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BRCA in breast cancer: ESMO Clinical Practice Guidelines

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prevalence and penetrance of *BRCA1/2* mutations

Familial susceptibility to breast cancer accounts for <25% of all breast cancer cases. *BRCA1* and *BRCA2* are high-penetrance breast cancer predisposition genes identified by genome-wide linkage analysis and positional cloning. Mutations in *BRCA1/2* explain ∼20% of the familial clustering of breast cancer. Germline mutations in the other high-risk genes *TP53*, *PTEN* and *STK11* are identified in <1% of breast cancer families and are usually associated with rare cancer syndromes (Li–Fraumeni, Cowden and Peutz–Jeghers syndromes, respectively). Screening of genes functionally related to *BRCA1* and/or *BRCA2* has identified mutations in *CHEK2*, *ATM*, *BRIP1* and *PALB2*. Mutations in these genes are rare and confer an intermediate risk of breast cancer, and therefore explain only a small proportion of the remaining predisposition. More recently, *RAD51C* has been discovered as a potentially high-risk cancer predisposition gene in breast/ovarian cancer families. Association studies have further identified 18 common variants associated with low-penetrance breast cancer predisposition. Despite these discoveries, the underlying cause of >70% of the familial breast cancer cases still remains unexplained.

The estimated population frequency of mutations in *BRCA1/2* genes is 1/800–1/1000 per gene. Overall this equates to 15–20% of the excess familial risk of breast cancer. The prevalence of *BRCA1* or *BRCA2* germline mutations varies considerably among ethnic groups and geographical areas. Population-specific mutations and recurrent mutations have been described among Ashkenazi Jews, in Iceland, The Netherlands, Sweden, Norway, Germany, France, Spain, Canada and countries of eastern and southern Europe.

BRCA1 and *BRCA2* mutation frequencies in breast and ovarian cancer patients unselected for family history or age at onset are generally low (<1–7% for *BRCA1* and 1–3% for *BRCA2*). Higher prevalence is associated with a family history of breast or ovarian cancer, young age at onset, male breast cancer or multiple tumors (bilateral breast cancer or breast and ovarian cancer in the same patient). Based on pooled data from cases unselected for family history it is estimated that average cumulative risks in *BRCA1* mutation carriers by age 70 years were 65% [confidence interval (CI) 44–78%] for breast cancer and 39% (18–54%) for ovarian cancer. The corresponding estimates for *BRCA2* were 45% (31–56%) and 11% (2.4–19%). However, due to the high allelic heterogeneity of these genes, the actual risk conferred by a particular mutation is likely to diverge from these estimates. The relative risk of male breast cancer is elevated for both genes, particularly *BRCA2* (6%). An elevated risk of prostate cancer has also been shown in *BRCA2* carriers, particularly in men aged <65 years. Other cancers at increased risk are pancreatic (up to 2%), stomach, and head and neck.

referral for BRCA testing

Genetic testing criteria may differ between countries based on mutation prevalence. Widely accepted clinical criteria for referral include: three or more breast and/or ovarian cancer cases, at least one <50 years; two breast cancer cases <40 years; male breast cancer and ovarian cancer or early onset female breast cancer; Ashkenazi Jew with breast cancer of <60 years; young onset bilateral breast cancer; and breast and ovarian cancer in the same patient [IV, C]. In some countries, the criterion for testing is based on an *a priori* 10–20% probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score, while less specific criteria include a potential benefit in the medical or surgical management of the individual or his/her relatives. The addition of pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of HER2neu) in women younger than 50 has been evaluated as a cost-effectiveness strategy for mutation detection.

In all cases, genetic testing should be performed in adults after they have received genetic counseling and given informed

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consent. Carriers should be encouraged to advise close family members to obtain genetic counseling.

mutation detection

The majority of clinically significant deleterious mutations are protein-truncating mutations and a small number are missense mutations. Several mutation detection techniques are in use, but direct DNA sequencing is the gold standard. Genomic DNA, extracted from blood, is used as a template and coding exons with flanking intronic sequences are analyzed. In addition, since 2–12% of high-risk families may harbor a large genomic alteration, specific techniques to detect duplications or deletions of one or more exons such as multiplex ligation-dependent probe amplification (MLPA) are needed [III, B].

risk reduction: non-surgical preventive options

surveillance

Surveillance of breast cancer in *BRCA* carriers includes monthly self-examinations, clinical breast examinations twice a year and yearly mammograms and magnetic resonance imaging (MRI) of breasts starting at age 25–30 [IIa, B]. There are as yet no data available to determine whether alternating mammogram and MRI every 6 months or having both once yearly is more effective at young ages, considering the high rate of interval cancers in *BRCA1* carriers.

chemoprevention

Adjuvant tamoxifen reduces the risk of contralateral breast cancer in affected *BRCA* mutation carriers [III, B], while benefit of tamoxifen for primary prevention of breast cancer in *BRCA* carriers has not been demonstrated [Ib,A].

risk modifiers

BRCA-associated breast cancer risk can be modified by external factors. Hormonal and reproductive factors such as pregnancy (number and age at first pregnancy), history of breast feeding and oral contraceptives have been associated with risk modification in *BRCA* mutation carriers with contradictory results. Parity seems to confer protection from breast cancer in women with *BRCA* mutations as in the general population [III, B].

risk reduction: prophylactic surgical options

The objective of preventive surgery is to reduce cancer risk and mortality. Risk reduction options include prophylactic bilateral mastectomy (PBM), prophylactic bilateral salpingo-oophorectomy (PBSO) and both. There are no randomized controlled trials to support recommendations on prophylactic surgery, but recent prospective cohort studies on prophylactic surgery have shown a consistent reduced risk in this population.

prophylactic bilateral mastectomy

This is the most effective strategy available for risk reduction of breast cancer in mutation carriers [III, B]. Studies have shown a risk reduction of at least 90% with PBM. In two prospective studies published to date, no breast cancers were diagnosed in the risk-reducing mastectomy group compared with 7–13% breast cancers in women under surveillance with a mean follow-up of 3 years. However, survival benefits have not been demonstrated with risk reduction breast surgery.

There have been no randomized trials comparing the effectiveness of different surgical techniques. Historically total mastectomy has been considered the preferred standard surgical procedure for prophylaxis, because the sparing of the skin and the nipple areola complex could leave a substantial amount of breast tissue. Other techniques including skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) have been investigated in order to improve the cosmetic results while maintaining the oncological safety. The SSM technique preserves all the skin of the breast, and its oncological safety has been reported in several large series that show similar local failures to total mastectomy [III, B]. An advantage of SSM is the cosmetic results, although the total loss of all nipple sensation makes the technique less satisfactory for patients.

The NSM preserves the skin envelope and the nipple areola complex. Although follow-up on this procedure is still short, preliminary reports show similar failures rates with superior cosmetic results compared with the other mastectomy techniques [III, C]. Types of prophylactic mastectomy and immediate breast reconstruction should be discussed with the patient, addressing the potential benefits and risks of the different techniques.

The possibility of finding an occult synchronous invasive tumor during a prophylactic mastectomy is quite low at ~5%. At this time, there is insufficient evidence to recommend routine sentinel node biopsy for patients undergoing prophylactic mastectomy.

Contralateral prophylactic mastectomy (CPM) is an option to consider in those *BRCA* mutation carriers with early breast cancer and unilateral mastectomy [IV, C]. CPM decreases the risk of contralateral breast cancer events; however, there are still limited data for decreased mortality after CPM.

prophylactic bilateral salpingo-oophorectomy

This is associated with a risk reduction of breast cancer in premenopausal *BRCA* mutation carriers, risk reduction of ovarian cancer and there is evidence of reduction in overall mortality. Bilateral salpingo-oophorectomy is recommended after age 35 and when childbearing decisions are complete [IIa, B].

The significantly reduced risk of breast cancer by PBSO seems to be higher in *BRCA2* mutation carriers than in *BRCA1* carriers. Several reports have addressed this question although additional research is required. Short-term hormonal replacement therapy after bilateral salpingo-oophorectomy seems not to decrease the overall benefit of this strategy for breast cancer risk reduction [III, B].

breast cancer treatment

surgery

One of the conflicting issues is whether the surgical options of breast conserving surgery (BCS) or mastectomy with or without reconstruction could be the same in mutation carriers as in patients with sporadic breast cancer. Recent studies have demonstrated comparable breast cancer-specific and overall survival in *BRCA1/2* mutation carriers treated with BCS or mastectomy. Chemotherapy has been the only independent predictor of local failure in those treated with BCS. Decisions about surgical treatment of breast cancer in *BRCA* mutation carriers should be based on the same parameters as sporadic cancer, while considering the higher risk of contralateral breast cancer [III, B].

Whether PBSO is associated with a significantly decreased risk of breast cancer in those patients with previous breast cancer in both *BRCA1* and *BRCA2* is still under investigation [III, C]. Recent studies show no effect of PBSO on second primary breast cancer risk.

systemic treatment

Current evidence suggests that the overall prognosis of breast cancer in *BRCA* carriers is similar to sporadic breast cancers, and BRCA deficiency seems to be predictive of chemosensitivity, especially to DNA-damaging agents [III, B].

An ongoing phase II randomized clinical trial in the metastatic setting is testing the sensitivity to platinum-based chemotherapy of triple negative breast cancer and BRCA tumors vs taxane-based chemotherapy.

A recent retrospective study has reported an increased sensitivity of *BRCA1*- and *BRCA2*-associated metastatic breast cancer to first-line chemotherapy with anthracyclines compared with sporadic patients. Another retrospective analysis in a Polish cohort has demonstrated a very high pathological complete response (83%) to cisplatin treatment in the neoadjuvant setting in *BRCA1*-associated breast cancer patients compared with other chemotherapies [i.e. cyclophosphamide, methotrexate and fluorouracil (CMF) and taxane based, 7–8%].

Still, there is no definitive conclusion on the best chemotherapy regimen for BRCA breast cancer patients [II, B], and standard prognostic features should be used to decide treatment in *BRCA* mutation carriers with breast cancer.

Poly (ADP-ribose) polymerase (PARP) inhibitors are being developed as single therapeutic agents for BRCA breast and ovarian cancer patients. These drugs inhibit a pathway of DNA single-strand break repair and lead to apoptosis in BRCA-deficient cancer cells, which already have a deficiency in homologous recombination repair. Two phase II trials with the oral PARP inhibitor olaparib in advanced breast and ovarian cancer patients with *BRCA* germline mutations have recently been reported. Both trials provide positive proof of concept of the efficacy and tolerability of targeted therapy with olaparib in *BRCA*-mutated tumors. The clinical efficacy at 400 mg twice a day continuously provided a response rate of 41% and a progression-free survival of 5.7 months in a heavily pre-treated population. Other PARP inhibitors are being evaluated either alone or in combination with chemotherapy for BRCA-associated tumors.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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