Recommendations of the Brazilian College of Radiology, the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics Associations for breast cancer screening in Brazil

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ABSTRACT

Objective: To present the updated recommendations of the Brazilian College of Radiology and Imaging Diagnosis, the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics Associations for breast cancer screening in Brazil.

Methods: Between January 2012 and July 2022, searches for scientific evidence published in MEDLINE, Embase, Cochrane Library, EBSCO, CINAHL and LILACS were carried out. The recommendations were based on this evidence, with the consensus of a committee of experts from the three institutions. Recommendations: The annual mammography screening is recommended for normal-risk patients aged between 40 and 74 years. For women aged more than 75 years, it is reserved for those whose life expectancy is longer than seven years. Women whose risk is higher than normal, such as those with dense breasts, personal history of atypical lobular hyperplasia, classic in situ lobular carcinoma, atypical ductal hyperplasia, women undergoing breast cancer treatment or thoracic irradiation before the age of 30, or those with genetic mutation or strong family history, benefit from complementary screening, being considered in an individual manner. Tomosynthesis is an evolution of mammography and should be considered in screening whenever accessible and available.

KEYWORDS: breast cancer screening; mammography; ultrasound; magnetic resonance.

INTRODUCTION

In 2021, breast cancer became the most frequently diagnosed cancer in the world, and the main cause of death among women1. In Brazil, in 2023 73,610 new cases of breast cancer were estimated, which represents an adjusted incidence rate of 41.89 cases per 100 thousand women1. Screening is an efficient method to detect the disease in an early stage, thus reducing its mortality. Besides, the early diagnosis allows a greater range of therapeutic options and reduces treatment morbidity2-4.

In 2012 and 2017, the Brazilian College of Radiology (CBR) and Imaging Diagnosis, the Brazilian Society of Mastology (SBM), and the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo), through the National Mammography Commission (CNM), published the recommendations of breast cancer screening5-6. The objective of this update is to publish the available evidence about screening and to provide information for the decision-making of women with different risks for developing the disease.
METHODS

The following databases were searched: MEDLINE (via PubMed), Embase, Cochrane Library, EBSCO, CINAHL and LILACS (via Bireme), using as many keywords, descriptors and MeSH terms as possible, in order to find scientific evidence about breast cancer screening with mammography (MG), ultrasound (US), magnetic resonance imaging (MRI) and tomosynthesis (TMS), in women at normal, intermediate and high risk for breast cancer, published between January 2012 and July 2022, in Portuguese, English, French and Spanish. Complementary searches were conducted in websites, on-line tools and in the references of the analyzed studies. The most recent and qualified processed evidence were selected for analysis (systematic reviews and meta-analyses), as well as those that better responded the structured questions. At their absence, primary studies (clinical trials or cohorts) were included. The risk of bias of the studies was assessed using the following tools: ROBIS (Risk of Bias in Systematic Reviews), RoB 2.0 (Cochrane Risk of Bias Tools for Randomized Controlled Trials version 2.0), QUADAS-C (Quality Assessment of Diagnostic Accuracy Studies – Comparative) and ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions). The global quality of the set of evidence for each outcome was assessed by GRADE (Grading of Recommendations Assessment, Development and Evaluation).

The recommendations were based on this evidence, with the consensus of the commission of experts from the three institutions (CBR, SBM and Febrasgo), defined after at least 75% of agreement among the members with the recommendation. In the absence of an initial agreement, a second round of discussion and voting took place, and the simple majority was required to define a consensus. The recommendations were classified in five categories:

- Category A – Strong recommendation in favor, based on high quality evidence.
- Category B – Strong recommendation in favor, based on moderate quality evidence.
- Category C – Weak recommendation in favor, based on low quality evidence.
- Category D – Recommendation in favor, based only on the consensus of experts.
- Category E – Recommendation against, because the evidence is insufficient to support its use.

Recommendations for screening

Screening for women at normal risk

Mammography

The annual screening with MG is recommended for women aged between 40 and 74 years, preferably with digital technology (category A).

After the age of 75, screening is recommended if there are no comorbidities that reduce life expectancy, which should be of at least seven years (category D).

Ultrasound

The US is not recommended as a supplementary or isolated screening method for women at normal risk (category E).

Note: The US is considered for specific situations of higher risk (see session about dense breasts, intermediate risk and high risk).

Magnetic resonance

MRI is not recommended as a supplementary or isolated screening method for women at normal risk (category E).

Note: The use of MRI is considered for specific situations of higher risk (see session about dense breasts, intermediate risk and high risk).

Tomosynthesis

TMS, when combined with synthesized 2D MG or with standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening among women with dense breasts

Mammography

The annual screening with MG is recommended for women aged between 40 and 74 years, preferably with digital technology (category A).

After the age of 75, screening is recommended if there are no comorbidities that reduce life expectancy, which should be of at least seven years (category D).

Ultrasound

The annual US can be considered as an adjunct to MG in women with dense breasts, except when MR is performed (category B).

Magnetic Resonance

The recommendation is that a biennial MRI can be considered as adjunct to MG in extremely dense breasts (category C).

Tomosynthesis

The recommendation is that TMS, combined with synthesized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Screening of women with personal history of biopsy with atypical lobular hyperplasia, classic in situ lobular carcinoma, and atypical ductal hyperplasia

Initial note: It is recommended that women with atypical lobular hyperplasia (ALH), classic in situ lobular carcinoma (ISLC) or atypical ductal hyperplasia (ADH) be assessed by risk calculation.
models that include these variables together with other clinical data, including family history and breast density, to estimate the risk of breast cancer.

**Mammography**
For women with risk estimation <20% throughout life, an annual MG is recommended after the age of 40 (category A).
For women with risk estimation ≥20% throughout life, an annual MG is recommended after the diagnosis (not before the age of 30) (category B).

**Ultrasound**
For women with risk estimation of 15 to 20% throughout life, the US can be considered as adjunct to MG (category D).
For women with risk estimation ≥20% throughout life, the US is recommended as an alternative method for those who cannot undergo MR, for any reason (category B).

**Magnetic Resonance Imaging**
For women with risk estimation ≥20% throughout life, an annual MRI should be considered as adjunct to MG after diagnosis (not before the age of 25) (category B).

**Tomosynthesis**
The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

**Screening of women with personal history of invasive breast cancer or in situ ductal carcinoma**

**Mammography**
Women treated with conservative surgery should undergo an annual MG (category A), starting at least six months after the conclusion of radiotherapy.
Women who underwent nipple-sparing mastectomy can consider MG after up to one year to assess the residual fibroglandular tissue, to determine the need for maintaining mammography screening (category D).

**Ultrasound**
The US can be used as complementary screening to MG when MR is indicated, however, for whatever reason, cannot be performed (category C).

**Magnetic Resonance Imaging**
Women treated with conservative surgery or mastectomy (for the evaluation of the contralateral breast), who were diagnosed with breast cancer before the age of 50, or with dense breasts, should have an annual MRI (category C), starting one year after the end of treatment.

**Tomosynthesis**
The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

**Screening of women with personal history of thoracic radiotherapy**

**Mammography**
Women with history of thoracic irradiation before the age of 30 should undergo an annual MG eight years after radiotherapy (not before the age of 30) (category A).

**Ultrasound**
The US should be used for screening only when MG, for whatever reason, cannot be performed (category B).

**Magnetic Resonance Imaging**
Women with history of thoracic irradiation before the age of 30 should undergo an annual MR eight years after radiotherapy (not before the age of 25) (category A).

**Tomosynthesis**
The recommendation is that TMS, combined with synthetized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

**Screening of women with genetic mutation or strong family history of breast cancer (risk ≥20% throughout life)**

**Mammography**
Women with pathogenic mutation of the BRCA1 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MG after the mutation is diagnosed (not before the age of 35) (category A).
Women with BRCA2 pathogenic variant or others, with moderate or high risk for breast cancer, besides those who are not tested, but have first-degree relatives who carry them, should undergo an annual MG after the mutation is diagnosed (not before the age of 30) (category A).
Women with BRCA2 pathogenic variant or others, with moderate or high risk for breast cancer, besides those who are not tested, but have first-degree relatives who carry them, should undergo an annual MG after the mutation is diagnosed (not before the age of 30) (category A).
Women with risk ≥20% throughout life, calculated by one of the mathematical models based on family history, should have
an annual MG starting 10 years before the age of the youngest relative at diagnosis (not before the age of 30) (category A).

Ultrasound
The US should be used for screening only when MRI, for whatever reason, cannot be performed (category B).

Magnetic Resonance Imaging
Women with pathogenic mutation of the BRCA1 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MRI after the mutation is diagnosed (not before the age of 25) (category A).

Women with pathogenic mutation of the TP53 gene, or those untested, but with first-degree relatives who carry it, should undergo an annual MG after the mutation is diagnosed (not before the age of 20) (category A).

Women with BRCA2 pathogenic variant or others, with moderate or high risk for breast cancer, besides those who were not tested, but with first-degree relatives who carry it, should perform an annual MR after the mutation is diagnosed (not before the age of 30) (category A).

Women with risk ≥20% throughout life, calculated by one of the mathematical models based on family history, should undergo an annual MRI starting 10 years before the age of the youngest relative at diagnosis (not before the age of 30) (category A).

Tomosynthesis
The recommendation is that TMS, combined with synthesized 2D MG (sMG) or standard 2D MG (Combo), should be considered for screening, when available (category B).

Justification
The benefits of mammography screening were assessed through cohort studies, systematic reviews and randomized clinical trials, demonstrating a reduction of mortality specifically caused by breast cancer from 22% to 30%, in women aged between 40 and 74 years. When other major outcomes were analyzed, it was possible to observe better quality of life measured by QALY (quality-adjusted life-years), resulting from less aggressive treatments, besides higher rates of initial tumors, with better prognostic characteristics and negative axilla, and 28% less advanced tumors.

Age of beginning and periodicity of screening
The beginning of screening at the age of 40 reduces mortality in 10 years by breast cancer in 25%; however, it increases the false-positive (FP) rate from 4.8 to 7%. In Brazil, it is observed that 41.1% of the women diagnosed with breast cancer are younger than 50, according to data from the AMAZONA study. As to screening interval, the biennial one is related to larger risk of advanced tumors (RR=1.28), larger than 15 mm and with worse prognostic factors. Therefore, CNM recommends the annual screening with MG after the age of 40.

Considerations about women aged less than 40 years
Screening is not recommended in this age group, due to the lower incidence of breast cancer (about 7% of the cases). However, the AMAZONA III study showed that, in Brazil, this rate is 17%, with larger tumors and worse prognosis at diagnosis, in comparison to women aged more than 40 years. Therefore, in agreement with other international societies, CNM recommends that the assistant doctor perform an evaluation of the estimated risk for breast cancer for all women who are older than 30, through mathematical models, to better stratify those with increased risk that might benefit from special screening.

When to interrupt screening
Prospective, controlled and randomized studies did not include women aged more than 74 years, so there are no direct data about screening at this age group. However, women's life expectancy has increased, and the incidence of breast cancer in the age group above 75 years is increasing as well. Currently, 26% of deaths caused by breast cancer occur in women diagnosed after the age of 74 years. Considering those factors, many medical organizations recommend the decision be individualized and discussed with the woman.

Adverse effects of screening
Some adverse effects have been reported, however, the quality of evidence for their analysis is low. Overdiagnosis is a discussed effect, but its estimation is variable due to the difficulty to determine which tumor would or would not lead the patient to death. The risk of carcinoma induced by the radiation used in mammography screening is low, however, it is higher in women with large breasts, for whom the dose of radiation is higher, as well as in those who undergo complementary incidences. It has also been associated with a 2.9% increase in the risk of biopsies with benign outcome (BO), which can create anxiety. However, the reduction in mortality of the cancer that is detected early through screening overcomes the risks of the damage caused by the exposure to radiation.

Considerations about breast TMS
TMS is an evolution of digital MG. Several studies confirm the efficacy of this technology in breast cancer screening, which increases the detection rate in up to 50% and reduces the rate of recall for additional images from 9 to 29%. The detected tumors have similar histological and immunohistochemical characteristics to those detected by the MG, and the results remain in the subsequent rounds. Therefore, TMS is recommended as a screening...
Considerations about screening of women with dense breasts

The dense breast is a risk factor for breast cancer and is associated with reduced mammography sensitivity. Therefore, supplementary methods have been proposed. All supplementary modalities improved sensitivity regarding isolated MG, thus allowing the detection of early-stage cancers hidden in MG. MRI is the supplementary technique with higher additional detection rate when it comes to cancer. This increases the chances of less invasive and more curative treatments. Data on critical outcomes, such as mortality, are not available. However, randomized trials showed that the supplementary use of US in the dense breast or the MR in extremely dense breasts reduced the rate of interval cancer, an important substitute outcome centered on the patient. Regarding damage, the use of supplementary modalities is associated with increasing False Positive (FP) rates and biopsies. Therefore, for women with dense breasts and no other risk factors, the CNM recommends annual screening with MG after the age of 40, and as an option the use of supplementary methods such as US or MRI. For extremely dense breasts, there is scientific evidence suggesting the superiority of MRI.

Considerations about screening in women with personal history of diagnosis of atypical lobular hyperplasia, classic lobular carcinoma in situ and atypical ductal hyperplasia

Atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and classic in situ lobular carcinoma in situ (LCIS) are considered as non-obligatory precursor lesions for in situ ductal carcinoma and invasive carcinoma; they represent increased relative risk for their subsequent development throughout life, being from 2.6 to 5.0 times for ADH; 3.2 to 4.8 times for ALH; and 6 to 10 times for LCIS.

There are few studies to evaluate screening in this group, based on retrospective series that estimated the risk for in situ and invasive subsequent carcinomas. The current strategy to define screening in this subgroup is based on the calculation of risk for breast cancer throughout life. Factors such as age of diagnosis and breast density have a direct impact on the risk of cancer, which can be estimated by risk calculation tools based on mathematical models. Currently, a few models contemplate this group in the calculation of risk, such as: Breast Cancer Risk Assessment Tool (the Gail model) and IBIS Breast Cancer Risk Evaluation Tool (Tyrer-Cuzick model), and these should be preferably used.

Considerations about screening of women with personal history of treatment for invasive breast cancer and ductal carcinoma in situ

Women with personal history of breast cancer present seven times more chances of developing a second ipsilateral or contralateral malignant breast neoplasm. In patients treated with conservative surgery, MG presents less sensitivity due to surgical changes and higher incidence of interval carcinoma, thus justifying the need for supplementary screening.

Complementary screening with MRI can detect from 8.2 to 18.1 additional cancers in relation to MG in one thousand women. The performance of MRI in this scenario has been similar to that of patients with high genetic risk, considering the sensitivity, detection rate, FP and positive predictive value (PPV) of biopsies. However, scientific evidence for MRI in this population is weak, based mostly on retrospective studies. In this heterogeneous group, the benefit of MRI is more well established in young patients (age of diagnosis <50 years), and with dense breasts.

A few studies assessed the accuracy of the US, with detection rate of additional cancers to MG of 2.4 to 4.1/1,000 women; however, with increasing FP and lower PPV for biopsies. When performed in addition to MRI, the US does not result in improved sensitivity, but it can be used as supplementary screening when the MRI is not available.

In patients with personal history of breast cancer treated with mastectomy, the image screening of the treated breast, with or without reconstruction, is not indicated due to the low detection of asymptomatic cancers through MG, US or MRI.

Considerations about screening in women with history of thoracic radiotherapy

Women treated with thoracic radiotherapy before the age of 30 have average risk of developing breast cancer 13.4 higher than the general population, similarly to patients with BRCA1 gene mutation. The increase in incidence occurs about 10 years after treatment, persisting 30 years later. The highest incidence occurs when the treatment took place between the ages of 10 and 14.
MG, its role in patients with BRCA1 mutation has been questioned. A metaanalysis demonstrated that the addition of MRI starting at the age of 25 or eight years after radiotherapy, in accordance with the recommendations of other medical institutions, such as the Children’s Oncology Group and the International Guideline Group.

Screening of women with genetic mutation or strong family history of breast cancer (risk ≥20% throughout life)

Gene mutations that lead to predisposition to breast cancer are classified as high risk when they cause an increase of five times or more in comparison to women who do not carry them (BRCA1, BRCA2, TP53, PTEN, among others), or intermediate risk when they increase the chances in 1.5-5 times (ATM, CHEK2, BARD1, among others). In Brazil, a study has shown that the most mutated genes were BRCA1 (27.4%), BRCA2 (20.3%), TP53 (10.5%), ATM (8.8%), CHEK2 (6.2%) and PALB2 (5.1%). The Brazilian variant TP53 R337H was strongly associated with the risk of breast cancer (OR = 17.4). In the case of women with strong family history of breast cancer, however, with no known mutation, high risk was defined for those with estimation ≥20% of risk throughout life, calculated using mathematical models. These women present cancer at an early age, with peaks of incidence between 20-35 years old for the PT53 mutation, as well as between 40-59 years old for high family risk.

For this risk group, there is strong scientific evidence about the importance of MRI screening, due to the reduction of interval cancer and higher rates of detecting tumors at early stages, which can reduce the need for chemotherapy and mortality, despite the higher number of FPs. As to MG, its role in patients with BRCA1 mutation has been questioned. A metaanalysis demonstrated that the addition of MG to MRI in patients with the BRCA1 mutation modestly increased sensitivity (3.99%), with reduction in specificity (4%). As to the BRCA2 mutation, the increase in sensitivity was higher (12.6%), with small reduction in specificity (5%). Thus, the CNM recommends screening with MRI associated with MG, however, not starting MG before the age of 35 for BRCA1, and the age of 30 for the other groups. Additional US examinations do not produce additional cancer detection, if the MRI is performed, so it should be reserved for a posterior evaluation or as a guide for the biopsy of findings identified in the MRI.

As to the impact on mortality, a relevant study was published by Bae et al., which, despite being retrospective, demonstrated that high risk women who underwent screening with MG and MRI presented better global survival rates and tumors diagnosed at stages with better prognosis than patients in the group who only underwent MG.

CONCLUSION

This guideline shows the consensus of the recommendations based on current data for breast cancer screening in Brazil, subdivided in sessions according to the risk for developing breast cancer, since the approach by women of normal risk, who represent approximately 80% of the patients diagnosed with breast cancer, until women with increased risk.

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AUTHORS’ CONTRIBUTIONS

LABD: Project administration, Formal analysis, Conceptualization, Data curatorship, Writing – first draft, Writing – Revision and editing, Investigation, Methodology, Obtaining funding, Resources, Software, Supervision, Validation, Visualization. LFC: Conceptualization, Data curatorship, Writing – first draft, Writing – Revision and editing, Investigation, Methodology, Obtaining funding, Software, Supervision, Validation, Visualization. IBP: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. SPB: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. MBS: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. IB: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. ALKO: Writing – first draft, Writing – revision and editing, Investigating, Software, Validation, Visualization. PCM: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. CS: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. TMGO: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. BMMM: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. EOC: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization. SJFR: Writing – first draft, Writing – revision and editing, Investigation, Software, Validation, Visualization.
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