Clinical practice guideline of BRCA1/2 testing for patients with breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guideline 2021

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Breast cancer is the most common female cancer around the world. Approximately 5% to 10% of breast cancer is associated with a hereditary predisposition from inherited germline mutations [1] with about 15% of mutations occurring in the breast cancer susceptibility genes (BRCA1/2) [2-4]. Individuals carrying BRCA1/2 mutations may reduce their risk of breast cancer through screening and preventing managements [5,6]. It is essential for breast oncologists to improve their ability of identifying individuals with high risk of BRCA1/2 mutations, providing reasonable genetic counselling guidance to high risk individuals. Chinese Society of Breast Surgery (CSBrS) evaluated the relevant evidences using the Grading of Recommendations Assessment, Development, and Evaluation system, and developed the Clinical Practice Guideline of BRCA1/2 Testing for Patients with Breast Cancer (Version 2021), with the aim of providing guidance to the clinical practices of breast surgeons in China.

Level of Evidence and Recommendation Strength

Level of evidence standard [7]

Recommendation strength standard [7]

Recommendation strength review committee

There were 78 voting committee members for the guideline: 65 breast surgeons (83.3%), four medical oncologists (5.1%), three radiologists (3.9%), two pathologists (2.6%), one radiation therapist (1.3%), and two epidemiologists (2.6%).

Target Audience
Clinicians specializing in breast diseases in China.

Recommendations

Recommendation 1: Indications for BRCA1/2 testing.

<table>
<thead>
<tr>
<th>Indications for BRCA1/2 testing</th>
<th>Level of evidence</th>
<th>Recommendation strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Breast cancer diagnosed ≤45 years old [6,8-11]</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1.2 Breast cancer diagnosed 46 to 50 years old with one or more of the following:</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1.2.1 An additional breast cancer primary at any age [6,11,12]</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1.2.2 ≥1 close blood relative with breast cancer at any age [6,11,12]</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1.2.3 An unknown or limited family history [6]</td>
<td>II</td>
<td>A</td>
</tr>
<tr>
<td>1.3 Diagnosed ≤60 years old with triple negative breast cancer [6,12]</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1.4 Breast cancer diagnosed at any age with one or more of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4.1 ≥1 close blood relative with breast cancer</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

(continued)

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Recommendation 2: Risk control for BRCA1/2 mutation carriers.

<table>
<thead>
<tr>
<th>Risk control for BRCA1/2 mutation carriers</th>
<th>Level of evidence</th>
<th>Recommendation strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Breast awareness starting at 18 years old. Physical exam every 6 to 12 months, starting at age 25.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2.2 Annual breast MRI screening with contrast starting at age 30.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2.3 Annual breast MRI screening with contrast starting at age 25 if ≥1 close relative was diagnosed with breast cancer before the age of 30.</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td>2.4 Annual breast clinical-exam for male carriers starting at age 35 years old.</td>
<td>II</td>
<td>A</td>
</tr>
<tr>
<td>2.5 Prophylactic mastectomy† combined with immediate breast reconstruction.</td>
<td>II</td>
<td>B</td>
</tr>
</tbody>
</table>

†Individualized risk control strategies should be developed for BRCA1/2 mutation carriers over 75 years of age. †Including nipple-areolar complex (NAC)-sparing or skin-sparing mastectomy. MRI: Magnetic resonance imaging.

Recommendation 3: Surgical options for breast cancer patients with BRCA1/2 mutation.

<table>
<thead>
<tr>
<th>Surgical options for breast cancer patients with BRCA1/2 mutation</th>
<th>Level of evidence</th>
<th>Recommendation strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Breast-conserving surgery with adjuvant radiotherapy (RT) to the whole breast.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>3.2 Mastectomy.†</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>3.3 Mastectomy† combined with immediate breast reconstruction.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>3.4 Contralateral prophylactic mastectomy† with or without immediate breast reconstruction.</td>
<td>II</td>
<td>B</td>
</tr>
</tbody>
</table>

†Including nipple-areolar complex (NAC)-sparing or skin-sparing mastectomy.
Discussion

Indications for BRCA1/2 testing were recommended by considering national conditions and referring to relevant guidelines and expert consensus. BRCA1/2 gene variants were devised into five classifications for quantitative assessment of variant pathogenicity [Supplementary File 1, http://links.lww.com/CM9/A625].

In BRCA1/2 mutation carriers who are younger than 30 years old, breast magnetic resonance imaging screening is preferred over mammography due to the potential radiation exposure risk and less sensitivity for detection of tumors associated with mammography. Ultrasound is also an appropriate primary imaging examination. Ultrasound combined with mammography may be considered in the condition of unavailable enhanced magnetic resonance [Supplementary File 2, http://links.lww.com/CM9/A626]. Chemoprevention is not recommended for BRCA1/2 mutation carriers [Supplementary File 3, http://links.lww.com/CM9/A627].

Studies have indicated that bilateral risk-reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers. However, this risk-reducing surgery was not significantly associated with reduced all-cause mortality. Carrying a BRCA1/2 mutation is not significantly associated with nodal metastasis, so sentinel lymph node biopsy is not recommended when RRM is performed.

Whether there is an increased risk of ipsilateral breast cancer recurrence in breast cancer patients with BRCA1/2 mutation after breast-conserving treatment has not been confirmed [Supplementary File 4, http://links.lww.com/CM9/A628]. The guidelines panel recommend that patients with BRCA1/2 mutation who are first diagnosed with breast conserving indications receive breast conserving surgery with the assurance of adjuvant therapy. Contralateral prophylactic mastectomy for breast cancer with BRCA1/2 mutations could be considered. If prophylactic mastectomy was performed, immediate breast reconstruction is recommended [Supplementary File 5, http://links.lww.com/CM9/A629].

Conflicts of interest

The expert committee for these guidelines declares no conflict of interest.

These guidelines are a reference for breast disease specialists in clinical practice. However, the guidelines are not to be used as the basis for medical evaluation, and do not play an arbitrating role in the handling of any medical disputes. The guidelines are not a reference for patients or non-breast specialists. The Chinese Society of Breast Surgery assumes no responsibility for results involving the inappropriate application of these guidelines, and reserves the right to interpret and revise the guidelines.

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