Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

FORSCHEN
LEHREN
HEILEN

Breast Cancer Risk, Genetics and Prevention

Breast Cancer Risk and Prevention

Guidelines Breast
Version 2024.1E

- **Versions 2003–2023:**
  Albert / Bischoff / Blohmer / Dall / Ditsch / Fasching / Fehm / Gerber / Kiechle / Maass / Müller-Schimpfle / Mundhenke / Park-Simon / Rhiem / Rody / Schmidt / Schmutzler / Schütz / Stickeler / Thomssen / Witzel

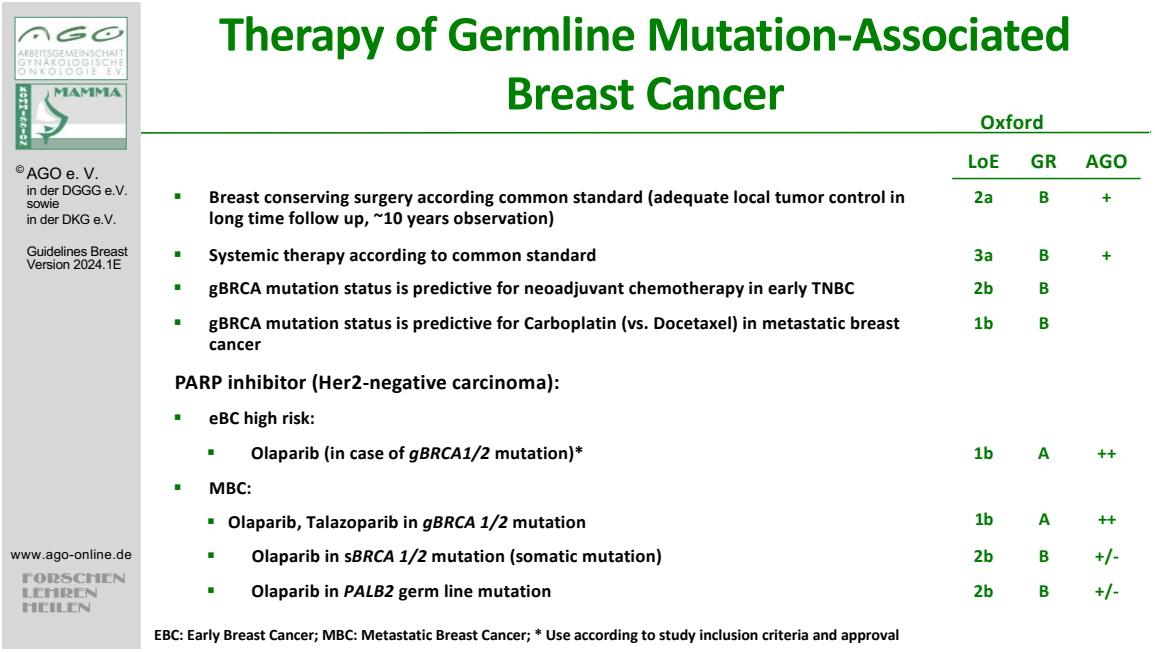
- **Version 2024:**
  Gluz / Untch

Guidelines Breast
Version 2024.1D

gBRCA-Testing – Therapeutic Consequences

Oxford LoE: 1b GR: A AGO: ++

gBRCA-Testing should be performed irrespective of family history, if it has therapeutic consequences



Therapy of Germline Mutation-Associated Breast Cancer

	Oxford LoE	GR	AGO
▪ Breast conserving surgery according common standard (adequate local tumor control in long time follow up, ~10 years observation)	2a	B	+
▪ Systemic therapy according to common standard	3a	B	+
▪ gBRCA mutation status is predictive for neoadjuvant chemotherapy in early TNBC	2b	B	
▪ gBRCA mutation status is predictive for Carboplatin (vs. Docetaxel) in metastatic breast cancer	1b	B	
PARP inhibitor (Her2-negative carcinoma):			
▪ eBC high risk:			
▪ Olaparib (in case of *gBRCA1/2* mutation)*	1b	A	++
▪ MBC:			
▪ Olaparib, Talazoparib in *gBRCA 1/2* mutation	1b	A	++
▪ Olaparib in s*BRCA 1/2* mutation (somatic mutation)	2b	B	+/-
▪ Olaparib in *PALB2* germ line mutation	2b	B	+/-

EBC: Early Breast Cancer; MBC: Metastatic Breast Cancer; * Use according to study inclusion criteria and approval

BCS bei BRCA 1/2 Mutationsträgern

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2. 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.
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PARP-inhibitors eBC high-risk

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PARP-inhibitors mBC

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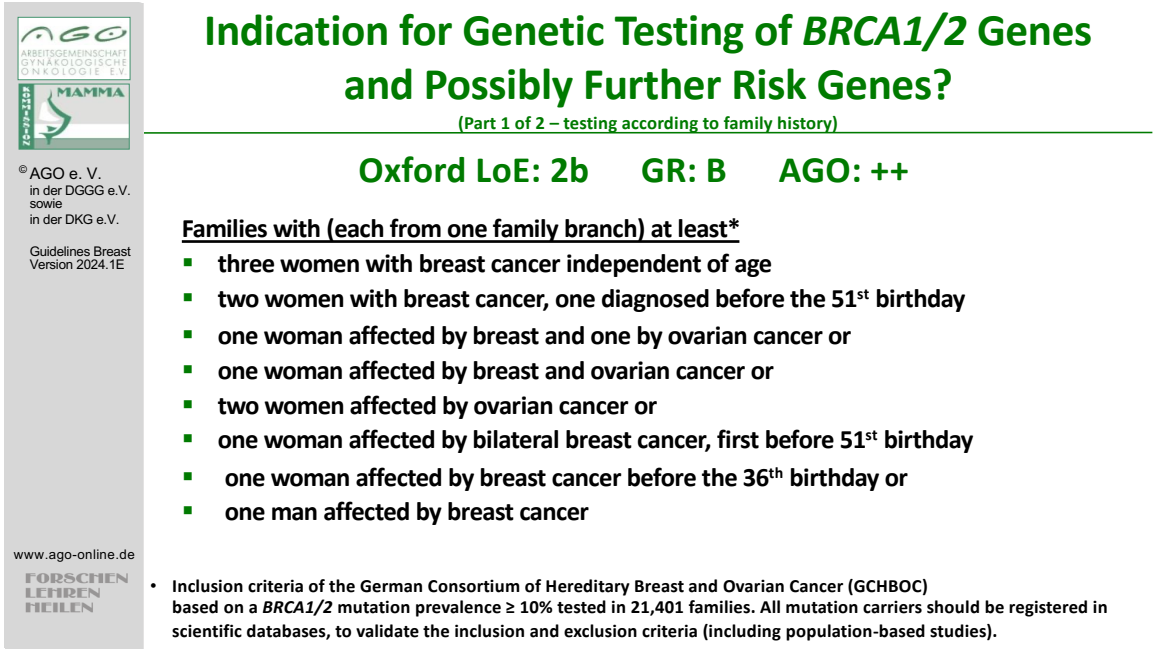
PARP-inhibitors mBC gPALB2mut

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.



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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).
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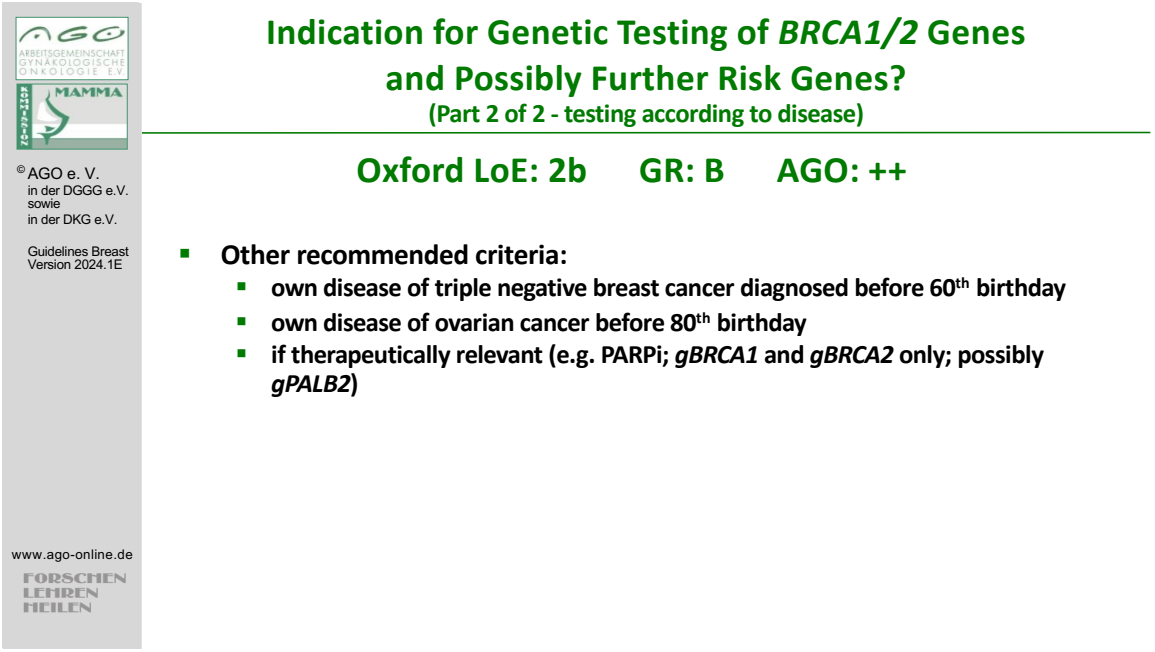

Indication for Genetic Testing of *BRCA1/2* Genes and Possibly Further Risk Genes?

(Part 2 of 2 - testing according to disease)

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

- **Other recommended criteria:**
  - **own disease of triple negative breast cancer diagnosed before 60th birthday**
  - **own disease of ovarian cancer before 80th birthday**
  - **if therapeutically relevant (e.g. PARPi; *gBRCA1* and *gBRCA2* only; possibly *gPALB2*)**

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
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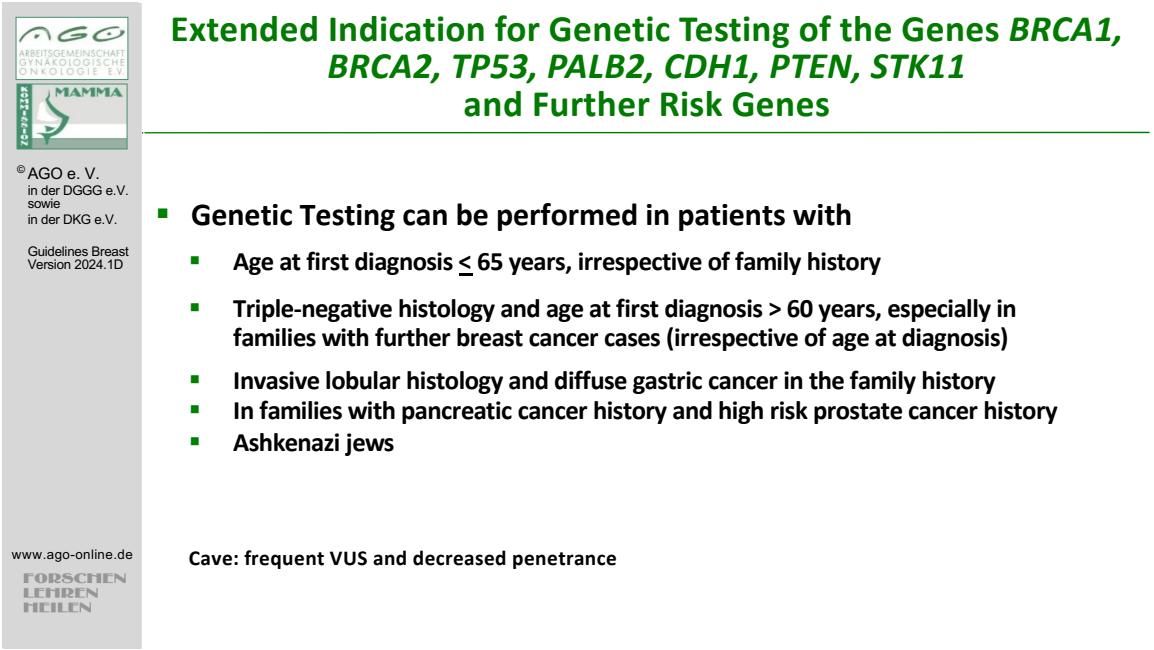

Literatur:

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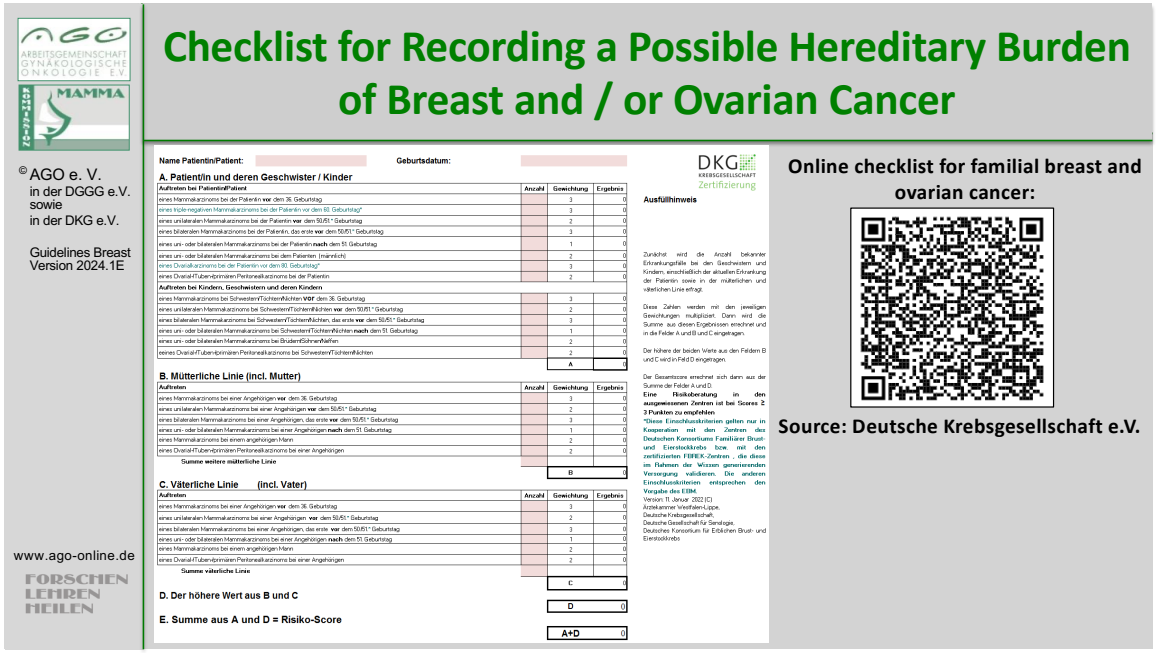

Hier ist das Online Tool zur Checkliste „Familiärer Brust- und Eierstockkrebs“ hinterlegt:
https://www.krebsgesellschaft.de/zertdokumente.html?file=files/dkg/deutsche-krebsgesellschaft/content/pdf/Zertifizierung/Checklisten-und-Algorithmen/checkliste_erbliche_belastung_brust_gyn-220118.xlsx&cid=98969

Referenzen:

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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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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.
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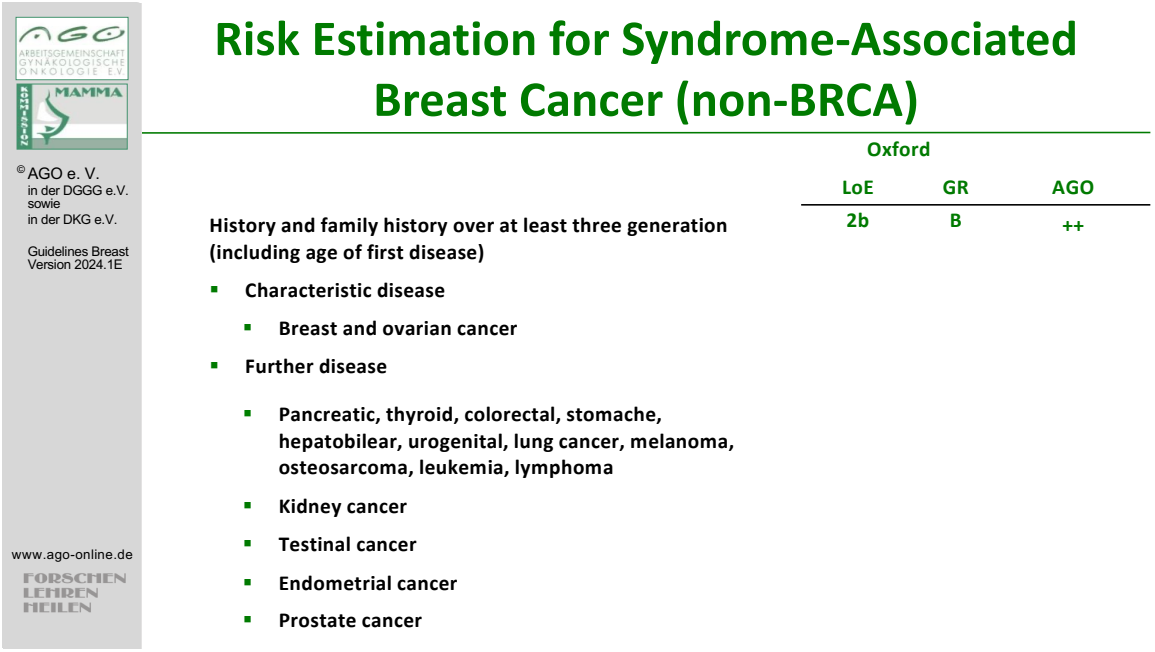

Risk Estimation for Syndrome-Associated Breast Cancer (non-BRCA)

	Oxford		
	LoE	GR	AGO
History and family history over at least three generation (including age of first disease)	2b	B	++

- **Characteristic disease**
  - **Breast and ovarian cancer**
- **Further disease**
  - **Pancreatic, thyroid, colorectal, stomache, hepatobilear, urogenital, lung cancer, melanoma, osteosarcoma, leukemia, lymphoma**
  - **Kidney cancer**
  - **Testinal cancer**
  - **Endometrial cancer**
  - **Prostate cancer**

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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
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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.
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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.
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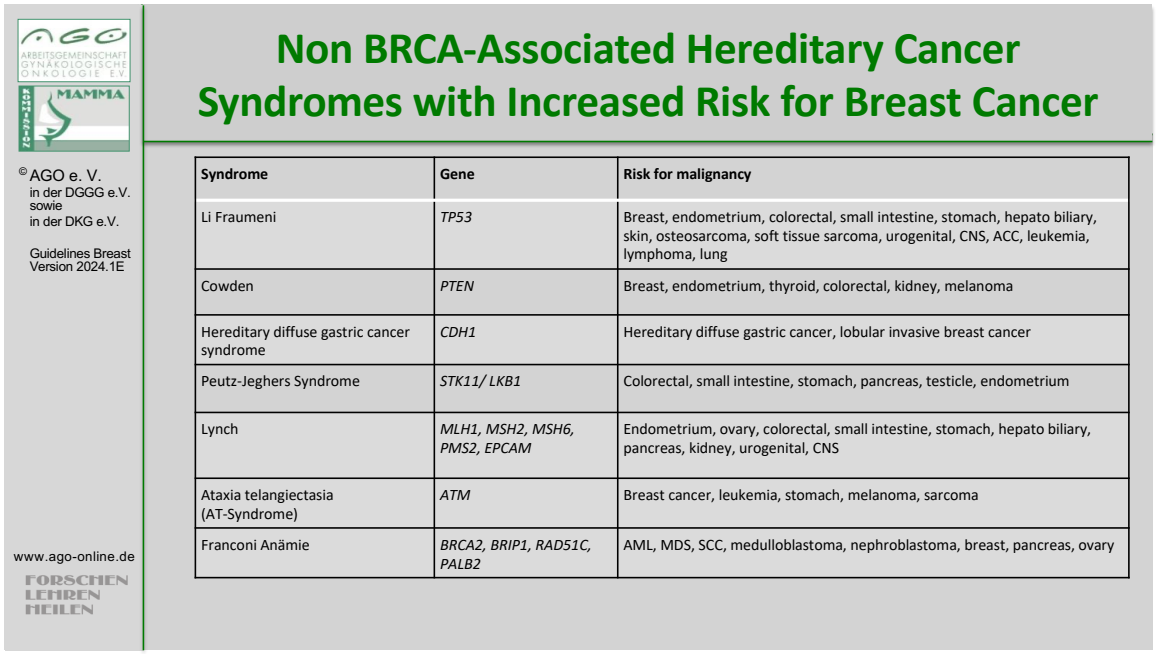
12. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015;33(26):2901-7.
13. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer 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
Franconi 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
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4. di Masi A, Antoccia A. NBS1 Heterozygosity and Cancer Risk. Curr Genomics. 2008;9(4):275-81.
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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.
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Non-Directive Counseling Regarding Preventive Measures

AGO ++

According to:

- **The Genetic Diagnostic Law**
- **The Medical Devices Act (e.g. risk assessment)**
- **Application of software for risk calculation requires professional training and experience**

Communicate:

- **Absolute cancer risks within a manageable timeframe**
- **Risk and benefit of a multimodal intensive surveillance program**
- **Risk and benefit of preventive clinical methods**
- **Competing risks, e.g. risk of disease progression in relation to risk of a secondary primary in case women already affected by primary breast cancer**

Allow appropriate time for consideration

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)

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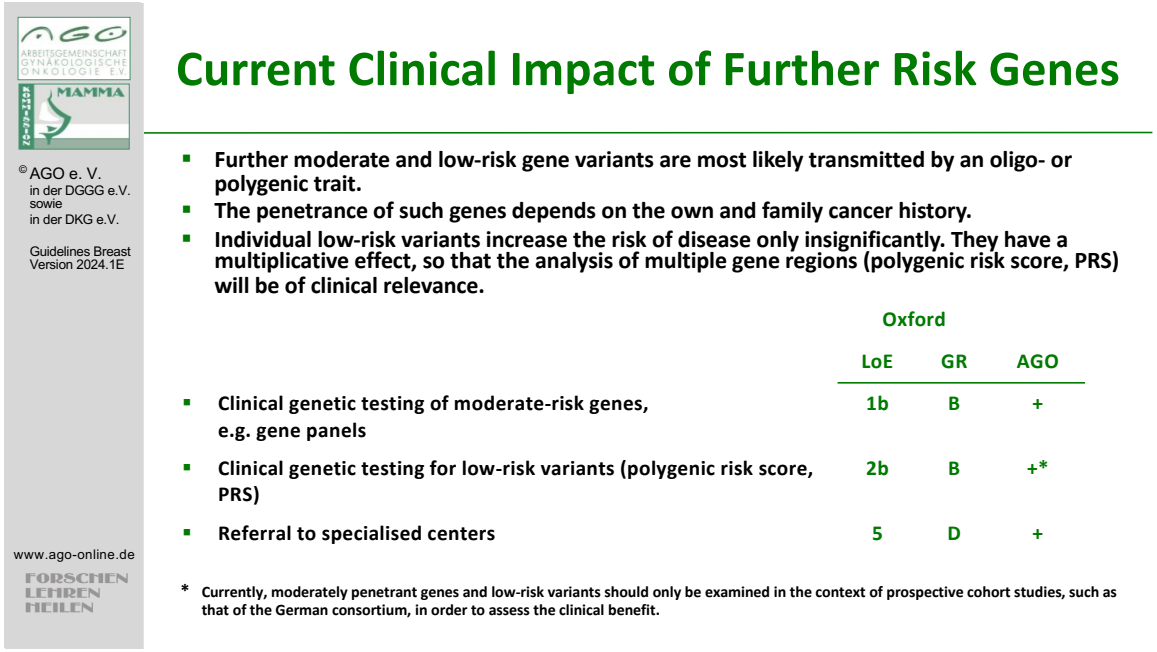

Current Clinical Impact of Further Risk Genes

- **Further moderate and low-risk gene variants are most likely transmitted by an oligo- or polygenic trait.**
- **The penetrance of such genes depends on the own and family cancer history.**
- **Individual low-risk variants increase the risk of disease only insignificantly. They have a multiplicative effect, so that the analysis of multiple gene regions (polygenic risk score, PRS) will be of clinical relevance.**

	Oxford		
	LoE	GR	AGO
▪ Clinical genetic testing of moderate-risk genes, e.g. gene panels	1b	B	+
▪ Clinical genetic testing for low-risk variants (polygenic risk score, PRS)	2b	B	+*
▪ Referral to specialised centers	5	D	+

* Currently, moderately penetrant genes and low-risk variants should only be examined in the context of prospective cohort studies, such as that of the German consortium, in order to assess the clinical benefit.

Analyse von moderaten Risikogenen e.g. Genpanel

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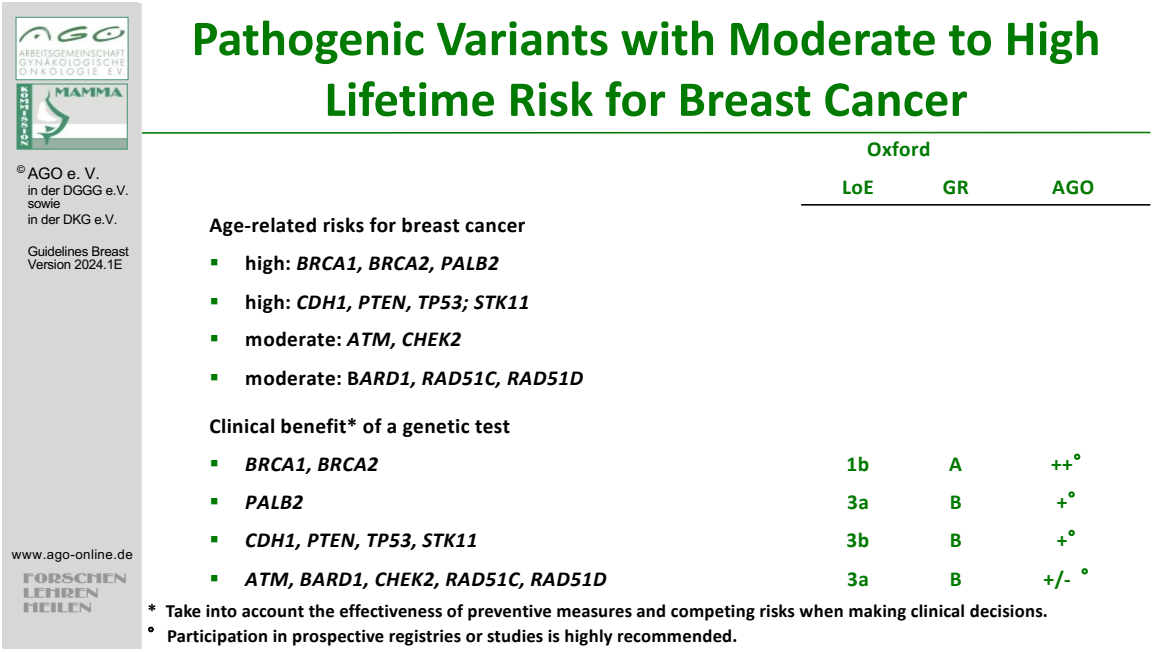

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FORSCHEN
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HEILEN

Pathogenic Variants with Moderate to High Lifetime Risk for Breast Cancer

	Oxford		
	LoE	GR	AGO
Age-related risks for breast cancer			
▪ high: ***BRCA1, BRCA2, PALB2***			
▪ high: ***CDH1, PTEN, TP53; STK11***			
▪ moderate: ***ATM, CHEK2***			
▪ moderate: B***ARD1, RAD51C, RAD51D***			
Clinical benefit* of a genetic test			
▪ ***BRCA1, BRCA2***	1b	A	++°
▪ ***PALB2***	3a	B	+°
▪ ***CDH1, PTEN, TP53, STK11***	3b	B	+°
▪ ***ATM, BARD1, CHEK2, RAD51C, RAD51D***	3a	B	+/- °

* Take into account the effectiveness of preventive measures and competing risks when making clinical decisions.
° Participation in prospective registries or studies is highly recommended.

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State of research: Relevance of Genetic and non-Genetic Risk Factors

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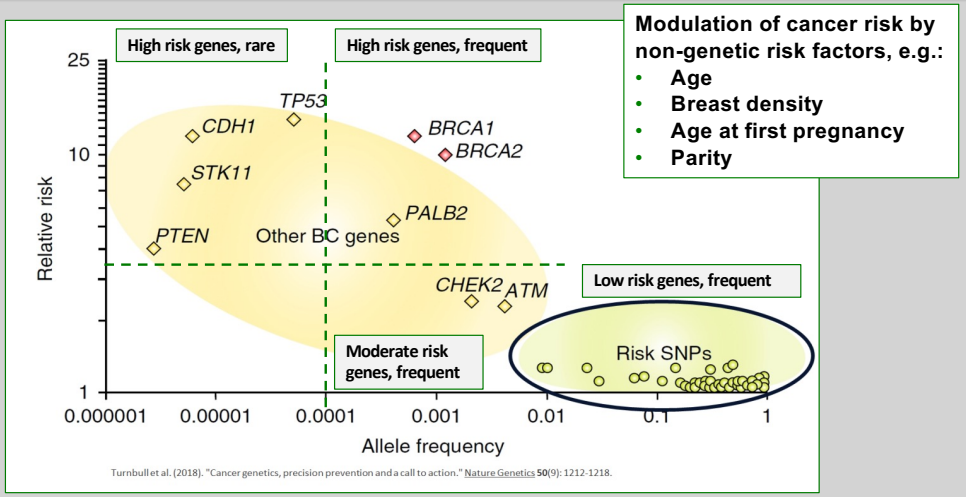

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Estimated Cumulative Risk of Breast Cancer with Protein-Truncating Variants in 8 Genes

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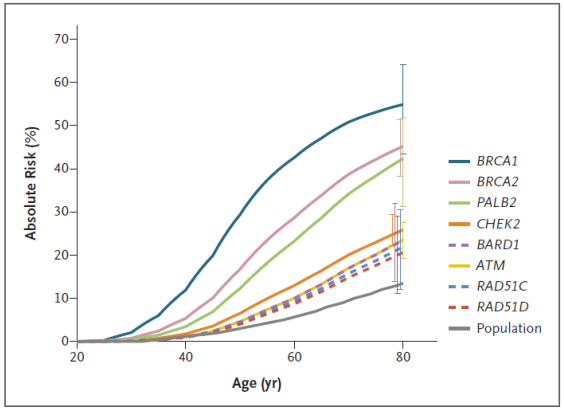

Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population 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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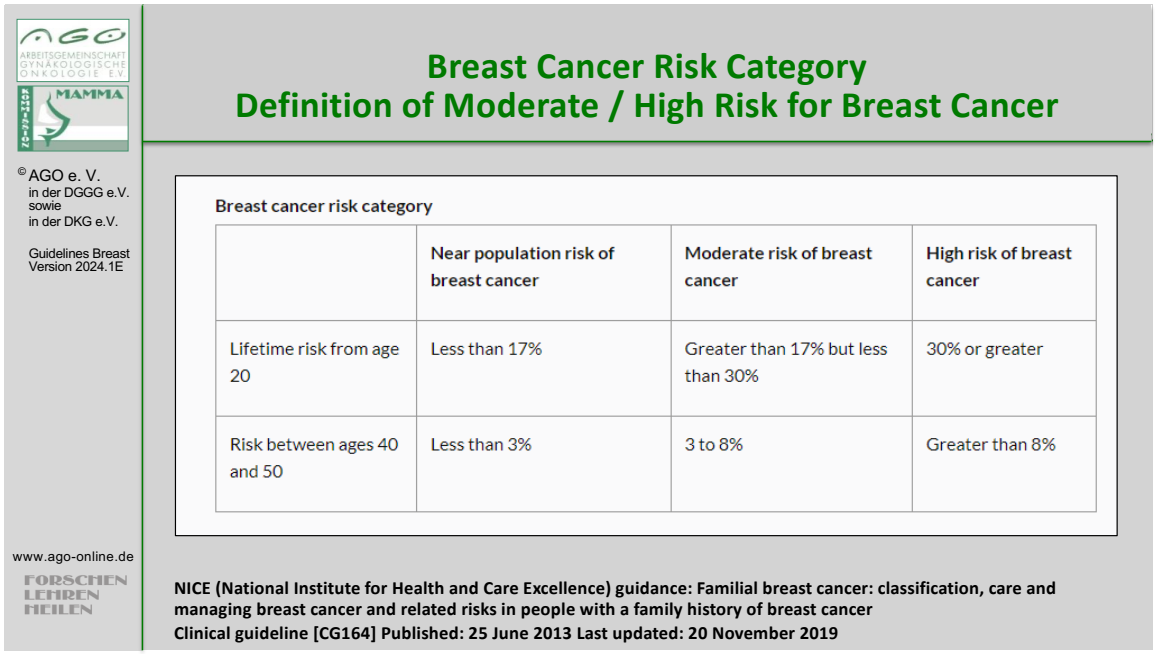

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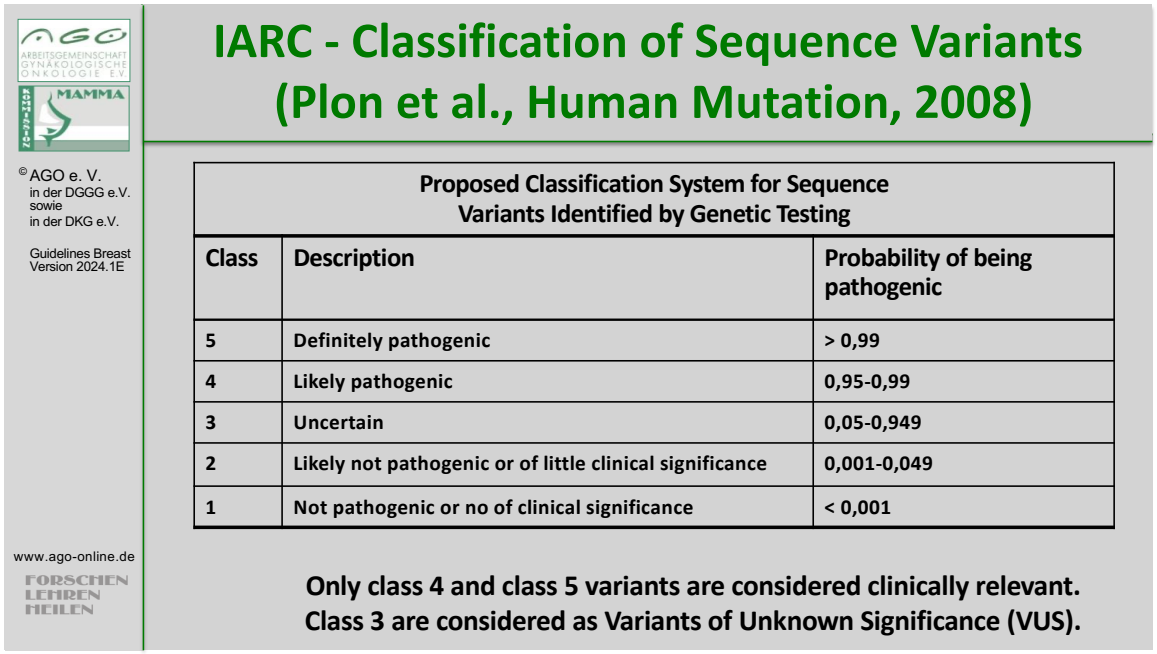

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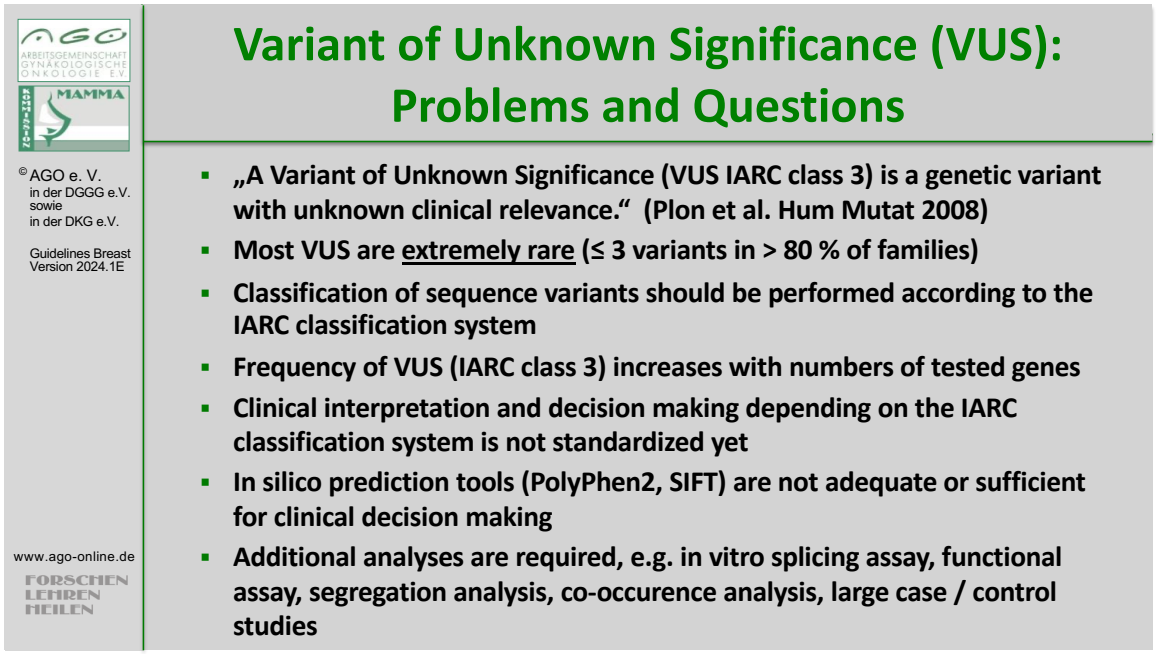

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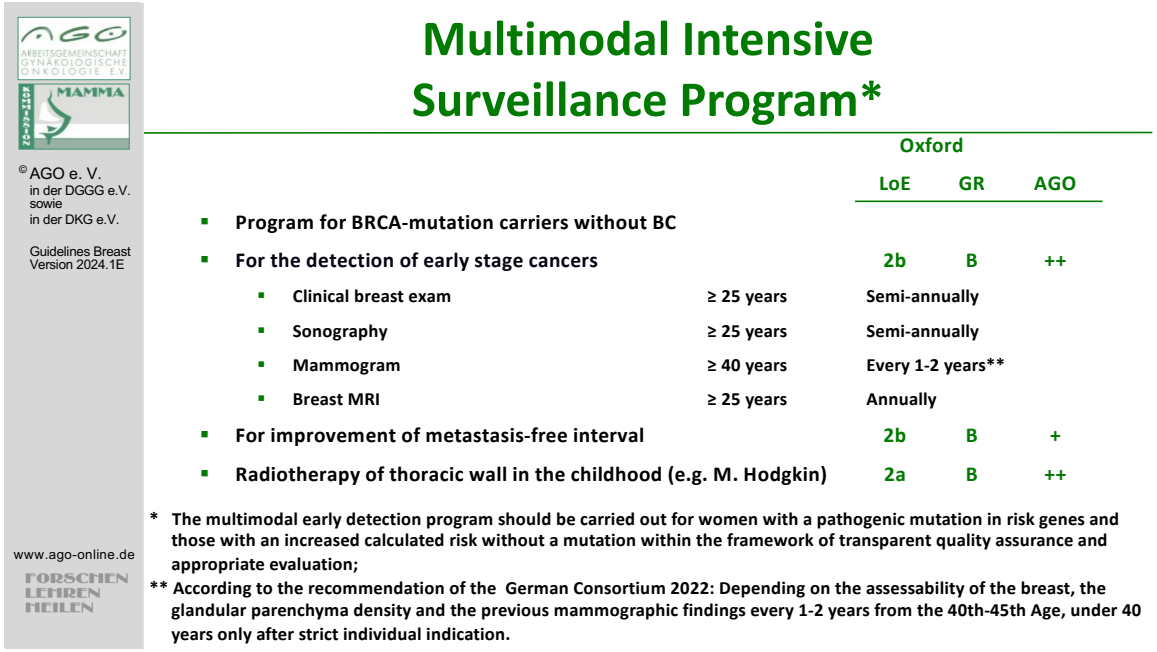

Multimodal Intensive Surveillance Program*

		Oxford LoE	GR	AGO
▪ Program for BRCA-mutation carriers without BC				
▪ For the detection of early stage cancers		2b	B	++
▪ Clinical breast exam	≥ 25 years	Semi-annually		
▪ Sonography	≥ 25 years	Semi-annually		
▪ Mammogram	≥ 40 years	Every 1-2 years**		
▪ Breast MRI	≥ 25 years	Annually		
▪ For improvement of metastasis-free interval		2b	B	+
▪ Radiotherapy of thoracic wall in the childhood (e.g. M. Hodgkin)		2a	B	++

* The multimodal early detection program should be carried out for women with a pathogenic mutation in risk genes and those with an increased calculated risk without a mutation within the framework of transparent quality assurance and appropriate evaluation;

** According to the recommendation of the German Consortium 2022: Depending on the assessability of the breast, the glandular parenchyma density and the previous mammographic findings every 1-2 years from the 40th-45th Age, under 40 years only after strict individual indication.

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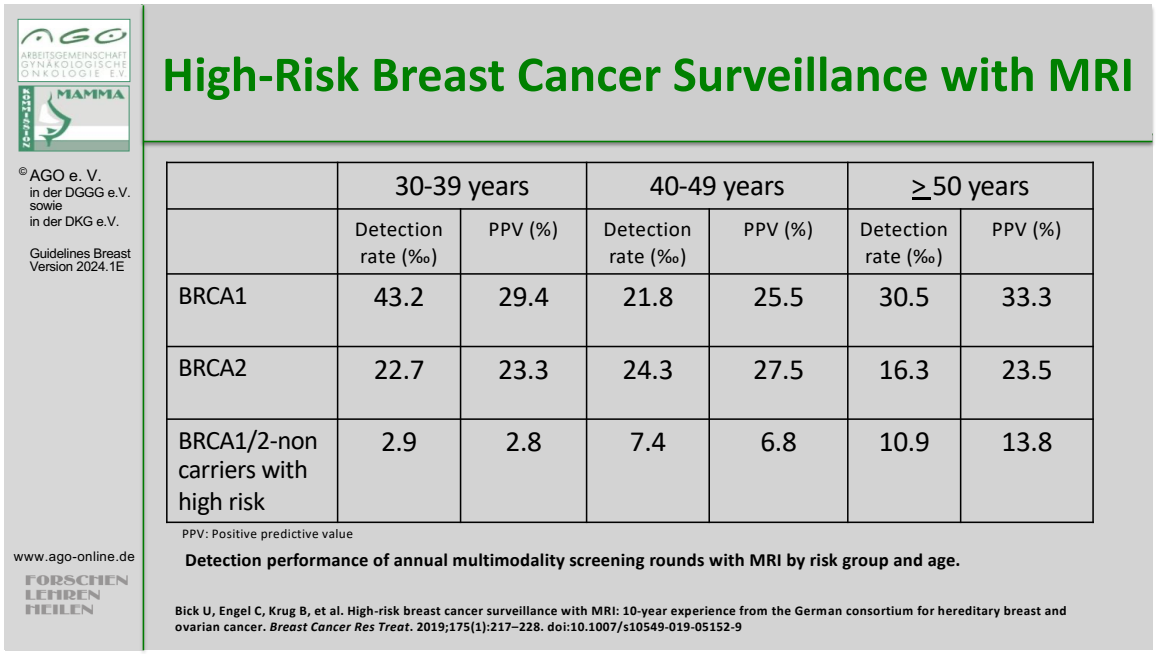

High-Risk Breast Cancer Surveillance with MRI

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

PPV: Positive predictive value

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

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

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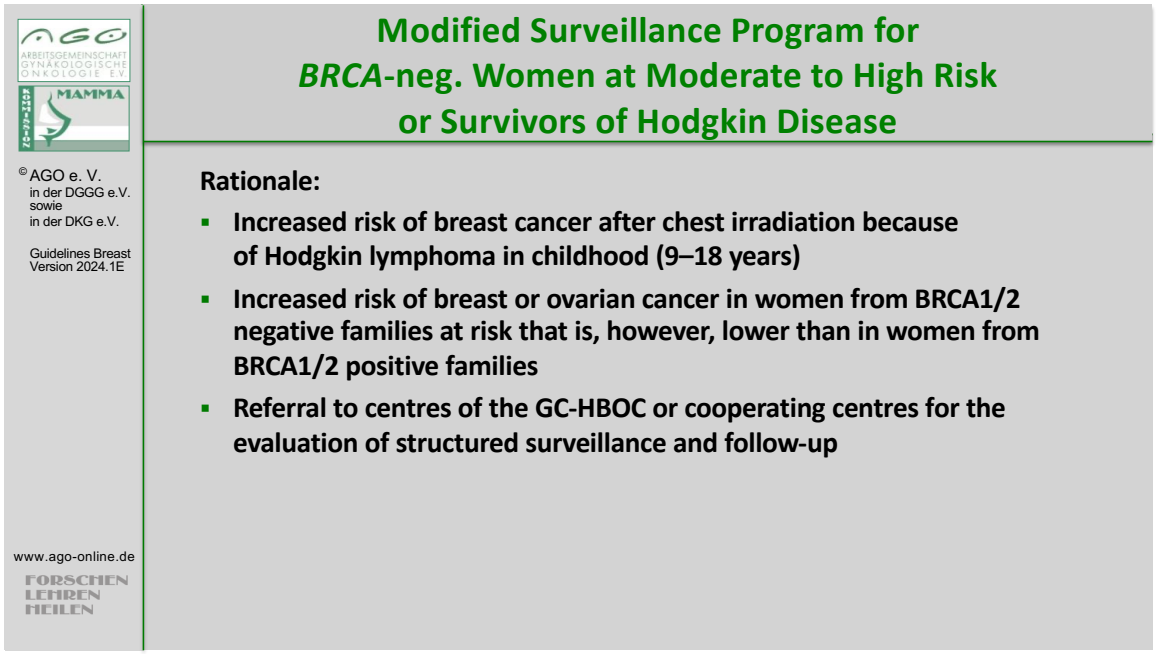

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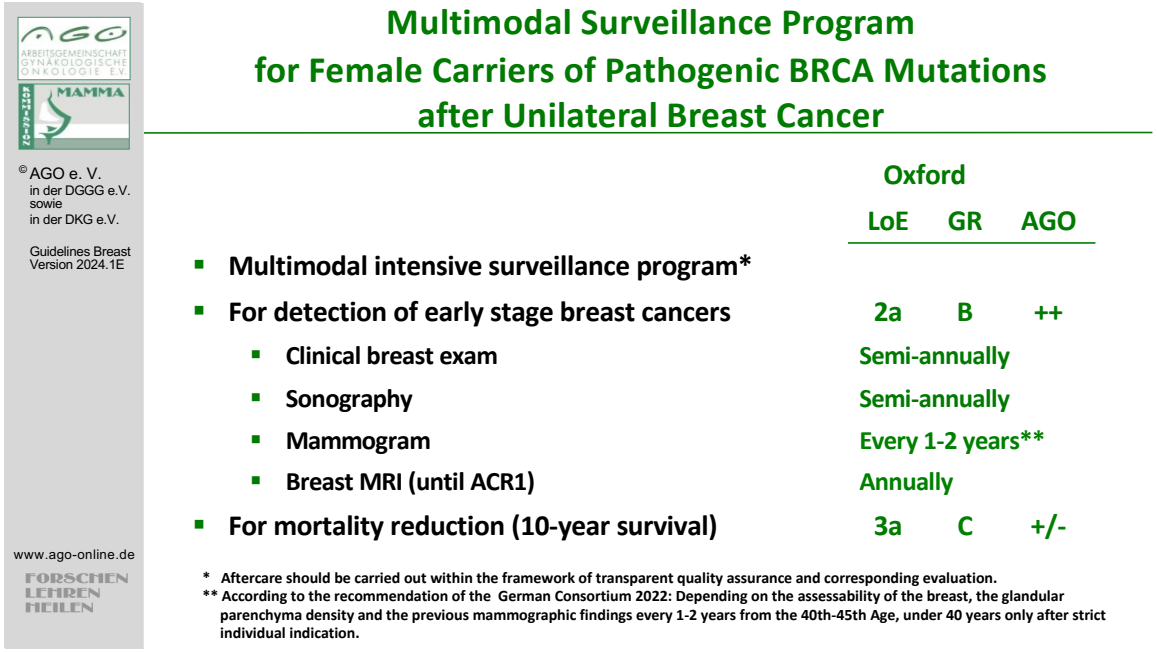

Multimodal Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Unilateral Breast Cancer

	Oxford LoE	GR	AGO
▪ **Multimodal intensive surveillance program***			
▪ **For detection of early stage breast cancers**	2a	B	++
▪ **Clinical breast exam**	Semi-annually		
▪ **Sonography**	Semi-annually		
▪ **Mammogram**	Every 1-2 years**		
▪ **Breast MRI (until ACR1)**	Annually		
▪ **For mortality reduction (10-year survival)**	3a	C	+/-

* Aftercare should be carried out within the framework of transparent quality assurance and corresponding evaluation.
** According to the recommendation of the German Consortium 2022: Depending on the assessability of the breast, the glandular parenchyma density and the previous mammographic findings every 1-2 years from the 40th-45th Age, under 40 years only after strict individual indication.

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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Surveillance for Male Carriers of Pathogenic BRCA Mutations*

	Oxford		
	LoE	GR	AGO
Currently, no specific surveillance is recommended → Early detection of cancer as part of standard care			
▪ **BRCA1/2 mutation carrier: explanation of risks for cancer disease including male family members**	5	D	++
▪ **For breast cancer: self examination**	5	D	+
▪ **For prostate cancer: Compare German Guideline program**	5	D	+

The lifetime risk of breast cancer in the general male population is 0.1%. *BRCA1* mutation carriers have a risk of breast cancer of about 1% and an up to 1.8 to 3.75 times higher risk for prostatic cancer ≤ 65y. *BRCA 2* mutation carriers have an up to 5–7% lifetime risk for breast cancer and an up to 2.5 to 8.6 times higher risk for prostatic cancer ≤ 65y.

* **Follow-up care / surveillance should be carried out as part of transparent quality assurance and appropriate evaluation.**

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8. Mikropoulos C, Selkirk CGH, Saya S, et al. Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition. Br J Cancer. 2018 Jan;118(2):266-276. doi: 10.1038/bjc.2017.429. Epub 2018 Jan 4. Erratum in: Br J Cancer. 2018 Mar 06.

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Surgical Prevention

	Oxford		
	LoE	GR	AGO
▪ **Risk-reducing unilateral or bilateral mastectomy (RRME) without the presence of clearly defined genetic risk factors**	2a	B	-*
▪ **Axillary dissection or Sentinel lymph node excision during RRME**	2a	B	--

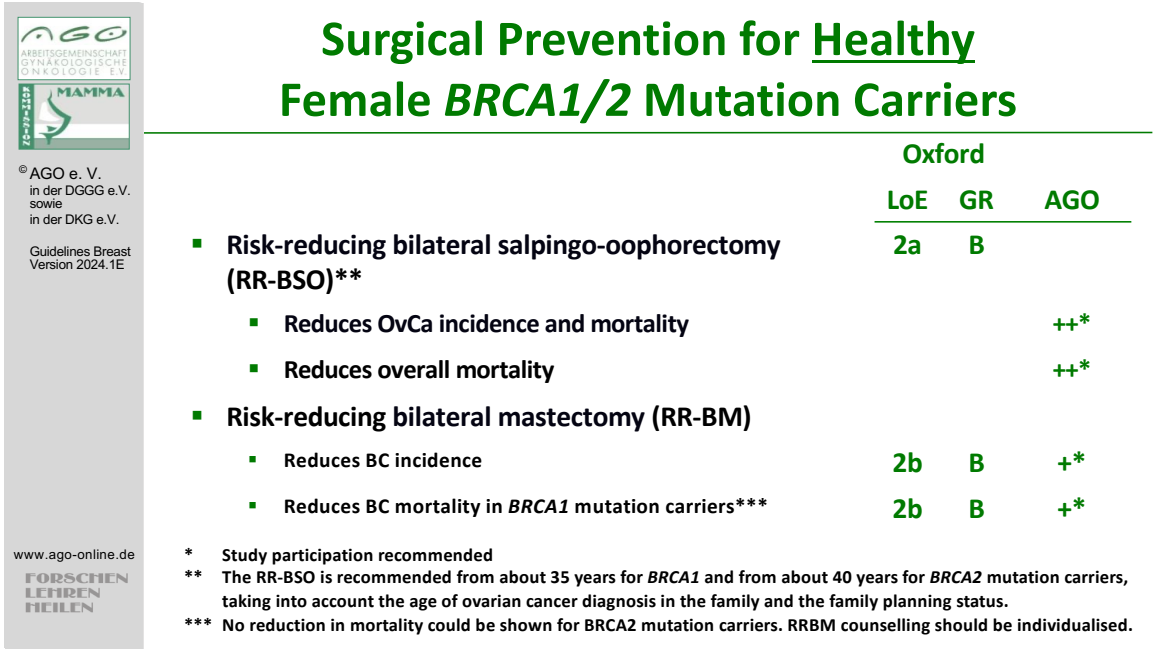
* **study participation recommended**

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.



Surgical Prevention for Healthy Female *BRCA1/2* Mutation Carriers

	Oxford LoE	Oxford GR	AGO
▪ **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)****	2a	B	
▪ **Reduces OvCa incidence and mortality**			++*
▪ **Reduces overall mortality**			++*
▪ **Risk-reducing bilateral mastectomy (RR-BM)**			
▪ **Reduces BC incidence**	2b	B	+*
▪ **Reduces BC mortality in *BRCA1* mutation carriers*****	2b	B	+*

* **Study participation recommended**
** **The RR-BSO is recommended from about 35 years for *BRCA1* and from about 40 years for *BRCA2* mutation carriers, taking into account the age of ovarian cancer diagnosis in the family and the family planning status.**
*** **No reduction in mortality could be shown for BRCA2 mutation carriers. RRBM counselling should be individualised.**

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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.
8. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev.

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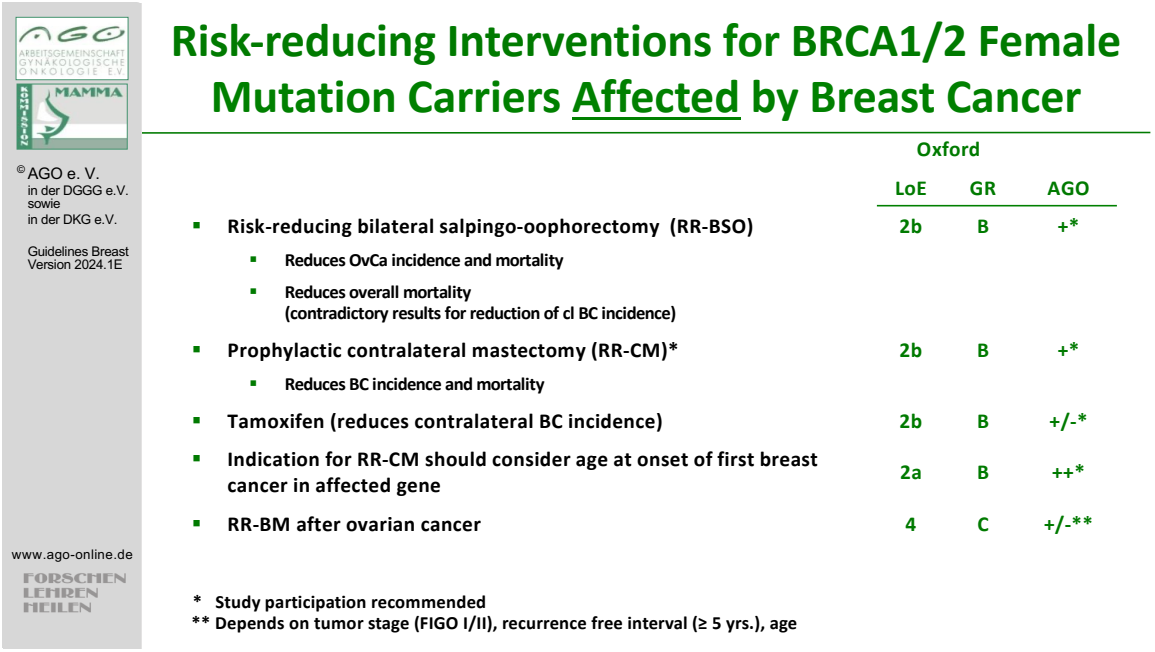

Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Risk-reducing bilateral salpingo-oophorectomy (RR-BSO)	2b	B	+*
▪ Reduces OvCa incidence and mortality			
▪ Reduces overall mortality (contradictory results for reduction of cl BC incidence)			
▪ Prophylactic contralateral mastectomy (RR-CM)*	2b	B	+*
▪ Reduces BC incidence and mortality			
▪ Tamoxifen (reduces contralateral BC incidence)	2b	B	+/-*
▪ Indication for RR-CM should consider age at onset of first breast cancer in affected gene	2a	B	++*
▪ RR-BM after ovarian cancer	4	C	+/-**

* Study participation recommended
** Depends on tumor stage (FIGO I/II), recurrence free interval (≥ 5 yrs.), age

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.
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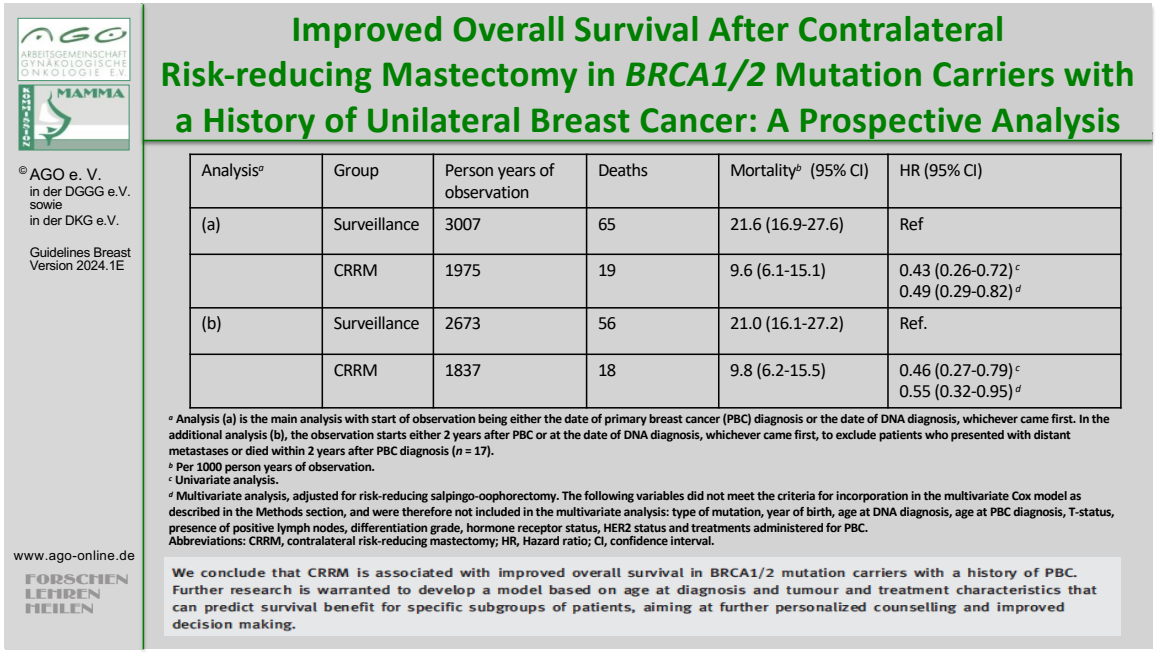

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in *BRCA1/2* Mutation Carriers with a History of Unilateral Breast Cancer: A Prospective Analysis

Analysis[a]	Group	Person years of observation	Deaths	Mortality[b] (95% CI)	HR (95% CI)
(a)	Surveillance	3007	65	21.6 (16.9-27.6)	Ref
	CRRM	1975	19	9.6 (6.1-15.1)	0.43 (0.26-0.72)[c] 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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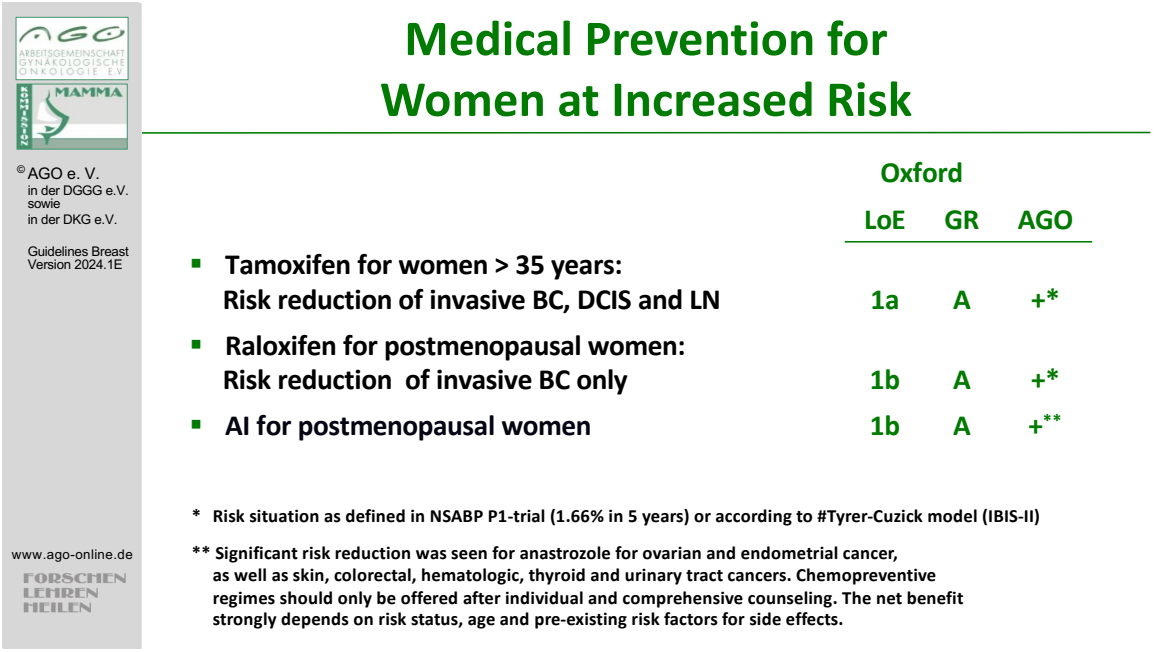

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