MGZ

Medical Genetics Center

Clinician Information

FACTS ABOUT *BRCA1* AND *BRCA2*

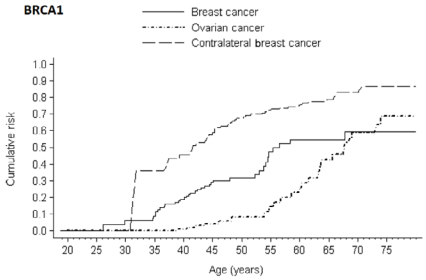
HEREDITARY BREAST AND OVARIAN CANCER (HBOC) / HEREDITARY BREAST CANCER (HBC)

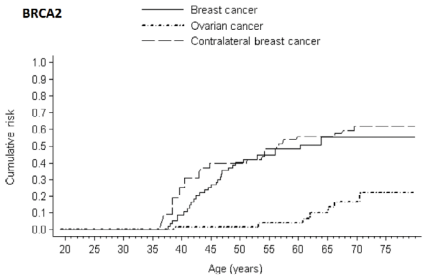
Approximately 5 % of all breast cancers are the result of a pathogenic variant in the high-risk genes *BRCA1* or *BRCA2*, which are associated with a cumulative breast cancer risk of over 30 %. A further 4 - 5 % of all breast cancers are caused by pathogenic variants in the genes *ATM, CHECK2, CDH1, NBN, PALB2, PTEN, STK11,* or *TP53*. Of these, pathogenic variants in *PALB2, STK11,* and *TP53* are associated with a high risk of breast cancer (BC); pathogenic variants in the other genes are associated with a moderately increased risk. The cumulative risk is 15 - 30 % in these instances.

Pathogenic variants in some of these genes also result in an elevated risk of developing other tumors. This includes, in particular, the risk of ovarian cancer (OC) caused by pathogenic variants in *BRCA1, BRCA2,* and *PALB2* and an elevated risk of diffuse gastric cancer for pathogenic variants in *CDH1*. Various cancers are associated with pathogenic variants in the genes *TP53* and *STK11*.

BREAST CANCER

In providing at-risk patients with accurate information regarding individual risk, an age-dependent probability of developing cancer is more useful than a cumulative lifetime risk assessment. It is important to note, however, that these figures come from at-risk groups and are thus likely to be overestimated in terms of actual risk. Population-based data show a lifetime risk of 56 % for *BRCA1* (95 % CI, 47 % to 66 %) and 45 % for *BRCA2* (95 % CI, 40 % to 57 %) (Chen and Parmigiani, 2007). There are more recent data, but these refer to risk collectives; thus the presentation here of the older data. It is particularly important to note that the development of a primary tumor around or prior to the age of 30 is associated with a high risk of contralateral breast cancer.

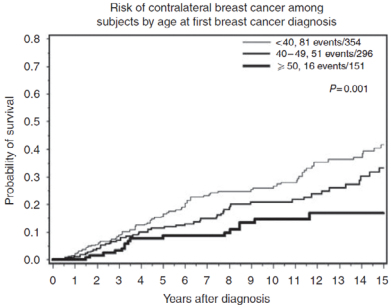


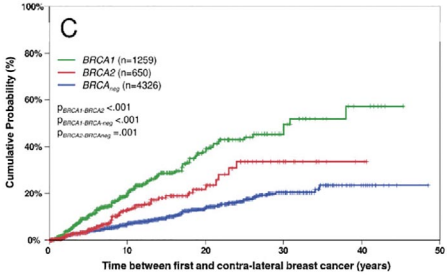


(Mavaddat et al. 2013)

CONTRALATERAL BREAST CANCER

Particularly for pathogenic variants in *BRCA1* and *BRCA2* there is good evidence that the earlier the first occurrence of the disease, the higher the risk. Furthermore, the risk of pathogenic variants in *BRCA1* is higher than in *BRCA2*.

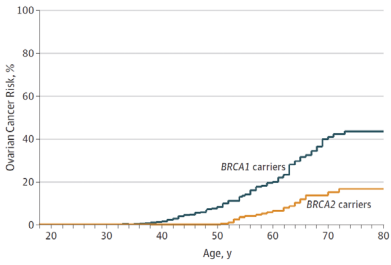




(Metcalfe et al. 2011; Rhiem et al. 2012)

OVARIAN CANCER

Ovarian cancer may develop earlier with pathogenic *BRCA1* variants than with pathogenic variants in *BRCA2*. The lifetime cancer risk is also higher for *BRCA1* than for *BRCA2*. However, these data refer to risk collectives, thus the presentation of the older data here. It is particularly important to note that the development of a primary tumor around or prior to the age of 30 is associated with a high risk of contralateral breast cancer. Of the remaining genes, pathogenic variants in *RAD51C, RAD51D, BRIP1*, and possibly *PALB2* are associated with an elevated risk of ovarian cancer.



(Kuchenbaecker et al. 2017)

The development of ovarian cancer, especially a serious high-grade ovarian cancer, corresponds to a probability of >10 % for a pathogenic germ line variant in *BRCA1* or *BRCA2* and a probability of 25 % for a pathogenic *BRCA1* or *BRCA2* variant in the tumor.

In both instances, the detection of this pathogenic variant has been shown to have beneficial therapeutic consequences, such as oxaliplatin-based therapy or a therapy with a PARP inhibitor. This is also reflected in the current S3 guidelines for malignant ovarian tumors.

9.4. Procedure for recurrence of serious high-grade platinum-sensitive ovarian cancer with pathogenic BRCA variants

8.9.	Evidence-based recommendation	2016
Recommendation Grade **B**	For cases in which a deleterious *BRCA1/2* variant was detected and the patient is suffering a recurrence of serious, high-grade ovarian cancer, maintenance therapy with a PARP inhibitor should be offered subsequent to a response to platinum-based therapy.	
Level of Evidence **2+**	primary studies: [367-369]	

PROPHYLACTIC / PREVENTIVE SURGERY

Ovarian cancer: Guidelines recommend an adnexectomy from the age of 40 for patients with pathogenic variants in *BRCA1* and *BRCA2*. This should also be considered for patients with pathogenic variants in *PALB2* and a positive familial history of ovarian cancer. For patients with pathogenic variants in the other genes, a prophylactic adnexectomy is not indicated.

Breast cancer: A prophylactic mastectomy is generally recommended. However, any risk assessment must take into account whether a pathogenic variant has been detected in *BRCA1* or *BRCA2* as well as whether there was a previous incidence of breast cancer and the age when it occurred. Generally speaking, a comprehensive interdisciplinary consultation is required for the precise determination of individual risk and the appropriate recommendations. A bilateral adnexectomy before the age of 50 reduces the risk of breast cancer by approx. 50 %.

FURTHER ASSOCIATED TUMOR RISKS ASSOCIATED WITH *BRCA1* AND *BRCA2*

Lifetime risks for associated tumor diseases

	BRCA1	*BRCA2*	General Population
BC male	1.2 %	8.9 %	0.1 %
Prostate CA *	8.6 %	15 %	6 %
Pancreatic CA	1 - 3 %	2 - 7 %	0.5 %

* Risk up to the age of 65

MONITORING

- High-risk provisions for pathogenic variants in *BRCA1, BRCA2, PALB2, TP53*
  From the age of 25: ultrasound examination every 6 months, annual MRI
  From the age of 40: supplementary mammography every 1 - 2 years
- Moderate provisions for pathogenic variants in
  ATM, CDH1, CHEK2, NBN, PTEN, RAD51C, RAD51D
  From the age of 30: annual ultrasound examination and MRI
  From the age of 40: supplementary mammography every 1 - 2 years

MOLECULAR GENETIC ANALYSIS

All analyses are performed using Next-Generation Sequencing (NGS). The patient or referring physician is free to choose the diagnostic scope. It is possible to analyze only *BRCA1* and *BRCA2*, but normally a panel of 12 genes (*BRCA1, BRCA2, ATM, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*) is analyzed. To date, MGZ has sequenced the genes *BRCA1* and *BRCA2* (Sanger and NGS) for approximately 5,500 women, of which about 1,600 were tested using NGS (as of June 2017).

All analyses are performed with a NGS-gene panel covering more than 100 genes described in association with hereditary tumor diseases. The patient must be informed about the scope of this analysis and decide whether he/she would like to be informed of secondary findings. If a patient consents only to the analysis of *BRCA1* and/or *BRCA2*, or only the 12 genes, only these genes will be evaluated; secondary findings remain unseen. If a patient would like to be informed of secondary findings, the data from the other genes can be technically evaluated; however, this evaluation does not meet our diagnostic quality requirements, as we will have had no mandate for this purpose. If a conspicuous variant is detected, this finding will be reported, and further diagnostics may be required to confirm this result. “Secondary findings” are clearly pathogenic variants in genes that are classified by experts (European Consensus) as "actionable," i.e., the variant represents a defined risk for the patient and his/her family members and is therefore of relevance to therapy or prevention (e.g., recommendations in accordance with guidelines for early detection). Variants of uncertain significance (VUS) in genes that have not been designated as "actionable" are not reported as secondary findings.

GENETIC COUNSELING

Ten specialists in human genetics and two additional specialists are available to provide patients with genetic counseling at our office in Munich. To make an appointment, please contact us at inquiry@mgz-muenchen.com

Genetic counseling is generally indicated when a patient has had multiple instances of cancer in his/her family, or when a patient has had ovarian or breast cancer prior to the age of 50. A genetic consultation includes an individual assessment of the risk of developing cancer, the initiation of molecular genetic diagnostics (if appropriate), and the formulation of a plan for preventative care/early detection tailored to the patient’s risk and

the risk to his/her family. The indication for molecular genetic analysis of the genes *BRCA1* and *BRCA2* follows specific criteria according to S3 breast cancer guidelines:

- 3 women of shared lineage with BC
- 2 women with BC, one before the age of 51
- 1 woman with BC and 1 woman with OC
- 2 women with OC
- 1 woman with BC and OC
- 1 woman with BC before 36 years of age
- 1 woman with bilateral BC, with one BC before the age of 51.
- 1 man with BC and 1 woman with BC and/or OC

Furthermore, a mutation probability of >10 % was found for a pathogenic variant in *BRCA1* or *BRCA2* for the following criteria:

- 1 triple-negative BC before the age of 60
- 1 woman with OC

Men with breast cancer should pursue genetic testing if the result could be relevant to therapy.

Furthermore, analysis of *BRCA1* and *BRCA2* may be relevant to therapy and can be carried out in this context.

Chen, S. and Parmigiani, G. 2007. Meta-Analysis of *BRCA1* and *BRCA2* Penetrance. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 25(11), pp. 1329–1333. doi: 10.1200/JCO.2006.09.1066.

Kuchenbaecker, K.B. et al. 2017. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA* 317(23), pp. 2402–2416. doi: 10.1001/jama.2017.7112.

Mavaddat, N. et al. 2013. Cancer Risks for BRCA1 and BRCA2 Mutation Carriers: Results From Prospective Analysis of EMBRACE. *JNCI Journal of the National Cancer Institute* 105(11), pp. 812–822. doi: 10.1093/jnci/djt095.

Metcalfe, K. et al. 2011. Predictors of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *British Journal of Cancer* 104(9), pp. 1384–1392. doi: 10.1038/bjc.2011.120.

Rhiem, K. et al. 2012. 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 Research: BCR* 14(6), p. R156. doi: 10.1186/bcr3369.

MGZ – Medical Genetics Center

Prof. Elke Holinski-Feder, MD
Angela Abicht, MD
Clinical Geneticists, MVZ

Bayerstrasse 3 - 5 | D-80335 Munich
Phone +49 (0)89 / 30 90 886 - 0 | Fax +49 (0)89 / 30 90 886 - 66
inquiry@mgz-muenchen.com | www.mgz-muenchen.com

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