J Breast Cancer. 2019 Sep 30;22(4):587-598.

- Hallam S, Govindarajulu S, Hockett B, et al. BRCA1/2 Mutation-associated Breast Cancer, Wide Local Excision and Radiotherapy or Unilateral Mastectomy: A Systematic Review. *Clin Oncol (R Coll Radiol)*. 2015;27(9):527-35.
- Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *J Clin Oncol*. 2006;24(16):2437-43.

Chemotherapiesprechen:

- Zheng F, Du F, Wang W et al. Updated efficacy of adjuvant epirubicin plus cyclophosphamide followed by taxanes versus carboplatin plus taxanes in early triple-negative breast cancer in phase 2 trial: 8.1-year median follow-up. *Breast Cancer Res Treat*. 2022 Jan;191(1):97-105.
- 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.
- Fasching PA, Loibl S, Hu C et al. BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study. *J Clin Oncol*. 2018 Aug 1;36(22):2281-2287.
- 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.
- Meisner E, Rollins R, Ensor J et al.: Efficacy of olaparib monotherapy in patients (pts) with HER2-negative metastatic breast cancer (MBC) with germline BRCA mutation (gBRCAm) or lesional BRCA mutation (lBRCAm). *J Clin Oncol* 2018, 36 (suppl; abstr 1074)
- 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, 3(10):1378-1385.

Carboplatin eBC:

- Caramelo O, Silva C, Caramelo F et al. Efficacy of different neoadjuvant treatment regimens in BRCA-mutated triple negative breast cancer: a systematic review and meta-analysis. *Hered Cancer Clin Pract*. 2022 Sep 9;20(1):34.
- Metzger-Filho O, Collier K, Asad S et al. Matched cohort study of germline BRCA mutation carriers with triple negative breast cancer in brightness. *NPJ Breast Cancer*. 2021 Nov 11;7(1):142.
- Pavese F, Capoluongo ED, Muratore M et al. BRCA Mutation Status in Triple-Negative Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Pivotal Role for Treatment Decision-Making. *Cancers (Basel)*. 2022 Sep 21;14(19):4571.

Carboplatin mBC:

1. Somlo G, Frankel PH, Arun BK et al. Efficacy of the PARP Inhibitor Veliparib with Carboplatin or as a Single Agent in Patients with Germline BRCA1- or BRCA2-Associated Metastatic Breast Cancer: California Cancer Consortium Trial NCT01149083. Clin Cancer Res. 2017 Aug 1;23(15):4066-4076.
2. Arun BK, Han HS, Kaufman B et al. Efficacy and safety of first-line veliparib and carboplatin-paclitaxel in patients with HER2- advanced germline BRCA+ breast cancer: Subgroup analysis of a randomised clinical trial. Eur J Cancer. 2021 Sep;154:35-45.
3. Tutt A, Tovey H, Cheang MCU et al.: Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med. 2018 May;24(5):628-637.

PARP-inhibitors eBC high-risk:

1. Zambelli A, Cortesi L, Gaudio M, et al. Parp-inhibitors in the therapeutic landscape of breast cancer patients with BRCA1 and BRCA2 pathogenic germline variants: An Italian consensus paper and critical review Cancer Treat Rev. 2024 Nov;130:102815. doi: 10.1016/j.ctrv.2024.102815.
2. Ganz PA, Bandos H, Španić T, et al. Patient-Reported Outcomes in OlympiA: A Phase III, Randomized, Placebo-Controlled Trial of Adjuvant Olaparib in g<i>BRCA1/2</i> Mutations and High-Risk Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer. J Clin Oncol. 2024 Apr 10;42(11):1288-1300. doi: 10.1200/JCO.23.01214.
3. Geyer CE Jr, Garber JE, Gelber RD et al.; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol. 2022 Dec;33(12):1250-1268.
4. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.
5. Litton JK, Scoggins M, Ramirez DL et al. A feasibility study of neoadjuvant talazoparib for operable breast cancer patients with a germline BRCA mutation demonstrates marked activity. NPJ Breast Cancer. 2017 Dec 6;3:49.

PARP-inhibitors mBC:

1. Qureshi Z, Jamil A, Altaf F, Siddique R, Safi A. Efficacy and Safety of BRCA-targeted Therapy (Polyadenosine Diphosphate-ribose Polymerase Inhibitors) in Treatment of BRCA-mutated Breast Cancer: A Systematic Review and Meta-analysis. Am J Clin Oncol. 2024 Nov 1;47(11):555-562. doi: 10.1097/COC.0000000000001120
2. Balmaña J, Fasching PA, Couch FJ, et al. LUCYinvestigators. Clinical effectiveness and safety of olaparib in BRCA-mutated,HER2-

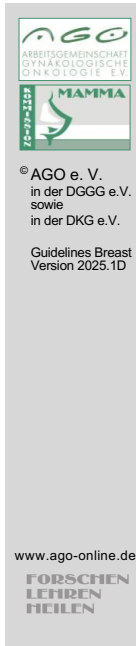
negative metastatic breast cancer in a real-world setting: final analysis of LUCY. *Breast Cancer Res Treat.* 2024 Apr;204(2):237-248. doi:10.1007/s10549-023-07165-x.

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4. Miglietta F, Fabi A, Generali D et al. Optimizing choices and sequences in the diagnostic-therapeutic landscape of advanced triple-negative breast cancer: An Italian consensus paper and critical review. *Cancer Treat Rev.* 2023 Jan 6;114:102511.
5. Tung NM, Robson ME, Ventz S et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol.* 2020 Dec 20;38(36):4274-4282.
6. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol.* 2019;30(4):558–566.
7. Robson M, Ruddy KJ, Im SA, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. *Eur J Cancer.* 2019 Oct;120:20-30.
8. Ettl J, Quek RGW, Lee KH, et al. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. *Ann Oncol.* 2018;29(9):1939–1947.
9. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med.* 2018;379(8):753–763.
10. 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.
11. Poggio F, Bruzzone M, Ceppi M et al.: Single-agent PARP inhibitors for the treatment of patients with BRCA-mutated Her2-negative metastatic breast cancer: a systematic review and meta-analysis. *ESMO Open* 2018, 3:e000361
12. 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;377(17):1700]. *N Engl J Med.* 2017;377(6):523–533.

PARP-inhibitors mBC gPALB2mut:

1. Tung NM, Robson ME, Ventz S et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol.* 2020 Dec 20;38(36):4274-4282. doi: 10.1200/JCO.20.02151. Epub 2020 Oct

29. PMID: 33119476.



Indikation für eine genetische Untersuchung des/der IndexpatientIN in den Genen *BRCA 1/2* und ggf. weiteren Risikogenen

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

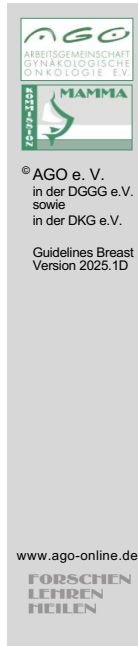
Bei Vorliegen eines dieser Kriterien des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs (DK-FBREC) liegt die Wahrscheinlichkeit für den Nachweis einer wahrscheinlich pathogenen / pathogenen Keimbahnvariante (pV) in den Genen *BRCA1*- und *BRCA2* bei $\geq 10\%$, EBM-Vergütung gesichert.

Untersuchung innerhalb und außerhalb eines FBREC-Zentrums möglich bei aus einer Familienseite mindestens*

- drei an Brustkrebs erkrankten Frauen unabhängig vom Alter
- zwei an Brustkrebs erkrankten Frauen (eine Erkrankung vor dem 51. Geburtstag)
- 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 (eine vor dem 51. Geburtstag)
- einer an Brustkrebs erkrankten Frau vor dem 36. Geburtstag
- einem Mann erkrankt an Brustkrebs und einer an Brust- oder Eierstockkrebs erkrankten Frau

* 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).

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



Indikation für eine genetische Untersuchung des/der IndexpatientIn in den Genen *BRCA 1/2* und ggf. weiteren Risikogenen

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

Für weitere empfohlene Kriterien:

- Eine Erkrankung mit triple-negativem Brustkrebs mit Erkrankungsalter vor dem 70. Geburtstag*
- Eine Erkrankung mit Eierstockkrebs vor dem 80. Geburtstag*
- Ein an Brustkrebs erkrankter Mann*

ist eine Signifikanz für eine mindestens 10%ige Nachweiswahrscheinlichkeit von wahrscheinlich pathogenen / pathogenen Varianten (pV) noch nicht abschließend gesichert. Deshalb müssen sie weiter systematisch unter Studienbedingungen validiert werden.

* Kostenübernahme an den Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs.

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).
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provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. *Int J Cancer*. 2002;97(4):472-80.

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9. Rhiem K, Zachariae S, Waha A, Grill S, Hester A, Golatta M, van Mackelenbergh M, Fehm T, Schläiß T, Ripperger T, Ledig S, Meisel C, Speiser D, Veselinovic K, Schröder C, Witzel I, Gallwas J, Weber BHF, Solbach C, Aktas B, Hahnen E, Engel C, Schmutzler R. Prevalence of Pathogenic Germline Variants in Women with Non-Familial Unilateral Triple-Negative Breast Cancer. *Breast Care (Basel)*. 2023 May;18(2):106-112. doi: 10.1159/000528972. Epub 2023 Jan 6. PMID: 37261134; PMCID: PMC10228253.



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Erweiterte Indikation für eine genetische Untersuchung in den Genen *BRCA1*, *BRCA2*, *TP53*, *PALB2*, *CDH1*, *PTEN*, *STK11* und ggf. weiteren Risikogenen (nach NCCN)


Eine genetische Untersuchung kann auch durchgeführt werden bei

- einem Erkrankungsalter ≤ 65 Jahre ohne fam. Anamnese
- triple-negativer Histologie und Erkrankungsalter > 60 Jahre, insbesondere bei Vorhanden eines weiteren Mammakarzinoms in der Familie (unabhängig vom Erkrankungsalter)
- invasiv lobulärer Histologie und Vorhandensein von diffusem Magenkarzinom in der Familie
- Vorhandensein von weiteren Fällen von Pankreaskarzinomen und Hochrisiko-Prostatakarzinomen in der Familie
- Personen Ashkenazi-jüdischer Abstammung

Diese Indikationen sind hinsichtlich ihrer Nachweiswahrscheinlichkeit von wahrscheinlich pathogenen / pathogenen Varianten (pV) nicht validiert.

Cave: hohe Anzahl von VUS, erniedrigte Penetranz

1. Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024 Feb 10;42(5):584-604. doi: 10.1200
2. NCCN Guideline 2024 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf



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

Name Patientin/Patient: _____ Geburtsdatum: _____

A. Patientin und deren Geschwister / Kinder

Auffreten bei Patientin/Patient	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei der Patientin vor dem 36. Geburtstag	3	0	0
eines bilateralen Mammakarzinoms bei der Patientin vor dem 50. Geburtstag	3	0	0
eines unilateralen Mammakarzinoms bei der Patientin vor dem 50. Geburtstag	2	0	0
eines bilateralen Mammakarzinoms bei der Patientin, das erst vor dem 50. Geburtstag	3	0	0
eines unilateralen Mammakarzinoms bei der Patientin nach dem 50. Geburtstag	1	0	0
eines uni- oder bilateralen Mammakarzinoms bei dem Patienten (Standard)	2	0	0
eines Ovarialkarzinoms bei der Patientin vor dem 50. Geburtstag	3	0	0
eines Ovarialkarzinoms bei der Patientin nach dem 50. Geburtstag	2	0	0
Auffreten bei Kindern, Geschwister und deren Kindern			
eines Mammakarzinoms bei Schwäger/Töchter/Nichten vor dem 36. Geburtstag	3	0	0
eines unilateralen Mammakarzinoms bei Schwäger/Töchter/Nichten vor dem 50. Geburtstag	3	0	0
eines bilateralen Mammakarzinoms bei Schwäger/Töchter/Nichten, das erst vor dem 50. Geburtstag	3	0	0
eines uni- oder bilateralen Mammakarzinoms bei Schwäger/Töchter/Nichten nach dem 50. Geburtstag	1	0	0
eines uni- oder bilateralen Mammakarzinoms bei Bruder/Schwäger	2	0	0
eines Ovarialkarzinoms bei Schwäger/Töchter/Nichten	2	0	0
Summe väterliche Linie	A		

B. Mütterliche Linie (incl. Mutter)

Auffreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen vor dem 36. Geburtstag	3	0	0
eines unilateralen Mammakarzinoms bei einer Angehörigen vor dem 50. Geburtstag	2	0	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, die erst vor dem 50. Geburtstag	3	0	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen nach dem 50. Geburtstag	1	0	0
eines Mammakarzinoms bei einem Angehörigen nach dem 50. Geburtstag	2	0	0
eines Ovarialkarzinoms bei einer Angehörigen	2	0	0
Summe mütterliche Linie	B		

C. Väterliche Linie (incl. Vater)

Auffreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen vor dem 36. Geburtstag	3	0	0
eines unilateralen Mammakarzinoms bei einer Angehörigen vor dem 50. Geburtstag	2	0	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, die erst vor dem 50. Geburtstag	3	0	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen nach dem 50. Geburtstag	1	0	0
eines Mammakarzinoms bei einem Angehörigen nach dem 50. Geburtstag	2	0	0
eines Ovarialkarzinoms bei einer Angehörigen	2	0	0
Summe väterliche Linie	C		

D. Der höhere Wert aus B und C

D	D
----------	----------

E. Summe aus A und D = Risiko-Score

A+D	0
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Online Tool zur Checkliste
Familiärer Brust- und Eierstockkrebs:



Ausfüllhinweis

Zurück ist die Anzahl beider Krebserkrankungen bei den Geschwister- und Kindern einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie.

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

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

Die Summe aus dem Wert in Feld D und dem Wert in Feld A ergibt das Risiko-Score.

Eine Risikobewertung an den angegebenen Zahlen ist bei Score 2 3 Punkten zu empfehlen.

Diese Einschätzungen gelten nur in Kooperation mit den Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs bzw. mit den zertifizierten FBCS-Zentren, die diese im Rahmen der Wissenschaftlichen Vereinigung verfolgen. Bei weiteren Einzelheiten entsprechen den Vorgaben des Leitfadens Version 11, Januar 2022 (2) Akademie Krebserkrankungen Deutscher Krebsgesellschaft, Deutscher Gesellschaft für Strahlentherapie, Deutscher Krebsrat für Brust- und Eierstockkrebs

Quelle: Deutsche Krebsgesellschaft e.V.

Aktualisierte Version ab 01.01.2025

Hier ist das Online Tool zur Checkliste „Familiärer Brust- und Eierstockkrebs“ hinterlegt:

1. 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

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Risikoabschätzung für syndromassoziierte Mammakarzinome (non-BRCA)

Oxford

LoE	GR	AGO
2b	B	++

Eigen- und Familienanamnese über mindestens drei Generationen (mit Angabe des Ersterkrankungsalters)

- Typische Erkrankungen:
 - Mamma- und Ovarialkarzinom
- Weitere Erkrankungen, insbesondere:
 - Pankreas-, Schilddrüsen-, Kolorektal-, Magenkarzinom, hepato-biläres 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.
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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.



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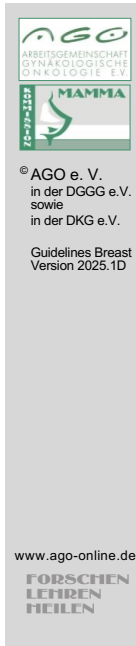
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Non BRCA-Associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

Syndrom	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

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.
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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 ++

- Nach Maßgabe des:
 - Gendiagnostikgesetzes
 - Medizinproduktegesetzes (z. B. Risikokalkulation)
- Anwendung von Software zur Risikokalkulation erfordert ein professionelles Training und Erfahrung (Software muss zertifiziert sein)
- Kommunikation und Abwägung 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

SOFTWARE (BOADICEA, IBIS):

1. Yang X, Mooij TM, Leslie G, et al. Validation of the BOADICEA model in a prospective cohort of BRCA1/2 pathogenic variant carriers. J Med Genet. 2024 Jul 19;61(8):803-809. doi: 10.1136/jmg-2024-109943. PMID: 38834293; PMCID: PMC11287562.

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Gegenwärtige klinische Bedeutung weiterer Risikogene und -varianten

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

	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	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
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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).

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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.
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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: <i>BRCA1, BRCA2, PALB2</i>			
▪ hoch und selten: <i>CDH1, PTEN, TP53, STK11</i>			
▪ moderat und häufig: <i>ATM, CHEK2</i>			
▪ moderat erhöht: <i>BARD1, NF1, RAD51C, RAD51D</i>			
Klinischer Nutzen* einer genetischen Untersuchung			
▪ <i>BRCA1, BRCA2</i>	1b	A	++**
▪ <i>PALB2</i>	3a	B	+**
▪ <i>CDH1, PTEN, TP53, STK11</i>	3b	B	+**
▪ <i>ATM, BARD1, CHEK2, RAD51C, RAD51D</i>	3a	B	+/-**

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

1. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer JAMA Oncol 2017;3:1190-1196.
2. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. Cancer 2017 May 15;123(10):1721-1730. doi: 10.1002/cncr.30498. Epub 2017 Jan 13
3. 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
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1. Tan MH, Mester JL, Ngeow J, et al: Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res*. 2012 Jan 15;18(2):400-7. doi: 10.1158/1078-0432.CCR-11-2283.
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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.
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1. Southey MC, Goldgar DE, Winqvist R et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. 2016 Dec;53(12):800-811. doi: 10.1136/jmedgenet-2016-103839.

RAD51C/D:

1. Yang X, Song H, Leslie G et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst. 2020 Dec 14;112(12):1242-1250. doi: 10.1093/jnci/djaa030. PMID: 32107557; PMCID: PMC7735771

TP53:

1. Kratz CP, Freycon C, Maxwell KN, et al. Analysis of the Li-Fraumeni Spectrum Based on an International Germline TP53 Variant Data Set: An International Agency for Research on Cancer TP53 Database Analysis. JAMA Oncol. 2021;7(12):1800-1805. doi:10.1001/jamaoncol.2021.4398

Klinischer Nutzen:

1. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science. 2014;343(6178):1466-70.
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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
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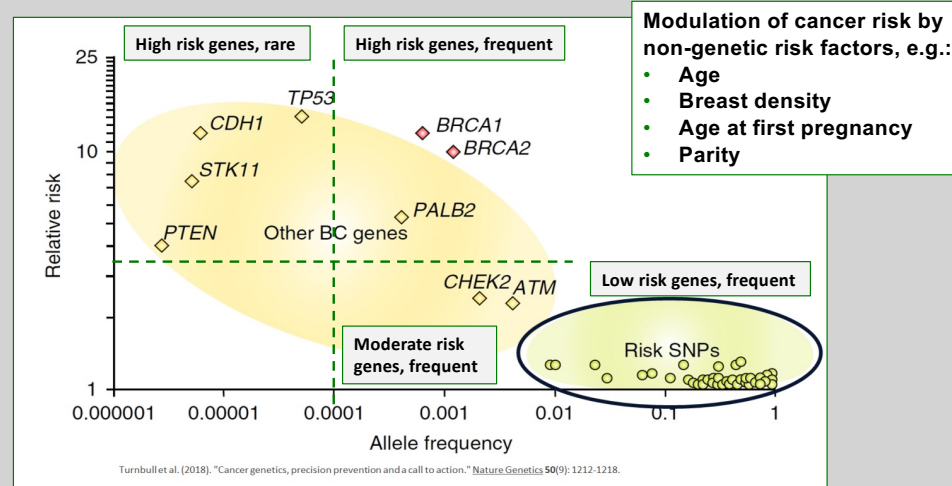
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9. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304(9):967-75.
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18. Rebbeck TR, Friebel 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.

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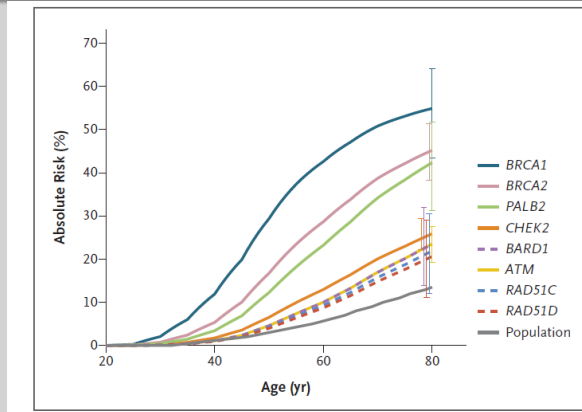
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Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes



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 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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ACMG/AMP Variant Classification Guidelines

(Tavtigian SV et al., Human Mutation, 2020)

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 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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Variant of Unknown Significance (VUS): Problems and Questions

- „A Variant of Unknown Significance (VUS) is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are extremely rare (≤ 3 families in $> 80\%$ of variants)
- Classification of sequence variants should be performed according to ACMG/ClinGen and genspecific recommendations should be taken into account
- Frequency of VUS increases with numbers of tested genes
- In silico prediction tools alone are not adequate or sufficient for clinical decision making
- The classification of variants should always be based on all available, preferentially quantitative, information including data from functional analyses, segregation analyses, large case-control studies and population databases such as gnomAD should be taken into account.

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Multimodales intensiviertes Früherkennungs- und Nachsorgeprogramm (IFNP)

	Oxford		
	LoE	GR	AGO
<p>Das IFNP unter Hinzunahme von MRT, Mammasonographie und Mammographie</p> <ul style="list-style-type: none"> ▪ sollte für <i>BRCA1/2</i> pV Trägerinnen ▪ kann für pV Trägerinnen anderer Risikogene für das Mammakarzinom ▪ kann für Frauen mit familiärer Belastung und ohne pV Nachweis zwischen 30 und 50 Jahren mit einem Mammakarzinomrisiko von $\geq 5\%$ in 10 Jahren ▪ kann für an Brustkrebs erkrankte Frauen mit ED ≤ 45 Jahren mit familiärer Belastung und ohne pV Nachweis <p>im Rahmen einer systematisch erhobenen, transparenten Qualitätssicherung und entsprechenden Ergebnisevaluation erfolgen.</p>			++
Zum Nachweis früher Tumorstadien	2b	B	++
Zur Verbesserung des metastasenfren Überlebens	2b	B	+
Zur Mortalitätsreduktion	3a	C	+/-
Z. n. therapeutischer Radiatio der Brustwand im Kindes- und Jugendalter (z. B. M. Hodgkin, siehe S3-Leitlinie M. Hodgkin) können in das IFNP aufgenommen werden.			

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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 (%)
<i>BRCA1</i>	43.2	29.4	21.8	25.5	30.5	33.3
<i>BRCA2</i>	22.7	23.3	24.3	27.5	16.3	23.5
<i>BRCA1/2</i> -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 (healthy women).

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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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

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Früherkennungsprogramm für Männer mit *BRCA1/2* Mutationen*

	Oxford		
	LoE	GR	AGO
Bei <i>BRCA1/2</i> -Mutation: Aufklärung über Erkrankungsrisiken auch für männliche Familienangehörige	5	D	++
Für Brustkrebs: Selbstuntersuchung	5	D	+
Für Prostatakarzinom: siehe S3-Leitlinie Prostatakarzinom	5	D	++

Aktuell kein spezifisches Brustkrebs-Früherkennungsprogramm → Krebsfrüherkennungsuntersuchung im Rahmen der Regelversorgung

- Bei *BRCA1/2*-Mutation: Aufklärung über Erkrankungsrisiken auch für männliche Familienangehörige
- Für Brustkrebs: Selbstuntersuchung
- Für Prostatakarzinom: siehe S3-Leitlinie Prostatakarzinom

Das Lebenszeitrisiko für Brustkrebs liegt in der männlichen Allgemeinbevölkerung bei ca. 0,1 %, das Lebenszeitrisiko für Prostatakrebs liegt bei 10-12 %.

BRCA1 Mutationsträger haben ein Erkrankungsrisiko für Brustkrebs bis 80 Jahre von ca. 0,4 %, ein dem Risiko der Allgemeinbevölkerung entsprechendes Prostatakarzinomrisiko.

BRCA2 Mutationsträger haben ein ca. 4%iges Lebenszeitrisiko für Brustkrebs, ein ca. 30%iges Lebenszeitrisiko für ein Prostatakarzinom.

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

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Chirurgische Prävention

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Risiko-reduzierende, unilaterale oder bilaterale Mastektomie (RRME) ohne Vorliegen von genetischen Risikofaktoren (führt nicht zu einer Mortalitätsreduktion) 	2a	B	-
<ul style="list-style-type: none"> ▪ Axilladisektion oder Sentinel-Lymphknoten Exzision bei RRME 	2a	B	--

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](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	GR	AGO
<ul style="list-style-type: none"> ▪ Risiko-reduzierende bilaterale Salpingo-Oophorektomie (RR-BSO)** <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 <i>BRCA1</i> 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.
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.
10. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2001;345(3):159-64.
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.
13. Xiao YL, Wang K, Liu Q, Li J, Zhang X, Li HY. Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review. *Clin Breast Cancer*. 2019 Feb;19(1):e48-e65. doi: 10.1016/j.clbc.2018.09.011. Epub 2018 Oct 4. PMID: 30470623.

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

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Risikoreduzierende Salpingo-Oophorektomie (RRSO, RR-BSO) <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.
2. 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.
3. 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.
4. Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol.* 2009;27(35):5887-92.
5. 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.
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8. McGee J, Giannakeas V, Karlan B, et al. Risk of breast cancer after a diagnosis of ovarian cancer in BRCA mutation carriers: is preventive mastectomy warranted? *Gynecol Oncol*. 2017 May;145(2):346–351.
9. Metcalfe K, Gershman S, Ghadirian P, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *BMJ*. 2014;348:g226.
10. Metcalfe K, Lynch HT, Foulkes WD, et al. Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. *JAMA Oncol*. 2015;1(3):306-13.
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14. Rhiem K, Engel C, Graeser M, et al. The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. *Breast Cancer Res*. 2012;14(6):R156.
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
16. Metcalfe K et. Al (GS02-04) Surgical Treatment of Women with Breast Cancer and a BRCA1 Mutation: An International Analysis of the Impact of Bilateral Mastectomy on Survival. *SABCS 2023*

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.

1. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* 2015;16(1):67-75.
2. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet.* 2020;395(10218):117–122. doi:10.1016/S0140-6736(19)32955-1
3. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet.* 2016;387(10021):866-73.
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6. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA.* 2006;295(23):2727-41.