Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2024.1E

Breast Cancer Risk, Genetics and Prevention

Breast Cancer Risk and Prevention

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- **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

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gBRCA-Testing – Therapeutic Consequences

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

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

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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

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

(Part 1 of 2 – testing according to family history)

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

Families with (each from one family branch) at least*

- three women with breast cancer independent of age
- two women with breast cancer, one diagnosed before the 51st birthday
- one woman affected by breast and one by ovarian cancer or
- one woman affected by breast and ovarian cancer or
- two women affected by ovarian cancer or
- one woman affected by bilateral breast cancer, first before 51st birthday
- one woman affected by breast cancer before the 36th birthday or
- one man affected by breast cancer

- Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a *BRCA1/2* mutation prevalence ≥ 10% tested in 21,401 families. All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria (including population-based studies).

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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)

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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*)**

Extended Indication for Genetic Testing of the Genes *BRCA1, BRCA2, TP53, PALB2, CDH1, PTEN, STK11* and Further Risk Genes

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- **Genetic Testing can be performed in patients with**
  - **Age at first diagnosis ≤ 65 years, irrespective of family history**
  - **Triple-negative histology and age at first diagnosis > 60 years, especially in families with further breast cancer cases (irrespective of age at diagnosis)**
  - **Invasive lobular histology and diffuse gastric cancer in the family history**
  - **In families with pancreatic cancer history and high risk prostate cancer history**
  - **Ashkenazi jews**

Cave: frequent VUS and decreased penetrance

Checklist for Recording a Possible Hereditary Burden of Breast and / or Ovarian Cancer

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Name Patientin/Patient: **Geburtsdatum:**

DKG KREBSGESELLSCHAFT Zertifizierung

A. Patient/in 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 Ovarialkarzinoms 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
eeines 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 eingetragen.

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 checklist for familial breast and ovarian cancer:

Source: Deutsche Krebsgesellschaft e.V.

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

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

Oxford		
LoE	GR	AGO
2b	B	++

History and family history over at least three generation (including age of first disease)

- **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**

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

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Non-Directive Counseling Regarding Preventive Measures

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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

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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.

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.

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

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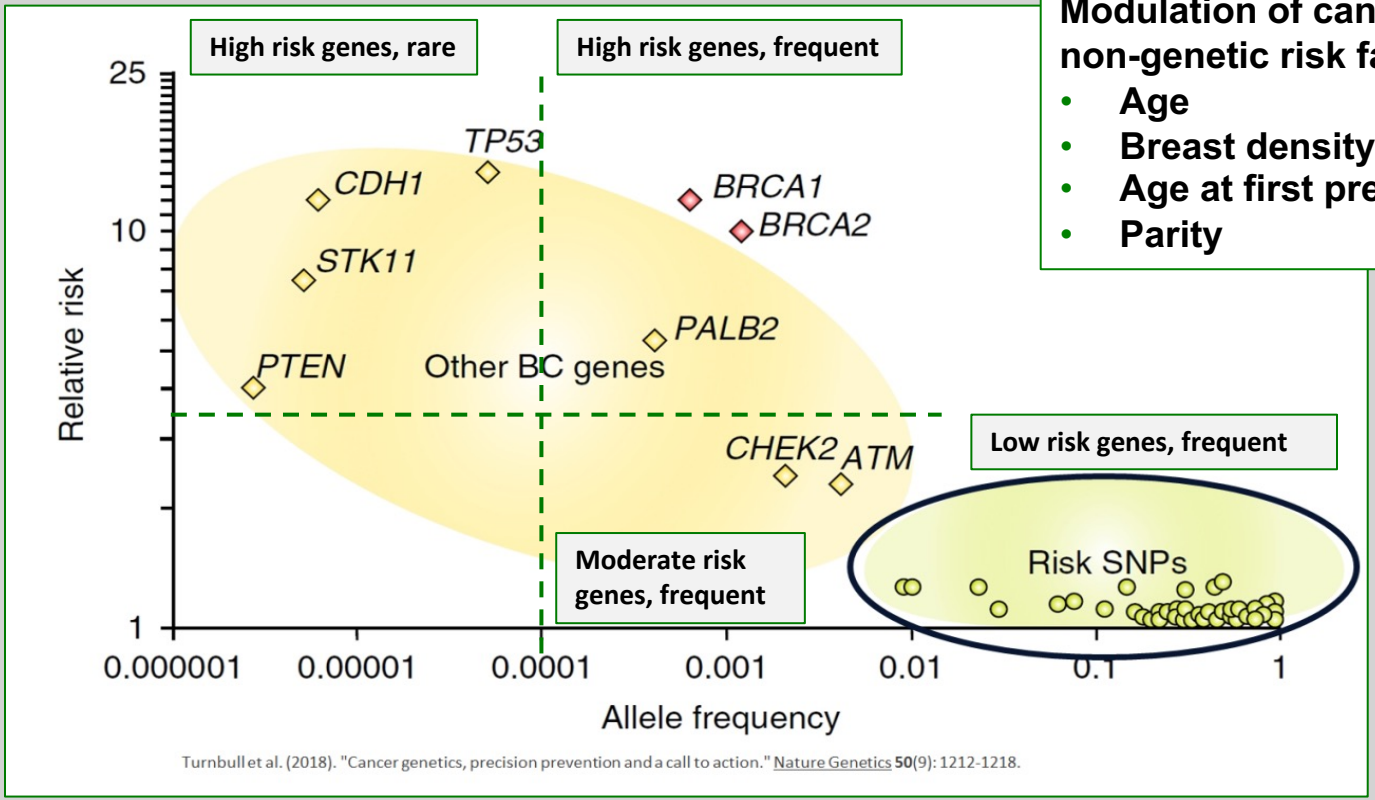

Turnbull et al. (2018). "Cancer genetics, precision prevention and a call to action." Nature Genetics 50(9): 1212-1218.

Modulation of cancer risk by non-genetic risk factors, e.g.:

- **Age**
- **Breast density**
- **Age at first pregnancy**
- **Parity**

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

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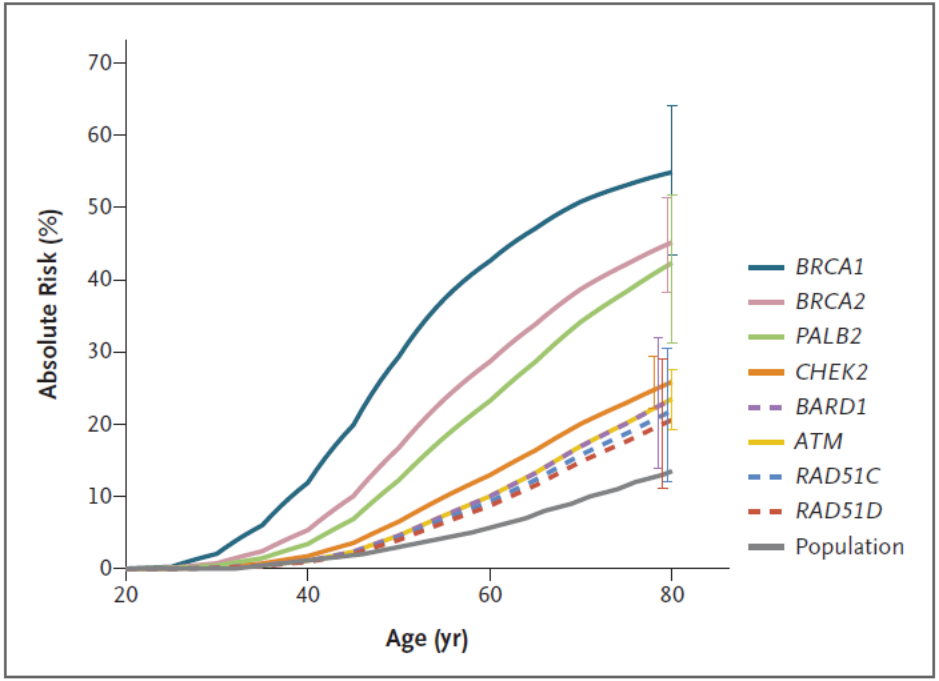

Shown are cumulative risks of breast cancer through 80 years of age for protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. Baseline absolute risks were derived from population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

IARC - Classification of Sequence Variants (Plon et al., Human Mutation, 2008)

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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).

Variant of Unknown Significance (VUS): Problems and Questions

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

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Multimodal Intensive Surveillance Program*

		Oxford LoE	Oxford 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.

High-Risk Breast Cancer Surveillance with MRI

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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

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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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**

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

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	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.

Surveillance for Male Carriers of Pathogenic BRCA Mutations*

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	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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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

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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.

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

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	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

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.

Medical Prevention for Women at Increased Risk

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	Oxford LoE	Oxford GR	AGO
▪ Tamoxifen for women > 35 years: Risk reduction of invasive BC, DCIS and LN	1a	A	+*
▪ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1b	A	+*
▪ AI for postmenopausal women	1b	A	+**

* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

** Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.