clinical practice guidelines

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BRCA in breast cancer: ESMO Clinical Practice Guidelines

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prevalence and penetrance of *BRCA* mutations

Familial susceptibility to breast cancer accounts for ~25% of all breast cancer cases. In familial breast cancer, mutations in *BRCA1*, *BRCA2*, *CHEK2*, *TP53* and *PTEN* genes account for ~5%–10% of breast and ovarian cancer cases overall.

BRCA1 and *BRCA2* are high-penetrance breast cancer predisposition genes while mutations in *CHEK2*, *ATM*, *BRIP1* and *PALB2* are rare and confer an intermediate risk of breast cancer. Association studies have further identified other common variants associated with low-penetrance breast cancer predisposition. Nevertheless, >70% of the genetic predisposition to breast cancer remains unexplained.

The estimated population frequency of mutations in *BRCA1/2* genes is ~1/800 to 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 tumours (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%). 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. Pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of HER2neu). In all cases, genetic testing should be performed in adults, usually >25 years old, after having received genetic counselling and informed consent. Carriers should be encouraged to advise close family members to obtain genetic counselling.

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 analysed. In addition, since 2%–12% of high-risk families may harbour a large genomic alteration, specific techniques to detect duplications or deletions of one or more exons such as

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multiplex ligation-dependent probe amplification (MLPA) are recommended [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, yearly mammograms and magnetic resonance imaging (MRI) of breasts starting at age 25–30 [IIa, B]. There are 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.

chemoprevention

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

risk reduction: prophylactic surgical options

prophylactic bilateral mastectomy

It is the most effective strategy available for risk reduction of breast cancer in mutation carriers [III, B], although no benefit in survival has been demonstrated and many women do not find this strategy acceptable for cosmetic reasons. Contralateral prophylactic mastectomy is an option to consider in those *BRCA* mutation carriers with early breast cancer undergoing unilateral mastectomy [III, B].

Types of prophylactic mastectomy may range from total mastectomy to skin-sparing mastectomy, and nipple-sparing mastectomy. The different options should be discussed with the patient and include the benefits and risks for each. A concurrent discussion of the benefits and risks of immediate breast reconstruction should be approached.

At this time, there is insufficient evidence to recommend routine sentinel node biopsy for patients undergoing prophylactic mastectomy.

prophylactic bilateral salpingo-oophorectomy

There is evidence that it is associated with a primary risk reduction of breast cancer in premenopausal *BRCA* mutation carriers (statistically significant for *BRCA2*), risk reduction of ipsilateral breast cancer recurrence after breast conserving surgery and radiotherapy, risk reduction of ovarian and gynaecological cancer, and reduction in overall mortality [III, B]. Bilateral salpingo-oophorectomy is recommended after age 35 and when childbearing decisions are complete [IV, C].

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].

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].

breast cancer treatment

surgery

Breast conserving surgery and radiotherapy in *BRCA* mutation carriers who undergo prophylactic oophorectomy have been associated with a similar rate of ipsilateral breast recurrence versus sporadic controls at 10 years. The risk of contralateral breast cancer in BRCA carriers is higher versus sporadic controls, regardless of hormonal intervention.

Decisions about the surgical treatment of breast cancer in *BRCA* mutation carriers should be based on the same parameters as sporadic cancer, while considering the overall higher risk of contralateral breast cancer, and ipsilateral recurrence if undergoing breast conserving surgery followed by radiotherapy in those not performing oophorectomy [III, B].

systemic treatment

Current evidence suggests that overall prognosis of breast cancer in BRCA carriers is similar to sporadic breast cancers and *BRCA1/2* deficiency seems to be predictive of chemosensitivity [III, B].

An ongoing Phase II randomized clinical trial in the metastatic setting is testing the sensitivity to platinum-based chemotherapy of *BRCA* tumours versus taxane-based treatment.

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. Several Phase II trials are testing the specific DNA-repair deficiency of BRCA-associated tumours with the use of PARP inhibitors in the metastatic setting. Two Phase II trials with the oral PARP inhibitor olaparib in advanced breast and ovarian cancer patients with BRCA germline mutations have recently reported an encouraging clinical efficacy at 400 mg bid continuously (response rate: 41% and 33%, and progression-free survival: 5.7 and 5.8 months, respectively).

Up to now there is no definitive conclusion on the best chemotherapy regimen for BRCA breast cancer patients [III, B]. Nowadays standard prognostic features should be used to decide adjuvant treatment in BRCA mutation carriers with breast cancer.

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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