

Clinical practice guidelines for risk assessment to identify women at high risk of breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021

Fei Wang¹, Xue-Ning Duan², Rui Ling³, Zhi-Gang Yu¹; Chinese Society of Breast Surgery

¹Department of Breast Surgery, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250033, China;

²Breast Disease Center, Peking University First Hospital, Beijing 100034, China;

³Department of Thyroid, Breast and Vascular Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, Shaanxi 710032, China.

Breast cancer is the most common malignancy among women in China. Approximately 304,000 new cases of breast cancer were diagnosed during 2015 in China, which ranked first in cancer diagnosis and accounted for 17.1% of all new cancers among women.^[1,2] Both the US Preventive Services Task Force (USPSTF)^[3] and National Comprehensive Cancer Network (NCCN) clinical practice guidelines^[4] have made recommendations regarding risk assessment, to identify women with increased risk for breast cancer, in whom risk-based cancer screening and/or risk-reducing medication use should be provided so as to lower the individual breast cancer risk.

In an effort to standardize the clinical application of risk assessment and identification of women with a high risk of breast cancer, the Chinese Society of Breast Surgery (CSBrS) engaged domestic experts to conduct a literature review and discuss the key clinical issues related to breast cancer risk assessment. With reference to the Grading of Recommendations Assessment, Development, and Evaluation system, the corresponding evidence was comprehensively evaluated, based on the availability in China. Herein, we report CSBrS recommendations on risk assessment to identify women at high risk of breast cancer, to provide a reference for clinical practice among Chinese breast clinicians and public health service staff.

Level of evidence and recommendation strength

Level of evidence standard^[5]

Recommendation strength standard^[5]

Recommendation strength review committee

There were 83 voting committee members for this guideline, including 69 breast surgeons (83.1%), four oncologists (4.8%),

four radiologists (4.8%), two pathologists (2.4%), two radiation therapists (2.4%), and two epidemiologists (2.4%).

Target Audience

Clinicians specializing in breast diseases in China.

Recommendations

Recommendation 1: Population under consideration

	Population under consideration	Level of evidence	Recommendation strength
1.1	Asymptomatic women ≥ 35 years who have no current or previous diagnosis of breast cancer or ductal carcinoma <i>in situ</i> (DCIS) ^[3]	I	A
1.2	Women with history of atypical hyperplasia or lobular carcinoma <i>in situ</i> ^[3,4]	I	A

Recommendation 2: Assessment tools

	Assessment tools	Level of evidence	Recommendation strength
2.1	Breast cancer risk assessment tool (Gail Model) ^[6]	I	B
2.2	Online tool of breast cancer risk assessment for Chinese women ^[7,8]	II	A

* Available at <http://sd2y.pingjiaxitong.com>.

Recommendation 3: Indications of genetic testing for *BRCA1/2* genetic mutations*

	Indications	Level of evidence	Recommendation strength
3.1	Women with a likelihood of inherited predisposition to breast cancer based on personal or family history [†] should be offered genetic counseling, in order to guide decision-making of genetic testing for <i>BRCA1/2</i> genetic mutations ^[9,10]	I	A

Correspondence to: Dr. Zhi-Gang Yu, Department of Breast Surgery, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250033, China
E-Mail: yzg@medmail.com.cn

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Chinese Medical Journal 2021;134(14)

Received: 01-03-2021 Edited by: Yuan-Yuan Ji

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000001502

	Indications	Level of evidence	Recommendation strength
3.2	Priority of genetic testing should be offered to the cancer patient(s) among the family members (index case) ^[9,10]	I	A

* The indications listed in this guideline apply only to healthy women at high risk of breast cancer. Indications of genetic testing for *BRCA1/2* mutations in patients with breast cancer can be found in the “Clinical Practice Guidelines for *BRCA1/2* Testing for Patients with Breast Cancer: Chinese Society of Breast Surgery (CSBrS) Practice Guidelines 2021.”
 † Individuals with one or more factors with respect to family history, as below, can be considered to have a likelihood of inherited predisposition to breast cancer: confirmed carriers of harmful *BRCA1/2* mutations among close family members (lineal blood relative, up to three generations); multiple cases of breast cancer in the family; male family members with breast cancer; close family members with a breast cancer diagnosis before age 50 years; close family members with two primary types (such as ovarian cancer and breast cancer) or two primary tumors (such as bilateral breast cancer or multifocal/multicentric breast cancer) of *BRCA*-related cancer. *BRCA1/2*: Breast cancer susceptibility gene 1/2.

Discussion

Assessment of breast cancer risk status is aimed to distinguish individuals at greater risk of breast cancer from those with average risk and to guide personalized risk reduction through risk stratification.^[11] Currently, there is no single cutoff for defining increased absolute risk of breast cancer for all women worldwide. A risk assessment tool is a kind of statistical method based on epidemiological risk factors, which can be used to predict individual probability of developing breast cancer over the next 5 or 10 years or a lifetime.^[12] The modified Gail model is now one of the most widely used breast cancer risk assessment tools, which sets risk thresholds of at least 1.67% for 5-year risk of breast cancer.^[6] Because it was initially developed for white women, the Gail model has been modified and validated for female Asian and Pacific Islander immigrants.^[13] However, the cutoff of the Gail model is still largely based on population reference standards of women from the United States.^[14] A meta-analysis showed that the Gail model may substantially overestimate the absolute breast cancer risk of Asian women and is therefore not suitable for use in this population.^[15] Our panel of experts proposes that development of a high-risk threshold exclusively for predicting breast cancer probability among Chinese women is warranted.

Limited breast cancer risk assessment tools have been developed for Chinese women. CSBrS guideline experts reviewed seven good- and fair-quality studies using six risk stratification models (Appendix, <http://links.lww.com/CM9/A546>).^[7,8,16-19] Similar to other international studies, most of these models reported only modest discriminatory accuracy, with C statistic values ranging from 0.61 to 0.66.^[16-18] However, for one model under review, levels of discriminatory accuracy above 0.70 were reported in both development and validation populations, with C statistic values of 0.73 and 0.72, respectively. Risk predictors included in this model are age, history of benign breast tumor, diabetes, residence, body mass index, life satisfaction score, and number of abortions.^[7,8] Online risk assessment services based on this model are now available to the public (<http://sd2y.pingjiaxitong.com>).

With reference to the USPSTF (medication use to reduce risk of breast cancer)^[3] and NCCN (breast cancer risk reduction)^[4] guidelines on populations under consideration of breast cancer risk assessment, the experts recommend that the present guideline on breast cancer risk assessment apply to all

asymptomatic women aged 35 years and older who have no current or previous diagnosis of breast cancer or ductal carcinoma *in situ*. Retrospective studies have shown that both atypical hyperplasia and lobular carcinoma *in situ* are important risk predictors, rather than precancerous diseases of breast cancer.^[20,21] Thus, the experts recommend that women with a history of atypical hyperplasia or lobular carcinoma *in situ* are also candidates for breast cancer risk assessment. Although direct evidence is unavailable regarding the optimal age or frequency for risk assessment or the best interval at which to reassess risk, the experts suggest that repeating risk assessment should be considered when there is a significant change in breast cancer risk factors (eg, when a family member is diagnosed with breast cancer or when there is a new diagnosis of breast disease on biopsy) or when any risk-reducing intervention (eg, lifestyle changes, control of body weight, or risk-reducing medications) has been undertaken. Considering that evidence for Chinese populations is still unavailable, no recommendation on risk-reducing medications for women with increased risk of breast cancer is made in the present guideline.

One large epidemiological survey showed that the prevalence of *BRCA1* or *BRCA2* mutations was 5.37% among women diagnosed with sporadic breast cancer in China.^[22] The probability of developing breast cancer before age 79 years among Chinese women who are carriers of *BRCA1* or *BRCA2* mutations is 37.9% and 36.5%, respectively, remarkably higher than that of the general population.^[22] Currently, both international and Chinese guidelines or expert consensus recommend that specific populations at high risk of cancer should be referred for genetic counseling and genetic testing to detect *BRCA1/2* mutations.^[9,10] Several familial risk stratification tools (eg, BOADICEA and BRCAPRO) have been developed and validated to predict the individual probability of carrying harmful *BRCA1/2* mutations among women with a family history of breast cancer.^[23] As shown in section 3.1, this guideline puts forth recommendations on the characteristics of a personal family history suggestive of high inherited susceptibility to cancer. These characteristics are based on predictors included in the abovementioned international familial risk stratification tools, factors associated with increased likelihood of potential harmful *BRCA1/2* mutations, as indicated by USPSTF as well as the diagnostic criteria of populations at high risk of inheritable cancer, as defined by the Chinese Anti-Cancer Association.^[9,24] To date, limited familial risk stratification tools are available to evaluate whether a family history of breast cancer is related to *BRCA1/2* mutations in Chinese women.^[25] The experts suggest that pretest genetic counseling should be offered before testing for *BRCA1/2* mutations, to balance both benefits and harm of this service for individuals with the above characteristics of family history. For women with confirmed harmful mutations in the *BRCA* genes, a variety of risk-reducing interventions may be considered. Detailed recommendations on these interventions can be found in the “Clinical Practice Guidelines for *BRCA1/2* Testing for Patients with Breast Cancer: CSBrS Practice Guidelines 2021.”^[26]

The experts recognize that risk assessment of breast cancer is a preventive measure designated for healthy women. Considering that current high-level evidence specific to Chinese women is still lacking, clinical decisions should involve additional considerations and should not rely on evidence alone. Clinicians and primary care providers should hold discussions with women undergoing risk assessment to address the aims of assessment, limitations of the current evidence, potential risk-reducing

interventions as well as their corresponding benefits and harm. Additionally, psychological counseling is necessary for women who are considered at high risk of breast cancer, to minimize the psychological distress associated with risk status.

List of Compiling Committee Members (In Alphabetical Order by Surname)

Rong Ma, Chuan Wang, Shui Wang, Ting Wang, Yu Wang, Jian-Dong Wang, Shu Wang, Fei Wang, Xiang Wang, Da-Hua Mao, Xing-Song Tian, Wei Zhu, Guo-Sheng Ren, Yun-Jiang Liu, Ke Liu, Yin-Hua Liu, Zhen-Zhen Liu, Qian Liu, Jin-Ping Liu, Ke-Jin Wu, Jiong Wu, Zhi-Gang Yu, Qiang Zou, Ling Xin, Er-Wei Song, Ai-Lin Song, Jian-Guo Zhang, Jing-Hua Zhang, Jin Zhang, De-Dian Chen, Zhi-Min Fan, Jiang-Hua Ou, Yong-Hui Luo, Feng Jin, Ang Zheng, Xiang Qu, Zuo-Wei Zhao, Yi Zhao, Xue-Ning Duan, Jun Jiang, Rui Ling, Li-Li Tang, Jian Huang, Zhong-Wei Cao, Hua Kang, Hong-Chuan Jiang, Yuan-Jia Cheng, Pei-Fen Fu, Fei Xie, Jing Fan.

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 should 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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How to cite this article: Wang F, Duan XN, Ling R, Yu ZG; Chinese Society of Breast Surgery. Clinical practice guidelines for risk assessment to identify women at high risk of breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021. *Chin Med J* 2021;134:1655–1657. doi: 10.1097/CM9.0000000000001502