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Summary An estimated 10 % of breast cancer cases exhibit a higher familial incidence, and functional mutations in BRCA (breast cancer-gene) 1 or 2 are responsible for the development of malignant tumors in approximately half of these cases. Women with a germline mutation in either of the two genes have a lifetime risk of up to 85 % to develop breast cancer, and of up to 60 % risk to develop ovarian cancer. This clinical practice guideline defines the individual and familial tumor constellations that represent an indication for BRCA germline testing. It also describes the therapeutic options (early detection programme vs prophylactic surgery) that arise from the result of a BRCA mutational analysis. This guideline further includes recommendations regarding the use of multigene panels and therapeutic aspects that arise from the selective use of poly ADP ribose polymerase (PARP) inhibitors in patients with known BRCA1 or 2 mutations. It replaces the previous version of the "Clinical Practice Guideline for the Prevention and Early Detection of Breast- and Ovarian Cancer in women from HBOC (hereditary breast and ovarian cancer) families" which was published in 2012.

Keywords BRCA · Hereditary Breast and Ovarian Cancer · PBSO · PBM

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Definitions

HBOC (hereditary breast and ovarian cancer) family Families with multiple cases of breast and/or ovarian cancer are classified as HBOC families (→high-risk patient).

BRCA1 and 2 (breast cancer genes 1 and 2) BRCA1 and 2 are tumor suppressor genes which play an important role in the repair of DNA double-strand breaks and in the regulation of intracellular functions. If either of the two genes carries a functionally relevant mutation, the risk of developing breast and ovarian cancer is significantly increased.

NGS (next generation sequencing NGS is a DNA-Sequencing technology which permits to sequence multiple genes with high throughput in parallel.

PBM (prophylactic bilateral mastectomy) Removal of breast tissue from both breasts. This procedure is often combined with simultaneous breast reconstruction. The complete removal of breast tissue from both breasts significantly reduces the breast cancer risk in women with a BRCA1 or 2 mutation.

CPM (contralateral prophylactic mastectomy) Prophylactic removal of breast tissue from the contralateral breast in women who have developed unilateral breast cancer. This procedure significantly reduces the contralateral breast cancer risk and increases survival.

PBSO (Prophylactic bilateral salpingo-oophorectomy) Prophylactic removal of both ovaries and both fallopian tubes in order to reduce the risk for developing breast and ovarian cancer.

Polymorphism Polymorphism is a clinically irrelevant genetic variation in a particular gene. It is characterized by the presence of one or several gene variations within a given population. The detection of one or multiple polymorphisms is not associated with an increased disease risk.

TNBC (triple-negative breast cancer) The term TNBC defines a subgroup of malignant breast tumors which is characterized by the absence of estrogen receptor, progesteron receptor, and HER2 receptor. BRCA1-associated breast cancer usually exhibits a TNBC phenotype.

Unclassified variant ("UV") An UV is a genetic alteration whose potential clinical relelvance cannot be assessed with the present medical knowledge. UV can, however, eventually be reclassified into either a functional mutation or a polymorphism according emerging scientific evidence.

High-risk patient Female who fulfills at least one of the following criteria:

a) Existence of a more than 20 % individual life time risk to develop breast cancer. This is particularly the case when one of the individual or familial criteria listed in Table 1 is fulfilled.
b) Presence of a known germline mutation or presence of an UV in BRCA 1 or 2.
c) History of mantle field irradiation before age 30.

Introduction

The present Austrian "Clinical Practice Guideline for the Prevention and Early Detection of Breast- and Ovarian Cancer in Women from HBOC (hereditary breast and ovarian cancer) families" is an updated version and replaces the previous Clinical Practice Guideline published in 2012. The intention of this guideline is to standardize and to facilitate both counseling and medical care for women with an increased risk to develop breast and ovarian cancer in Austria.

Background

BRCA1 and 2 germline mutations

An estimated 10 % of all breast cancer cases exhibit a higher familial incidence, and functional mutations in BRCA (breast cancer-gene) 1 or 2 are responsible for the development of malignant tumors in approximately half of these cases (i.e., 5 % of all breast cancer cases).

Table 1 Indications for molecular analysis of BRCA 1 and 2

One case of breast cancer before age 35
Two cases of breast cancer, at least one of these before age 50*
Three cases of breast cancer before age 60*
One case of breast cancer and one case of ovarian cancer
Two cases of ovarian cancer
One case of male breast cancer
Patient with TNBC before age 60; if a therapeutic consequence is considered in TNBC patients irrespective of age
Patient with epithelial ovarian cancer**
Presence of BRCA1 or 2 mutation in the family

*Bilateral breast cancer counts for two cases of breast cancer
**This recommendation is also pertinent to patients with cancer of the fallopian tube and primary peritoneal cancer

The BRCA1 gene is located on the long arm (q-arm) of chromosome 17, while BRCA2 is located at the long arm (q-arm) of chromosome 13. A germline mutation in either of the two genes is associated with a profound increase in the lifetime risk to develop breast and/or ovarian cancer. BRCA germline mutations are transmitted in an autosomal-dominant fashion. Consequently, the risk of offsprings from an affected parent to inherit the mutated allele is 50 %. In diseases with autosomal dominant inheritance, the presence of one mutated allele affects the phenotype (the appearance of a feature, in this case the occurence of breast and/or ovarian cancer) with a high probability ("high penetrance") during the life span of an individual [1]. Characteristic familial tumor constellations which suggest the presence of a BRCA germline mutation, and which thus represent an indication for the molecular analysis of BRCA1 and 2 are listed in Table 1. The tumors in Table 1 have to occur in one (paternal or maternal) familial line, but are independent of the degree of kindship. A molecular analysis should always be attempted in already diseased individuals. BRCA1 and 2 mutational analysis should also be offered to individuals who develop TNBC before age 60 (in case of a therapeutic relevance also beyond age 60), and to women who have developed serous ovarian cancer, even in the absence of a suggestive familial history.

In principle, genetic testing for BRCA1 and 2 can yield three possible results with distinct clinical consequnces (Table 2):

1. Absence of a functionally relevant mutation in BRCA1 or 2 (in absence of polymorphisms)
2. Variation of unknown significance (UV)
3. Functionally relevant mutation in BRCA1 or 2

If a BRCA1 or 2 germline mutation is identified, affected women should be offered the following options in the course of a comprehensive genetic counseling session [2]:

a. Intensified early detection programme (see below)
b. In nonaffected carriers: PBM in order to decrease the individual breast cancer risk (see below)

Table 2 Alterations in BRCA1 and 2 and their clinical consequences

Alteration is	Protein function is	Clinical consequences	Risk	Clinical consequence
Wild type or polymorphism	Not compromised	None	a) If a BRAC1/2 mutation has been identified in family: background population risk b) If BRAC1/2 mutation has not been identified in family: increased risk based on family history	Participation in Austrian Breast Cancer Screening Programme High-Risk Early Detection Programme
Variation of unknown significance (UV)	Unknown	Unknown	Unknown	High-Risk Early Detection Programme
BRAC1/2 mutation	Compromised	Yes	BRAC1: 85 %, BC, 53 % OC BRAC2: 84 % BC, 27 % OC	High-Risk Early Detection Programme PBM, CPM, PBSO

c. In women who have developed unilateral breast cancer: CPM in order to decrease the risk of contralateral breast cancer and to increase survival
d. PBSO in order to decrease the ovarian and breast cancer risk (see below)

Additional genes which predispose for breast and ovarian cancer

The recent introduction of NGS now allows for a rapid and comparatively cheap simultaneous analysis of multiple genes. If a familial breast and ovarian cancer syndrome is suspected and BRCA1 and 2 germline mutation testing is indicated, multi-gene assays can be used as long as the employed gene panel comprises BRCA1 and 2 testing as well as testing for other genes that are associated with an increased risk for breast and ovarian cancer. Multi-gene testing can be used if, due to a strong familial predisposition in the absence of a functional mutation in BRCA1 and 2, a genetic disposition still appears likely. Multi-gene testing is, however, also associated with potential disadvantages: Simultaneous testing for multiple genes leads to an increased rate of variations of unknown significance ("VUS" or "UV") whose potential clinical consequences are presently unclear. Also, multi-gene assays can comprise genes of intermediate penetrance ("moderate-risk genes"). For many of these genes, no or only limited data exist in respect to the associated cancer risks. Consequently, the clinical relevance of detected mutations is presently unclear, and thus the value of early detection programmes and prophylactic surgery remains elusive. Following the NCCN guidelines (July 2015), possible risk-adapted clinical management options are listed in Table 3.

Table 3 Risk-adapted clinical management in selected gene mutations (based on NCCN Clinical Practice Guidelines, July 2015)

	Recommend MRI (> 20 % BC risk)	Offer PBSO	Offer PBM
Intervention reasonable because of genetic risk	ATM BRCA1 BRCA2 CDH1 CHEK2 PALP2 PTEN STK11 TP53	BRCA1 BRCA2 Lynch syndrome	BRCA1 BRCA2 CDH1 PTEN TP53
Insufficient evidence for intervention	BARD1 BRIP1	BARD1 BRIP1 PALB2 RAD51C RAD51D	ATM BARD1 CHEK2 PALB2 STK11

Early detection strategies

Intensified early detection programme

Breast magnetic resonance imaging (MRI) is the most sensitive diagnostic modality in high-risk patients and should therefore be included in every early detection programme. This recommendation is based on the results of large cohort studies which could demonstrate that, by using annual breast MRI, incident breast cancer cases can be detected with a sensitivity of 81 %, as compared with annual mammography with a detection rate of only 40 % and to breast ultrasound with a detection rate of only 42 % [3–6]. It is the high sensitivity and the lack of irradiation that renders this method the one screening modality that is uniformly recommended by European guidelines. It should be initiated at age 25 or 5 years prior to the age at which the youngest affected family member had developed breast cancer.

Annual mammographies (MGs) should be withheld until age 35 because of the exquisite radiosensitivity of breast tissue in mutation carriers, and because of the decreased sensitivity that is observed in the relatively dense breast tissue that is characteristic for young age. It is because of these reasons that most guidelines recommend annual MG only in women older than 35.

The value of MG in the early detection of breast cancer in BRCA1 mutation carriers is increasingly challenged. Patients should therefore be informed that the potential benefit of an early, MG-detected breast cancer is probably small and has to be weighed against the risks associated with MG-inherent irradiation and against the possibility of false positive results [7].

Until now, the possible advantages of regular serum CA125 measurements and transvaginal ultrasound

investigations in the early detection of ovarian cancer have never been demonstrated.

The following early detection strategies are recommended for women at high risk for breast and ovarian cancer in Austria (Table 4):

Table 4 Early detection strategies for female HBOC family members

Intervention	Age	Age	Age	If indicated
Gynecological exam	1 x per year			
Breast exam	1 x per year			
Breast ultrasound[a]				x
Mammography[b,c]			1 x per year	
Breast MRI[b,c,d,e]		1 x per year		
TVUS[c,f]			1 x per year	
Tumor marker (CA125)[c,f]			1 x per year	

([a]): if MRI is not available; also in pregnant and in lactating women—in 3-monthly intervals.
([b]): Annual mammography and MRI examinations can be performed simultaneously every 12 months or alternating, every 6 months.
([c]): If applicable, should be initiated 5 years prior to the age at which the youngest family member has developed the respective cancer.
([d]) An MRI should be performed within 3 months of the date on which PBM or CPM is forseen if such a procedure is planned in order to detect clinically occult breast cancer.
([e]): In women who have breastfed, MRI should be initiated not earlier than 2 months after lactation has ceased.
([f]): Although a potential benefit of this examination on the early detection of ovarian cancer has not been demonstrated.

Special cases

Male mutation carrier

Despite the fact that informative studies related to the early detection of male breast cancer in BRCA1 and 2 mutation carriers do not exist, a regular self examination is nevertheless recommended. The use of MG in males is restricted to cases where a suspicious lesion is palpated. Regular cancer early detection examinations, particularly PSA serum measurements according to the recommendations of the Austrian Cancer Society (Österreichische Krebshilfe) are recommended.

Women after PBSO

In women who have undergone PBSO regular TVUS examinations and serum CA125 measurements are not indicated.

Women after PBM

In women who have undergone PBM regular MG examinations are not indicated. Annual MRI examinations can be offered in healthy women but should be offered as for follow up in women who have a history of breast cancer.

Non-Mutation Carriers from HBOC Families

Female nonmutation carriers from HBOC families in which a BRCA mutation has already been diagnosed in one or multiple family members do not require an intensified early detection programme and should participate in the regular National Breast Cancer Early Detection Programme.

Lifetime risk-based breast cancer early detection

No sufficient evidence exists to recommend a high-risk early detection programme for breast cancer in women with an estimated lifetime-risk between 15 and 20 %, and for women with lobular in situ carcinomas or atypical ductal hyperplasia. The same is true for women with heterogenous or extremely dense breast tissue, and women with a history of breast cancer, who do not fulfill the criteria for HBOC.

High-risk breast cancer screening is not recommended for women with an estimated life time breast cancer risk of 15 % and less.

Breast and ovarian cancer prevention

PBM, CPM, and PBSO are surgical interventions whose beneficial effects on cancer morbidity and mortality have been demonstrated in a number of clinical trials [8–11].

Prophylactic bilateral mastectomy (PBM)

The PBM can be performed as a means of primary prevention in BRCA1 and 2 mutation carriers who have not yet been diagnosed with breast cancer. It is associated with a reduction of breast cancer risk by 95 %. Recent studies even indicate a survival benefit after PBM, although the follow-up period is too short to draw definite conclusions. In women with a history of breast cancer, the prophylactic removal of the remaining ipsi- and contralateral breast tissue can be offered as a means of secondary prevention [12]. In women from HBOC families in which no BRCA mutation has been identified, the value of prophylactic surgery in respect of a mortality reduction remains to be determined.

Contralateral prophylactic mastectomy (CPM)

Recent studies demonstrate that women with unilateral breast cancer have a 27 % risk to develop breast cancer in the contralateral breast within the next 10 years [13]. CPM not only reduces morbidity associated with contalateral breast cancer but also increases overall survival [14].

Prophylactic bilateral salpingo-ophorectomy (PBSO)

In women with a BRCA1 and 2 germline mutation, PBSO results in a reduction in breast cancer risk by approximately 50 %, and in a reduction in ovarian cancer risk by 80 %. Furthermore, in a recently published large multicenter trial it could be demonstrated that PBSO in women with a BRCA germline mutation does not only lead to a significant reduction of ovarian cancer-specific, but is also associated with a decline in breast cancer-specific and overall mortality [15]. When compared with women who only undergo intensified early detection strategies, women who have undergone PBSO have a significantly better overall survival [16].

Decision for or against prophylactic surgery

Because of individual differences in risk perception, and because of individual life planning, particularly in respect of a potential desire to have children, the Austrian genetic law prohibits directive counseling for or against prophylactic surgery. PBM, CPM, and PBSO may only offered to affected women after detailled information regarding the age- and mutation-dependent disease risk, and regarding the effect of PBSO on fertility and hormone levels.

Legal framework

In § 69 the Austrian Genetic Law (Gentechnikgesetz) mandates that genetic counseling includes a "comprehensive discussion of all relevant results pertaining to genetic testing as well as possible medical, social, and psychological consequences". Genetic counseling must be nondirective. The explicit recommendation of PBSO, for example, is therefore not acceptable under the current Austrian legislation. The results of genetic analyses are subject to a particularly strict protection in respect of safe-keeping and disclosure of data. In particular, the disclosure of BRCA1/2 testing results to employer and insurance companies is explicitly forbidden.

Related clinical practice guidelines

European Society for Medical Oncology:

BRCA in Breast Cancer—ESMO Clinical Recommendations [17]

American College of Obstetricians and Gynecologists

ACOG Practice Bulletin #103: Hereditary Breast and Ovarian Cancer Syndrome [18]

Society of Obstetricians and Gynaecologists of Canada:

Clinical Management Recommendations for Surveillance and Risk-Reduction Strategies for Hereditary Breast and Ovarian Cancer Among Individuals Carrying a Deleterious BRCA1 or BRCA2 Mutation [19]

American Cancer Society:

American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography [20]

American Society of Breast Surgeons:

BRCA Genetic Testing for Patients With and Without Breast Cancer [21]

NCCN Guidelines for Genetics Screening Version 1.2015

Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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