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BRCA in breast cancer: ESMO Clinical Recommendations

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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 the *BRCA1*, *BRCA2*, *CHEK2*, *TP53* and *PTEN* genes account for ~5–10% of breast and ovarian cancer cases overall. The prevalence of *BRCA1* or *BRCA2* mutations varies considerably between ethnic groups and geographical areas. Population-specific mutations have been described in Iceland, the Netherlands, Sweden, Norway, Germany, France, Spain, countries of central and eastern Europe and among Ashkenazi Jews. The prevalence of BRCA mutation carriers in the general population is estimated at between 1/800 and 1/1000. *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).

Women with an inherited *BRCA1* mutation have a lifetime risk of 65–80% of developing breast cancer and 37–62% of developing ovarian cancer, while *BRCA2* mutation carriers have a lifetime risk of 45–85% for breast cancer and 11–23% for ovarian cancer. There is an increased risk of prostate cancer among *BRCA* carriers (5–25%) and breast cancer among males with *BRCA2* mutations (6%). 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 criteria for referral include: three or more breast and/or ovarian cancer cases, at least one aged <50 years; two breast cancer cases aged <40 years; male breast cancer and early onset female breast cancer; and breast and ovarian cancer in the same patient [IV, C]. In some countries, the criterion for testing is that there should be at least a 10–20% probability of finding a mutation. In all cases, genetic testing should be performed after genetic counseling and informed consent.

mutation detection

Most clinically deleterious mutations are protein-truncating mutations and a small number are missense mutations. Genetic testing should include complete sequencing of coding regions, either directly or after a screening method. 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 may be indicated [III, B].

risk reduction: non-surgical preventive options

surveillance

Surveillance of breast cancer in *BRCA* carriers includes monthly self-examinations, clinical breast examinations once or twice a year and 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 has not been demonstrated [III,B].

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 and unilateral mastectomy [IV, C].

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prophylactic bilateral salpingo-oophorectomy

It 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].

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

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].

Standard prognostic features should be used to decide adjuvant treatment in BRCA mutation carriers with breast cancer. Ongoing clinical trials in the metastatic setting are testing the sensitivity to platinum-based chemotherapy of *BRCA* tumors and the specific DNA-repair deficiency with the use of PARP inhibitors.

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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