

Guidelines for early detection of breast cancer in Brazil. II – New national recommendations, main evidence, and controversies

Diretrizes para detecção precoce do câncer de mama no Brasil. II – Novas recomendações nacionais, principais evidências e controvérsias

Directrices para la detección precoz del cáncer de mama en Brasil. II – Nuevas recomendaciones nacionales, principales evidencias y controversias

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Abstract

Breast cancer is the leading cause of cancer mortality in Brazilian women. The new Brazilian guidelines for early detection of breast cancer were drafted on the basis of systematic literature reviews on the possible harms and benefits of various early detection strategies. This article aims to present the recommendations and update the summary of evidence, discussing the main controversies. Breast cancer screening recommendations (in asymptomatic women) were: (i) strong recommendation against mammogram screening in women under 50 years of age; (ii) weak recommendation for mammogram screening in women 50 to 69 years of age; (iii) weak recommendation against mammogram screening in women 70 to 74 years of age; (iv) strong recommendation against mammogram screening in women 75 years or older; (v) strong recommendation that screening in the recommended age brackets should be every two years as opposed to shorter intervals; (vi) weak recommendation against teaching breast self-examination as screening; (vii) absence of recommendation for or against screening with clinical breast examination; and (viii) strong recommendation against screening with magnetic resonance imaging, ultrasonography, thermography, or tomosynthesis alone or as a complement to mammography. The recommendations for early diagnosis of breast cancer (in women with suspicious signs or symptoms) were: (i) weak recommendation for the implementation of awareness-raising strategies for early diagnosis of breast cancer; (ii) weak recommendation for use of selected signs and symptoms in the current guidelines as the criterion for urgent referral to specialized breast diagnosis services; and (iii) weak recommendation that every breast cancer diagnostic workup after the identification of suspicious signs and symptoms in primary care should be done in the same referral center.

Neoplasms; Early Detection of Cancer; Mass Screening; Mammography; Practice Guidelines as Topic

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Introduction

Breast cancer is the most frequent cancer in Brazilian women, except for non-melanoma skin cancer. In 2017, there were an estimated 57,960 new cases of the disease ¹, and in 2014 the Brazilian Mortality Information System recorded 14,622 deaths in women due to breast cancer, the principal cause of death from cancer in Brazilian women. In Central and South America, the highest incidence and mortality rates were in Argentina, Brazil, and Uruguay ². In the last three decades, breast cancer mortality increased in all five major geographic regions of Brazil ³. This increase may have resulted partially from the increase in incidence due to women's greater exposure to risk factors from the urbanization process and lifestyle changes ⁴, aggravated by Brazil's intense population aging ⁵. The leading risk factors for breast cancer – advanced age at first pregnancy, low parity, and short breastfeeding duration ⁶ – are less amenable to public health interventions, especially in modern societies where women have increased their professional and social participation. Other known risk factors for the disease (alcohol consumption, overweight, and physical inactivity after menopause) are already the target of preventive measures for other chronic non-communicable diseases ⁷. Thus, early detection and treatment are generally considered the most effective means to reduce mortality from breast cancer.

The new guidelines for early detection of breast cancer in Brazil were based on systematic literature reviews of the risks and possible benefits of various early detection strategies ^{8,9}. The current article's objective is to present the new guidelines and a summary of the evidence for the recommendations, discussing the main controversies in light of the best and most current available evidence.

Methods

The detailed methods for definition of the scope, research questions, search strategies, selection of studies, evaluation of the quality of evidence, and formulation of recommendations in the guidelines have been published elsewhere ^{8,9}.

This article begins with a summary of the evidence for the new guidelines and their recommendations. We also updated the original searches for the guidelines in MEDLINE ⁸ up to March 31, 2017. The new articles were assessed according to the same eligibility criteria originally used, and their results and implications for the new guidelines were included in the sections on evidence synthesis and discussion of this article, except for the new abstracts on the strategies for early diagnosis, whose new eligibility criteria only included systematic reviews or clinical trials. We also searched for updated publications with new follow-up data of the clinical trials on screening.

The guidelines were divided into recommendations for screening and for early diagnosis, that is, strategies aimed at asymptomatic women and at those with signs and symptoms of cancer, respectively. For screening, we evaluated mammography and the following methods, independently, or in combination with mammography: breast self-examination; clinical breast examination; ultrasonography; magnetic resonance image; breast tomosynthesis and thermography. The recommendations do not refer to the population at high risk of developing breast cancer. For early diagnosis we evaluated strategies of awareness of suspicious signs and symptoms for breast cancer, clinical criteria for identifying suspected cases in primary health care and the diagnostic confirmation in a single health care unit ⁹.

Recommendations

The recommendations of the new guidelines for screening are described in Box 1 and for early diagnosis in Box 2. Box 3 explains the interpretation of each type of recommendation according to the guideline's target populations, that is, health professionals, health managers and the general population.

Box 1

Brazilian Ministry of Health recommendations for breast cancer screening.

Ministry of Health recommendations for breast cancer screening		
Mammography	< 50 years	Recommends against mammographic screening in women less than 50 years of age. (Strong recommendation: possible harms clearly outweigh possible benefits).
	50 to 59 years	Recommends mammographic screening in women 50 to 59 years of age. (Weak recommendation: possible benefits and harms are probably similar).
	60 to 69 years	Recommends mammographic screening in women 60 to 69 years of age. (Weak recommendation: possible benefits probably outweigh possible harms).
	70 to 74 years	Recommends against mammographic screening in women 70 to 74 years of age. (Weak recommendation: balance between possible harms and benefits is uncertain).
	≥ 75 years	Recommends against mammographic screening in women 75 or older. (Strong recommendation: possible harms probably outweigh possible benefits).
	Periodicity	Recommends biennial screening in the recommended age brackets. (Strong recommendation: possible benefits probably outweigh possible harms when compared to intervals shorter than every other year).
Breast self-examination		Recommends against teaching self-examination as a breast cancer screening method. (Weak recommendation: possible harms probably outweigh possible benefits).
Clinical breast examination		Absence of recommendation: the balance between possible harms and benefits is uncertain.
Magnetic resonance imaging		Recommends against breast cancer screening with MRI in women with standard risk of developing this cancer, either alone or with mammography. (Strong recommendation: possible harms probably outweigh possible benefits).
Ultrasonography		Recommends against breast cancer screening with breast ultrasound, either alone or with mammography. (Strong recommendation: possible harms probably outweigh possible benefits).
Thermography		Recommends against breast cancer screening with thermography, either alone or with mammography. (Strong recommendation: possible harms probably outweigh possible benefits).
Tomosynthesis		Recommends against breast cancer screening with tomosynthesis, either alone or with mammography. (Strong recommendation: possible harms probably outweigh possible benefits).

Note: these recommendations are not directed at the 1% of the female population who are at high risk of breast cancer.

Evidence synthesis

Screening with mammography

Originally, six systematic reviews of clinical trials contributed results to the evaluation of the effectiveness of screening mammography in the new guidelines^{10,11,12,13,14,15,16}. None of them showed a statistically significant reduction in overall mortality. In the meta-analysis that only included clinical trials with adequate or suboptimal randomization, there was a 19% reduction in mortality from breast cancer with screening mammography in 13 years of follow-up (RR = 0.81; 95%CI: 0.74-0.87), corresponding to an absolute benefit, i.e., a difference in the risk of death from breast cancer, between screened and unscreened groups, of 0.05%^{11,16}.

When updating the evidence on benefits and harms of mammography screening for this article, 36 references were retrieved and three references that reported the results of systematic reviews were selected^{17,18,19}. Regarding mortality from breast cancer, the U.S. Preventive Services Task Force (USPSTF) continued to present similar results to the previous version, except for the loss of statistical significance in the 40 to 49 years age group (RR = 0.92; 95%CI: 0.75-1.02)¹⁷.

Box 2

Brazilian Ministry of Health recommendations for early diagnosis of breast cancer.

Ministry of Health recommendations for early diagnosis of breast cancer	
Breast awareness	Recommends implementation of breast awareness strategies for early diagnosis of breast cancer. (Weak recommendation: possible benefits probably outweigh possible harms).
Identification of suspicious signs and symptoms	Recommends that the following signs and symptoms be considered for urgent referral to breast diagnostic services (Weak recommendation: possible benefits probably outweigh possible harms): <ul style="list-style-type: none"> • Any breast lump in women over 50 years of age; • Breast lump in women over 30 years of age that persists for more than one menstrual cycle; • Breast lump with hardened and fixed consistency or that has increased in size in adult women of any age; • Unilateral bloody nipple discharge; • Eczematous breast skin lesion that fails to respond to topical treatments; • Men over 50 years of age with a unilateral palpable lump; • Presence of axillary lymphadenopathy; • Progressive increase in breast size with signs of edema, such as orange-peel skin; • Retraction of breast skin; • Change in nipple shape.
One-stop diagnostic confirmation	Recommends that every breast cancer diagnostic workup after identification of suspicious signs and symptoms in primary care be done in a single referral center. (Weak recommendation: possible benefits probably outweigh possible harms, when compared to the traditional organization of diagnostic services).

The most common harm from screening mammography is a false-positive result, the cumulative probability of which after ten years of screening is 61% in annual and 42% in biennial screening intervals, according to USA data ¹⁹.

Meanwhile, the most serious harm from screening is overdiagnosis and overtreatment, i.e., unnecessary diagnoses and treatments ⁹. After 25 years of follow-up of Canadian clinical trials, 50% of the cases of non-palpable invasive cancer, detected by screening mammography alone, were classified as overdiagnosis ²⁰. According to a Cochrane meta-analysis based on data from the clinical trials that did not introduce screening mammography in the control group while the study was being conducted, screening generates an excess of 30% of women treated unnecessarily ¹¹. The increase in breast surgeries in the screened group (including mastectomies and breast-conserving surgeries) was approximately 30% (RR = 1.31; 95%CI: 1.22-1.42) when compared to unscreened women, even without considering probable reoperations, since the number of excess surgeries was like the number of excess diagnoses. The percentage of overtreatment was even greater in trials with suboptimal randomization, reaching more than 40% (RR = 1.42; 95%CI: 1.26-1.61), analyzing only the period prior to introduction of screening in the control group ¹¹. In absolute terms, this would translate as ten women treated unnecessarily and possibly one death avoided for every two thousand women invited for screening over the course of ten years ¹¹.

No clinical trial directly measured the association between screening mammography and induction of cancer from the radiation ²¹. The available data are extrapolations from acute exposures to higher doses of ionizing radiation ²¹. According to the modeling study cited by the Canadian Task Force on Preventive Health Care and the new USPSTF review, annual mammograms performed from 40 to 80 years of age could induce 20 to 25 fatal cancer cases for every 100,000 women screened ^{19,21}.

Clinical trials on screening mammography included women aged between 39 and 74 years, varying between studies ⁸. All the selected systematic reviews of clinical trials showed that the greatest benefit of screening occurs in women aged 60 to 69 years, while the lowest benefit occurs in women

Box 3

Interpretation of the degrees of recommendation according to the target audience.

Target audience	Degrees of recommendation			
	Strong (in favor)	Weak (in favor)	Weak (against)	Strong (against)
Managers	The intervention should be adopted as health policy in most situations	The intervention can be adopted as health policy in some specific contexts, taking into account the balance between benefits and harms of other interventions and health priorities	The intervention should NOT be adopted as a health policy. However, in some specific contexts, may be subject to debate	The intervention should NOT be adopted as a health policy
Health professionals	Most patients should receive the recommended intervention	Different choices will be appropriate for each person and the shared and informed decision-making process should give greater weight to patients' values and preferences	Different choices will be appropriate for each patient, and the shared and informed decision process should give greater weight to patients' values and preferences	Most patients should NOT receive the intervention
Population	Most people, when well informed, would like the intervention, only a minority would not	Most people, when informed, would like the intervention, but many would not	Most people, when well informed, would NOT want the intervention, but many would	Most people, when well informed, would NOT want the intervention, only a minority would

from 40 to 49 years, and for this last age group controversy on the real effectiveness in breast cancer mortality reduction persists.

In addition, harms associated with screening are greater in the 40 to 49 years age group, including the need for further screening mammograms, imaging tests, and biopsies for the detection of one additional case of invasive breast cancer¹². For example, the proportion of false-positive results is heavily dependent on age and is higher in younger women. Even assuming that screening from 40 to 49 years of age reduces the risk of dying from breast cancer, for every woman that theoretically could have her life prolonged by having participated in four rounds of screening, 2,108 women would have to be screened, 690 would receive false-positive results, and 75 would be biopsied unnecessarily. For women 50 to 69 years of age, the figures would be 721, 204, and 26²¹.

In the screening mammography trials included in the selected meta-analyses, the interval between screening rounds varied from 12 to 33 months²¹. Stratified analyses of one of these systematic reviews did not show a statistically significant difference in the reduction of mortality according to different screening intervals in the target population from 50 to 69 years of age (comparing intervals of two years or greater and intervals of less than two years)²¹. A randomized clinical trial designed specifically to compare different intervals found that the risk of dying from breast cancer did not differ between the annual versus three-year interval; the three-year interval between tests was thus adopted in the screening program in the UK²¹. While intervals shorter than two years would not provide an additional benefit, evidence based on modeling suggests that a reduction in the interval from two years to one year would double the magnitude of harms associated with screening¹². Thus, intervals of 24 to 30 months between screening round in women 50 to 69 years of age are safe in terms of maintaining the possible benefits and reducing potential harms.

Screening with clinical breast examination

All five selected systematic reviews on screening with clinical breast examination concluded that there is still no evidence on this intervention's efficacy for the reduction of breast cancer mortality ^{12,22,23,24}. Randomized clinical trials in Kerala ²⁵ and Mumbai ²⁶ in India and a trial in the Philippines ²⁷ reported that screening with clinical breast examination resulted in diagnosis of disease in stages with better prognosis ²⁵, which however could be attributed to length bias, overdiagnosis, or even a possible effect from the simultaneous application of a breast awareness strategy in the intervention group ⁹. Evidence shows that screening with clinical breast examination is associated with a higher standardized breast cancer incidence rate ²⁵, which could indicate some degree of overdiagnosis. In addition, since the trial in the Philippines was suspended and the two clinical trials in India have still not presented definitive results to evaluate the outcome on mortality, it is still not possible to determine whether screening with clinical breast examination is really effective.

Meanwhile, in the clinical trial in Kerala, false-positives accounted for 99% of all positive cases in clinical breast examination screening ²⁵. In the same study, screening sensitivity was 51.7% (95%CI: 38.2-65.0), with a high proportion of false-negatives; the number of interval cancers was practically identical to the number of cancers detected by screening ²⁵. There is also evidence that in clinical practice, the screening sensitivity of clinical breast examination is lower than in clinical trials, around 28% to 36% ²³.

In the search update carried out in 2017, one identified meta-analysis compared the outcomes in clinical trials of mammography screening with versus without clinical breast examination. The results showed a smaller point estimate of mortality reduction in the trials with supplementary clinical breast examination, although the confidence intervals of the two groups overlapped ²⁸.

Screening with breast self-examination

As for teaching breast self-examination for cancer screening purposes, none of the selected systematic reviews of clinical trials demonstrated efficacy in the reduction of breast cancer mortality ^{12,16,22,23,24,29}. Meanwhile, the reviews identified evidence of excess unnecessary interventions for diagnostic workup due to false-positive results with screening. For example, in one of the two clinical trials analyzed in the reviews, practically twice as many benign lesions were diagnosed in the intervention group, accompanied by an increase in the number of biopsies ²².

Screening with other imaging methods

We found no clinical trials that evaluated ultrasound screening with or without mammography, thermography, or breast tomosynthesis ⁸. Concerning tomosynthesis, two systematic reviews of studies on diagnostic accuracy identified heterogeneous results for sensitivity and specificity between the studies, besides validity problems ^{30,31}. Thus, there is still no sufficient evidence to evaluate whether breast cancer screening with these methods can bring some benefit and whether the possible benefits outweigh the harms associated with them.

None of the three selected systematic reviews presented the results of clinical trials on the efficacy of screening with magnetic resonance imaging (MRI) for reducing breast cancer mortality ^{12,16,32}. According to estimates, the number of cases with indeterminate diagnosis in the initial workup after screening, i.e., requiring biannual follow-up with new imaging tests, would increase tenfold with MRI screening ³². MRI screening would also potentially increase the amount of overdiagnosis, especially due to its greater sensitivity in detection of ductal carcinoma in situ (DCIS) ³². In the search update carried out in 2017, no conclusive evidence was found on screening effectiveness on overall or breast cancer mortality, when the aforementioned image techniques were used alone or in addition to mammography ^{33,34,35}.

Early diagnosis strategies

As for the breast awareness strategy⁹, the studies either included other interventions alongside breast cancer warning signs awareness-raising, for example encouragement for screening mammography, thus preventing the evaluation of this strategy's efficacy per se or considered surrogate endpoints with no clinical relevance^{8,36}. On the other hand, no harms associated with this strategy were identified. In contrast to the breast self-examination technique, the rationale of the awareness strategy is not to teach a screening method, but to make women more aware of early signs of breast cancer in everyday normal life, hopefully improving the quality of their breast health care demands³⁷. In the search updated in 2017, one new systematic review was selected³⁸. In this review two clinical trials on awareness strategy were identified. However, they were heterogeneous in relation to quality, intervention and outcomes. In the trial of better quality – level of evidence “moderate” according to the GRADE system – the intervention, that is, a leaflet plus one individual meeting with a health care professional significantly increased the knowledge about early signs of breast cancer and about the increased risk of the disease with age³⁸.

As for the strategy of identifying suspicious signs and symptoms in primary care and priority referral for diagnostic workup⁹, the selected studies did not evaluate clinically relevant outcomes for patients. Still, they indicated that protocols for priority referral from primary care have a cancer detection rate of some 10%³⁹ and sensitivity of some 90%^{39,40,41}. The sign most commonly associated with breast cancer is breast lump, present in 90% of cases confirmed subsequently as cancer^{42,43,44}.

As for the strategy of diagnostic confirmation at a single service⁹, two clinical trials were identified^{45,46}, but neither addressed the outcomes defined in the protocol for revision of new guidelines⁹. Two observational studies were identified, but with important quality problems⁸.

Discussion

The new Brazilian national guidelines are probably the most critical government guidelines for screening ever published in the world, and the most recent available evidence corroborates the new recommendations¹⁹. Three clinical trials for screening mammography have published new follow-up results in recent years: the Canadian trial, Gothenburg trial (Sweden), and UK Age Trial. Even after 25 years of follow-up, the Canadian breast cancer trial failed to demonstrate a reduction in breast cancer mortality from screening^{18,20}. The new results of the UK Age Trial also failed to show a reduction in long-term mortality, indicating that the initially observed reduction in mortality may have meant, at most, that deaths from breast cancer were only slightly postponed⁴⁷.

On the other hand, the new results of the Gothenburg trial⁴⁸ showed a statistically significant protective effect against breast cancer mortality in women under 50 years of age in long-term follow-up. This result is difficult to explain, precisely in a clinical trial in which there was contamination of approximately 20% of the control group during the intervention period and where more than 50% of the women aged 39 to 49 years had already received at least one mammogram at baseline. Not to mention that screening was offered to the control group and that it would be difficult to determine whether deaths that occurred 24 years later were associated with cancers discovered during the intervention period. All this contamination would tend to decrease rather than increase the intervention's efficacy. This explains how odd the results appear, considering the existing clinical trials as a whole. Another unexpected finding in this clinical trial is that the difference in breast cancer mortality between the interventions appears at the beginning of follow-up. One likely explanation for these results would be the presence of biases. This clinical trial has at least two well-documented potential sources of bias: selection bias due to problems in the generation and concealment of the random allocation sequence. The result is that the intervention groups are not totally comparable. In addition, part of the reduction in breast cancer mortality in the Swedish clinical trials is probably due to the higher awareness of women in the screened group, as well as the better diagnosis and treatment standards⁴⁹.

Of all the breast screening trials, the Canadian trial and the UK Age Trial were the only two designed specifically to assess the impact of screening in the 40 to 49-year bracket and are considered high quality studies^{11,16}. In the 2016 version of the systematic review commissioned by the USPSTF,

that included new results of these two clinical trials, the statistical significance in the reduction of breast cancer mortality, previously borderline, disappeared completely¹⁷. Considering the risks involved in screening mammography for women under 50 years, these results suggesting absence of efficacy further reinforce the strong recommendation against screening in the new guidelines. This type of recommendation entails the shared decision process in the case where there is active demand of the woman to screen in this age group, in which the uncertainties about benefits and the risks involved should be discussed. Thus, the practical implication is that our recommendation is similar to that of the USPSTF guidelines that states that this procedure should not be offered routinely⁵⁰. Had the new version of the USPSTF guidelines been based on their systematic review results, their guidelines would have been even more unfavorable in relation to this practice, given the lack of evidence of statistically significant benefits. However, the implication would be that this procedure would be not covered according to the *Affordable Care Act*. Importantly, the issue is not lack of evidence. On the contrary, the 39 to 49-year bracket was the most widely studied in clinical trials.

Some factors explain these unfavorable results in women under 50, such as lower breast cancer incidence and higher breast density in this age group. In addition to the lower prevalence of breast cancer in women under 50 years of age, mammograms performed in younger women show lower sensitivity and specificity and a higher proportion of false-negative and false-positive results due to the higher breast density, which decreases the sensitivity of mammography⁵¹. The biological rationale for this absence of efficacy is also backed by other findings, such as the lack of down-staging through screening in this age bracket, contrary to women 50 years or older¹⁷. Even if we overlook all this evidence and assume that there is some efficacy in screening mammography between 40 and 49 years, the absolute benefit would still be seven times less than in the 60 to 69 year group¹⁷ and would have to be weighed against the risks from screening, which are greater precisely in younger women.

Using the proportion of cases per stage as an outcome is a frequent source of bias in assessments of studies about screening and screening programs. This occurs due to the redistribution of cases in which cases of overdiagnosis are included and recorded as a positive outcome. Therefore, the proportion of cases per stage should not be used as an outcome in studies assessing the effectiveness of screening. A publication from 2016 on the Canadian mammographic screening study showed that in women 40 to 49 years of age, 100% of cancers detected by mammographic screening alone – non-palpable tumors – were considered overdiagnosis⁵². In other words, in this age bracket, early detection by screening mammography would only have brought harm to women's health and an illusion of benefit. This proportion drops to 44% in women 50 to 59 years of age⁵². Estimates of overdiagnosis in this clinical trial are considered high quality¹⁷ and may even be underestimated due to contamination of the control group, although women in this group had not been actively invited to participate in the screening as in other clinical trials^{17,47}.

Annual screening starting at 40 years, very popular in Brazil, is also associated with increased likelihood of developing radio-induced cancer. When biennial screening beginning at 50 years is compared to annual screening starting at 40, the number of radio-induced cancers from screening increases nearly fivefold (or more than 100 additional cases of radio-induced cancer in 100,000 screened women)⁵³. Additionally, this number can nearly double when considering women with large breasts, which require higher doses of radiation per test⁵³. All this assuming that there are quality programs in which the dose of ionizing radiation in the tests is monitored. Although this risk is relatively small and the evidence is indirect – based on modeling – these risks add to others such as overdiagnosis, overtreatment, false-positives, false-negatives, and lack of evidence of benefits from annual screening starting at 40 years. For all these reasons, it is expected that when women are well informed most would opt for not submitting to mammography screening under the age of 50.

Even the American Cancer Society new guideline changed its traditional recommendation that women should start routine screening at age 40, to 45, and the periodicity of screening from 50 years of age from annual to biannual⁵⁴. Still, the justification for starting screening at 45 instead of 50 years of age was weak, using incidence rates of breast cancer per age group, as in the USA (as it is also the case in Brazil), the disseminated screening starting at younger ages potentially increases the incidence before age 50 due to lead time bias and overdiagnosis.

Regarding the recommendation to screen women aged 70 years or older, while the present guidelines make recommendations against this practice, the USPSTF recommends screening in the 70 to

74-year bracket and classifies screening of women aged 75 years or older as uncertain. However, the USPSTF demonstrated in its own systematic review that there is no evidence of efficacy of screening for women aged 70 years or more¹⁷. The strong recommendation against screening in this age group is in accordance with the GRADE system that expects this type of recommendation in situations of absence of evidence of effectiveness and the existence of well recognized risks associated with the intervention⁵⁵. Although the new Brazilian guidelines allow shared decision making in these cases (Box 3) it is necessary to explicitly consider in this process the uncertainty of benefits as well as the increase in overdiagnosis through the detection of indolent cases of breast cancer and by the higher incidence of competitive causes of death. The balance between possible benefits and risks becomes more unfavorable as life expectancy diminishes. This is the reason for the more unfavorable recommendation for women aged 75 or over in the present Brazilian guidelines. Thus, as with women younger than 50 years of age, it is expected that those aged 75 or more opt for not submitting to screening (Box 3).

Part of the problem with overdiagnosis and overtreatment in the mammographic screening is due to the excess detection and treatment of cases of DCIS. In the past, mastectomy was the treatment of choice for such cases, but four randomized studies in the 1980s and 1990s showed a significant reduction in the risk of relapse with lumpectomy followed by radiotherapy⁵⁶. An increase in survival with the addition of radiotherapy was suggested in a population-based cohort study⁵⁷. Two randomized studies showed a reduction in relapse with adjuvant tamoxifen in the estrogen receptor-positive subgroup, with no increase in survival^{56,58}. Three other studies evaluated the inclusion of hormone therapy with tamoxifen to adjuvant therapy, with the results indicating a reduction in the incidence of ipsilateral and contralateral DCIS, but with no impact on the incidence of invasive tumors⁵⁸. In this context, the use of anastrozol did not show superior results when compared to tamoxifen⁵⁹. Although breast-conserving surgery followed by radiotherapy and hormone therapy is consecrated in the treatment of DCIS, there has been an important recent increase in bilateral mastectomies in the United States, associated with the widespread use of MRI in the evaluation of these patients, resulting in the discovery of new foci outside the quadrant and even in the contralateral breast⁶⁰. Although adjuvant therapy is not risk-free, it seems contradictory that diagnosis of DCIS is associated with an increase in bilateral mastectomies, when one of the arguments generally used to defend mammographic screening is the possibility of performing more conservative surgeries. In the future, the results of clinical trials on the treatment of DCIS and the development of new tests to better stratify the risk of these cases may contribute to decrease the overtreatment of these cases⁶¹.

A common criticism for breast screening studies is their generalization to the present⁶². The increase in the sensitivity of mammography over recent decades⁶³ may have resulted in an increase in overdiagnosis when compared to those when the screening studies were conducted. Meanwhile, the evolution in adjuvant therapy in recent decades has improved the treatment efficacy in cases of locally advanced cancer identified by signs and symptoms, tending to decrease the effectiveness of screening mammography⁶⁴. Hormone therapy has played an outstanding role in the evolution of adjuvant therapy, initially with tamoxifen and later also with aromatase inhibitors⁶⁵.

Brazil witnessed an important drop in breast cancer mortality rates beginning in the late 1990s in the state capitals in the Southeast and South regions, possibly associated with improved access to diagnosis and treatment⁶⁶. It would be difficult to ascribe this decrease in mortality to screening mammography, given its limited dissemination in Brazil in the 1990s. Meanwhile, there was a major increase in breast cancer deaths among women in the countryside, especially in the North and Northeast regions. This suggests that reproductive and sexual changes may have been adopted rapidly by women living outside the state capitals, including in low-income areas with worse access to health services.

Given the questioning of mammographic screening, it is natural to see an increase in interest in other screening methods. Still, the new systematic review commissioned by the USPSTF found no evidence of the efficacy of screening with tomosynthesis, MRI, or breast ultrasound⁵⁰, as in the new Brazilian guidelines⁸ and two other previous systematic reviews^{31,67}. In addition, no clinical trials were identified that evaluate the impact of the use of techniques applied to ultrasound, such as elastography and Doppler. Likewise, there is no conclusive evidence on greater efficacy of the combination of ultrasonography and mammography in breast cancer screening, when compared to screening

mammography alone⁶⁸. Meanwhile, there is indirect evidence suggesting that screening with clinical breast examination together with mammography is more effective than mammography alone²⁸, while the results are still lacking from clinical trials designed specially to answer this question.

The perception of lack of access to health services, ignorance of cancer warning signs, and the existence of myths on the disease are factors that can generate user-related diagnostic delays⁶⁹. The evidence of a decrease in the role of screening and the national scenario of breast cancer control points to the importance of strengthening strategies for early diagnosis of cases with early signs and symptoms, in order to act on these determinants of diagnostic delay. Still, there is no good evidence on best strategies to be adopted. Thus, the three strategies proposed in the new guidelines should have their results monitored. The detection of a suspicious breast lump in primary care appears to have good positive predictive value, but there is a lack of studies evaluating the predictive value of the association of several signs and symptoms⁷⁰. The strategy of population awareness-raising on warning signs, accompanied by improved access to primary care and diagnostic confirmation through the establishment of clinical regulation of appointments and concentration of diagnostic workup in specialized centers has the potential to overcome various barriers to access and to improve prognosis for these patients. Still, if there is no adherence to guidelines for referral and prioritization of appointments, and if most cases continue to be excluded from fast-track diagnostic workup, there may be a paradoxical increase in difficulty in obtaining diagnosis, precisely for the cases that most need this kind of care⁷¹. Having diagnostic confirmation at the same secondary tier of care can help avoid repeat biopsies and delays in receiving the histopathology report, thereby reducing the intervals between unnecessary consultations, booked merely to present the imaging test and biopsy results.

Limitations

As the present screening guidelines are not for population at high risk of breast cancer development, mistaken interpretation about family history or other risk factors may jeopardize its implementation. The present guidelines apply to 99% of the female population; which are not considered to be at high risk⁷². High-risk situations occur in women with a history of supra diaphragmatic radiotherapy before age 36 for the treatment of Hodgkin lymphoma⁷³ or those with strong hereditary predisposition for breast cancer. The genetic mutations more frequently linked to high risk of breast cancer are those of the genes BRCA 1 and 2 (hereditary syndrome of breast and ovary cancer), which account for 70 to 80% of cases⁷⁴, followed by TP53 (Li-Fraumeni syndrome) and PTEN (Cowden syndrome)⁷⁵. It is important to note that the existence of family history of cancer, in most cases, does not indicate the presence of familial cancer syndromes. In a study of randomly selected breast cancer cases in health care units in Rio de Janeiro, 2.3% of the identified cases showed BRCA genes mutations⁷⁶. There are several tools available for the initial triage to classify women as having probable high familial risk^{77,78}, including one validated in southern Brazil⁷⁹. Generally, the criteria considered are the following: family history of breast or ovary cancer in a first degree relative; cases of breast cancer before the age of 50; case of breast and ovary cancer in one single relative; bilateral breast cancer; case of breast cancer in a man; Ashkenazi Jewish ancestry^{77,78,79}. The discussion about uncertainties, controversies, risks and benefits of special screening protocols and other alternative conducts for the high risk population, such as chemoprophylaxis and prophylactic surgeries, are beyond the scope of the present guidelines.

Another limitation of the present guidelines is that they are based on the best available evidence, not using modeling to formulate the recommendations. This may also be considered a strength of these guidelines, as modeling often super-estimates the benefits and under-estimates the risks of screening⁸⁰. Some of the main gaps in the available evidence are the lack of data on effectiveness of the screening in the Brazilian population and also, the paucity of studies about the harms resulting from overdiagnosis and overtreatment. The use of modeling techniques to fill in these gaps in knowledge is a possibility for future versions of these guidelines.

Conclusion

The best available evidence reinforces the recommendations of the new Brazilian national guidelines. Currently, the only recommended screening strategy is biennial mammography from 50 to 69 years, and even so as a conditional recommendation, respecting each woman's values and preferences. In order to achieve a favorable balance between benefits and harms from screening, it is at least necessary to respect the recommendations for the target age bracket and periodicity in the new guidelines. Early diagnostic strategies targeted to cases with signs and symptoms should complement the screening, although further studies are needed to prove its efficacy.

Contributors

A. Migowski undertook the literature review and conceived, wrote and revised the text. G. Azevedo e Silva, M. B. K. Dias, M. D. P. E. Diz, D. R. Sant'Ana, and P. Nadanovsky collaborated to the writing and review of the paper.

References

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2016: incidência de câncer no Brasil. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva; 2015.
2. Di Sibio A, Abriata G, Forman D, Sierra MS. Female breast cancer in Central and South America. *Cancer Epidemiol* 2016; 44 Suppl 1:S110-20.
3. Azevedo e Silva G, Gamarra CJ, Girianelli VR, Valente JG. Tendência da mortalidade por câncer nas capitais e interior do Brasil entre 1980 e 2006. *Rev Saúde Pública* 2011; 45:1009-18.
4. Porter P. "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J Med* 2008; 358:213-6.
5. Victora CG, Barreto ML, do Carmo Leal M, Monteiro CA, Schmidt MI, Paim J, et al. Health conditions and health-policy innovations in Brazil: the way forward. *Lancet* 2011; 377:2042-53.
6. Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. *Breast Cancer Res* 2004; 6:213-8.
7. Malta DC, Silva Jr. JB. Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis no Brasil após três anos de implantação, 2011-2013. *Epidemiol Serv Saúde* 2014; 23:389-95.

8. Migowski A, Dias MBK, organizadores. Diretrizes para a detecção precoce do câncer de mama no Brasil. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva; 2015.
9. Migowski A, Stein AT, Ferreira CBT, Ferreira DMTP, Nadanovsky P. Diretrizes para detecção precoce do câncer de mama no Brasil. I – Métodos de elaboração. *Cad Saúde Pública* 2018; 34:e00116317.
10. Leung GM, Lam TH, Thach TQ, Hedley AJ. Will screening mammography in the East do more harm than good? *Am J Public Health* 2002; 92:1841-6.
11. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2013; (6):CD001877.
12. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; 151:727-37.
13. Paesmans M, Ameye L, Moreau M, Rozenberg S. Breast cancer screening in the older woman: an effective way to reduce mortality? *Maturitas* 2010; 66:263-7.
14. Magnus MC, Ping M, Shen MM, Bourgeois J, Magnus JH. Effectiveness of mammography screening in reducing breast cancer mortality in women aged 39-49 years: a meta-analysis. *J Womens Health (Larchmt)* 2011; 20:845-52.
15. Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. *Ann Intern Med* 2007; 146:516-26.
16. Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *CMAJ* 2011; 183:1991-2001.
17. Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 U.S. Preventive Services Task Force Recommendation. *Ann Intern Med* 2016; 164:244-55.
18. Nelson HD, Cantor A, Humphrey L, Fu R, Pappas M, Daeges M, et al. Screening for breast cancer: a systematic review to update the 2009 U.S. Preventive Services Task Force Recommendation. Rockville: Agency for Healthcare Research and Quality; 2016. (Report, 14-05201-EF-1).
19. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive Services Task Force Recommendation. *Ann Intern Med* 2016; 164:256-67.
20. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ* 2014; 348:g366.
21. Fitzpatrick-Lewis D, Hodgson N, Ciliska D, Peirson L, Gaud M, Liu YY. Breast cancer screening. <http://canadiantaskforce.ca/wp-content/uploads/2011/11/2011-breast-cancer-systematic-review-en.pdf> (accessed on 19/Apr/2017).
22. Kösters JP, Gøtzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. *Cochrane Database Syst Rev* 2003; (2):CD003373.
23. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. *JAMA* 2005; 293:1245-56.
24. Green BB, Taplin SH. Breast cancer screening controversies. *J Am Board Fam Pract* 2003; 16:233-41.
25. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Prabhakar J, Augustine P, et al. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst* 2011; 103:1476-80.
26. Mitra I, Mishra GA, Singh S, Aranke S, Notani P, Badwe R, et al. A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. *Int J Cancer* 2010; 126:976-84.
27. Pisani P, Parkin DM, Ngelangel C, Esteban D, Gibson L, Munson M, et al. Outcome of screening by clinical examination of the breast in a trial in the Philippines. *Int J Cancer* 2006; 118:149-54.
28. Hamashima C, Ohta K, Kasahara Y, Katayama T, Nakayama T, Honjo S, et al. A meta-analysis of mammographic screening with and without clinical breast examination. *Cancer Sci* 2015; 106:812-8.
29. Hackshaw AK, Paul EA. Breast self-examination and death from breast cancer: a meta-analysis. *Br J Cancer* 2003; 88:1047-53.
30. Fitzgerald A, Berentson-Shaw J. Thermography as a screening and diagnostic tool: a systematic review. *N Z Med J* 2012; 125:80-91.
31. Reugdenburg TD, Willis CD, Mundy L, Hiller JE. A systematic review of elastography, electrical impedance scanning, and digital infrared thermography for breast cancer screening and diagnosis. *Breast Cancer Res Treat* 2013; 137:665-76.
32. Heywang-Köbrunner SH, Schreer I, Heindel W, Katalinic A. Imaging studies for the early detection of breast cancer. *Dtsch Arztebl Int* 2008; 105:541-7.
33. Melnikow J, Fenton JJ, Whitlock EP, Migliorini DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Service Task Force. *Ann Intern Med* 2016; 164:268-78.
34. Health Quality Ontario. Magnetic resonance imaging as an adjunct to mammography for breast cancer screening in women at less than high risk for breast cancer: a health technology assessment. *Ont Health Technol Assess Ser* 2016; 16:1-30.

35. Health Quality Ontario. Ultrasound as an adjunct to mammography for breast cancer screening: a health technology assessment. *Ont Health Technol Assess Ser* 2016; 16:1-71.
36. Austoker J, Bankhead C, Forbes LJ, Atkins L, Martin F, Robb K, et al. Interventions to promote cancer awareness and early presentation: systematic review. *Br J Cancer* 2009; 101 Suppl 2:S31-9.
37. Thornton H, Pillarisetti RR. 'Breast awareness' and 'breast self-examination' are not the same. What do these terms mean? Why are they confused? What can we do? *Eur J Cancer* 2008; 44:2118-21.
38. O'Mahony M, Comber H, Fitzgerald T, Corrigan MA, Fitzgerald E, Grunfeld EA, et al. Interventions for raising breast cancer awareness in women. *Cochrane Database Syst Rev* 2017; (2):CD011396.
39. Neary M, Lowery AJ, O'Conghaile A, Pervaz M, Kerin MJ, Sweeney KJ. NCCP breast cancer referral guidelines: are breast cancer patients prioritised? *Ir Med J* 2011; 104:39-41.
40. McCain S, Newell J, Badger S, Kennedy R, Kirk S. Referral patterns, clinical examination and the two-week-rule for breast cancer: a cohort study. *Ulster Med J* 2011; 80:68-71.
41. Eberl MM, Phillips Jr. RL, Lamberts H, Okkes I, Mahoney MC. Characterizing breast symptoms in family practice. *Ann Fam Med* 2008; 6:528-33.
42. McCowan C, Donnan PT, Dewar J, Thompson A, Fahey T. Identifying suspected breast cancer: development and validation of a clinical prediction rule. *Br J Gen Pract* 2011; 61: e205-14.
43. Cochrane RA, Singhal H, Monypenny IJ, Webster DJ, Lyons K, Mansel RE. Evaluation of general practitioner referrals to a specialist breast clinic according to the UK national guidelines. *Eur J Surg Oncol* 1997; 23: 198-201.
44. Laver RC, Reed MW, Harrison BJ, Newton PD. The management of women with breast symptoms referred to secondary care clinics in Sheffield: implications for improving local services. *Ann R Coll Surg Engl*; 81:242-7.
45. Dey P, Bundred N, Gibbs A, Hopwood P, Baildam A, Boggis C, et al. Costs and benefits of a one stop clinic compared with a dedicated breast clinic: randomized controlled trial. *BMJ* 2002; 324:507.
46. Harcourt D, Ambler N, Rumsey N, Cawthorn SJ. Evaluation of a one-stop breast lump clinic: a randomized controlled trial. *The Breast* 1998; 7:314-9.
47. Moss SM, Wale C, Smith R, Evans A, Cuckle H, Duffy SW. Effect of mammographic screening from age 40 years on breast cancer mortality in the UK age trial at 17 years' follow-up: a randomised controlled trial. *Lancet Oncol* 2015; 16:1123-32.
48. Bjurstam NG, Björneld LM, Duffy SW. Updated results of the Gothenburg Trial of Mammographic Screening. *Cancer* 2016; 122:1832-5.
49. Autier P, Boniol M, Smans M, Sullivan R, Boyle P. Statistical analyses in Swedish randomised trials on mammography screening and in other randomised trials on cancer screening: a systematic review. *J R Soc Med* 2015; 108: 440-50.
50. Siu AL; U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2016; 164:279-96.
51. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Service Task Force. *Ann Intern Med* 2016; 164:268-78.
52. Baines CJ, To T, Miller AB. Revised estimates of overdiagnosis from the Canadian National Breast Screening Study. *Prev Med* 2016; 90:66-71.
53. Miglioretti DL, Lange J, van den Broek JJ, Lee CI, van Ravesteyn NT, Ritley D, et al. Radiation-induced breast cancer incidence and mortality from digital mammography screening: a modeling study. *Ann Intern Med* 2016; 164:205-14.
54. Oeffinger KC, Fontham ETH, Etzioni R, Herzog A, Michaelson JS, Shih YC, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA* 2015; 314:1599-614.
55. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013; 66:719-25.
56. Wapnir IL, Dignan JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst* 2011; 103:478-88.
57. Sgara Y, Freedman RA, Vaz-Luis I, Mallory MA, Wong SM, Aydogan F, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. *J Clin Oncol* 2016; 34:1190-6.
58. Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol* 2011; 12:21-9.
59. Margolese RG, Cecchini RS, Julian TB, Ganz PA, Constantino JP, Vallow LA, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomized, Double-blind phase 3 clinical trial. *Lancet* 2016; 387:849-56.

60. Baum M. 'Catch it early, save a life and save a breast': this misleading mantra of mammography. *J R Soc Med* 2015; 108:338-9.
61. Sagara Y, Julia W, Golshan M, Toi M. Paradigm shift toward reducing overtreatment of ductal carcinoma in situ of breast. *Front Oncol* 2017; 7:192.
62. Biller-Andorno N, Jüni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. *N Engl J Med* 2014; 370:1965-7.
63. Chen TH, Yen AM, Fann JC, Gordon P, Chen SL, Chiu SY, et al. Clarifying the debate on population-based screening for breast cancer with mammography: a systematic review of randomized controlled trials on mammography with Bayesian meta-analysis and causal model. *Medicine (Baltimore)* 2017; 96:e5684.
64. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. *N Engl J Med* 2016; 375:1438-47.
65. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. *J Clin Oncol* 2016; 34:1689-701.
66. Girianelli VR, Gamarra CJ, Azevedo e Silva G. Os grandes contrastes na mortalidade por câncer do colo uterino e de mama no Brasil. *Rev Saúde Pública* 2014; 48:459-467.
67. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and harms of breast cancer screening: a systematic review. *JAMA* 2015; 314:1615-34.
68. Gartlehner G, Thaler K, Chapman A, Kaminski-Hartenthaler A, Berzaczy D, Van Noord MG, et al. Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. *Cochrane Database Syst Rev* 2013; (4):CD009632.
69. Khakbazan Z, Taghipour A, Latifnejad Roudsari R, Mohammadi E. Help seeking behavior of women with self-discovered breast cancer symptoms: a meta-ethnographic synthesis of patient delay. *PLoS One* 2014; 9:e110262.
70. Huggenberger IK, Andersen JS. Predictive value of the official cancer alarm symptoms in general practice: a systematic review. *Dan Med J* 2015; 62:pii:A5034.
71. Patel RS, Smith DC, Reid I. One stop breast clinics: victims of their own success? A prospective audit of referrals to a specialist breast clinic. *Eur J Surg Oncol* 2000; 26:452-4.
72. Price P, Sikora K, editors. *Treatment of cancer*. 6th Ed. Oxford: Taylor & Francis Group; 2015.
73. Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. *J Clin Oncol* 2012; 30:2745-52.
74. Mitchell RN, Kumar V, Abbas AK, Aster JC. *Robbins & Cotran fundamentos de patologia*. 9ª Ed. Rio de Janeiro: Elsevier; 2017.
75. Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. *Clin Obstet Gynecol* 2016; 59:651-72.
76. Gomes MC, Costa MM, Borojevic R, Monteiro AN, Vieira R, Koifman S, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. *Breast Cancer Res Treat* 2007; 103:349-53.
77. National Institute for Health and Clinical Excellence. *Familial breast cancer: classification, care and managing breast cancer in people with a family history of breast cancer*. NICE Clinical Guideline, 164. <https://www.nice.org.uk/guidance/cg164> (accessed on 15/Jan/2018).
78. Nelson HD, Fu R, Goddard K, Mitchell JP, Okinaka-Hu L, Pappas M, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: systematic review to update the U.S. Preventive Services Task Force Recommendation. Rockville: Agency for Healthcare Research and Quality; 2013. (AHRQ Publication, 12-05164-EF-1).
79. Ashton-Prolla P, Giacomazzi J, Schmidt AV, Roth FL, Palmero EI, Kalakun L, et al. Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. *BMC Cancer* 2009; 9:283.
80. Zahl PH, Jørgensen KJ, Gøtzsche PC. Lead-time models should not be used to estimate overdiagnosis in cancer screening. *J Gen Intern Med* 2014; 29:1283-6.

Resumo

O câncer de mama é a principal causa de morte por câncer em mulheres no Brasil. As novas diretrizes para detecção precoce no Brasil foram elaboradas com base em revisões sistemáticas da literatura sobre riscos e possíveis benefícios de diversas estratégias de detecção precoce. O objetivo do presente artigo é apresentar as recomendações e atualizar a síntese de evidências, discutindo as principais controvérsias existentes. As recomendações para o rastreamento do câncer de mama (mulheres assintomáticas) foram: (i) recomendação contrária forte ao rastreamento com mamografia em mulheres com menos de 50 anos; (ii) recomendação favorável fraca ao rastreamento com mamografia em mulheres com idades entre 50 e 69 anos; (iii) recomendação contrária fraca ao rastreamento com mamografia em mulheres com idades entre 70 e 74 anos; (iv) recomendação contrária forte ao rastreamento com mamografia em mulheres com 75 anos ou mais; (v) recomendação favorável forte de que o rastreamento nas faixas etárias recomendadas seja bienal, quando comparada às periodicidades menores do que a bienal; (vi) recomendação contrária fraca ao ensino do autoexame das mamas para rastreamento; (vii) ausência de recomendação favorável ou contrária ao rastreamento com exame clínico das mamas; e (viii) recomendação contrária forte ao rastreamento com ressonância nuclear magnética, ultrassonografia, termografia ou tomosíntese, seja isoladamente, seja como complemento à mamografia. As recomendações para o diagnóstico precoce do câncer de mama (mulheres com sinais ou sintomas suspeitos) foram: (i) recomendação favorável fraca à implementação de estratégias de conscientização para o diagnóstico precoce do câncer de mama; (ii) recomendação favorável fraca ao uso de sinais e sintomas selecionados nas presentes diretrizes como critério de referência urgente para serviços de diagnóstico mamário; e (iii) recomendação favorável fraca de que toda a avaliação diagnóstica do câncer de mama, após a identificação de sinais e sintomas suspeitos na atenção primária, seja feita em um mesmo centro de referência.

Neoplasias da Mama; Detecção Precoce de Câncer; Programas de Rastreamento; Mamografia; Guias de Prática Clínica como Assunto

Resumen

El cáncer de mama es la principal causa de muerte por cáncer en mujeres en Brasil. Las nuevas directrices para la detección precoz en Brasil fueron elaboradas basándose en revisiones sistemáticas de la literatura sobre riesgos y posibles beneficios de diversas estrategias de detección precoz. El objetivo del presente artículo es presentar las recomendaciones y actualizar la síntesis de evidencias, discutiendo las principales controversias existentes. Las recomendaciones para el tamizaje del cáncer de mama (mujeres asintomáticas) fueron: (i) fuerte recomendación contraria al tamizaje con mamografía en mujeres con menos de 50 años; (ii) baja recomendación favorable al tamizaje con mamografía en mujeres con edades entre 50 y 69 años; (iii) baja recomendación contraria al tamizaje con mamografía en mujeres con edades entre 70 y 74 años; (iv) fuerte recomendación contraria al tamizaje con mamografía en mujeres con 75 años o más; (v) fuerte recomendación favorable de que el tamizaje en las franjas etarias recomendadas sea bienal, cuando se compara con periodicidades menores a la bienal; (vi) baja recomendación contraria a la enseñanza del autoexamen de las mamas para tamizaje; (vii) ausencia de recomendación favorable o contraria al tamizaje con examen clínico de las mamas; y (viii) fuerte recomendación contraria al tamizaje con resonancia magnética nuclear, ultrasonografía, termografía o tomosíntesis, bien sea aisladamente, bien sea como complemento a la mamografía. Las recomendaciones para el diagnóstico precoz del cáncer de mama (mujeres con señales o síntomas sospechosos): (i) baja recomendación favorable a la implementación de estrategias de concienciación para el diagnóstico precoz del cáncer de mama; (ii) baja recomendación favorable al uso de señales y síntomas seleccionados en las presentes directrices como criterio de referencia urgente para servicios de diagnóstico mamario; y (iii) baja recomendación favorable de que toda la evaluación diagnóstica del cáncer de mama, tras la identificación de señales y síntomas sospechosos en la atención primaria, sea realizada en un mismo centro de referencia.

Neoplasias de la Mama; Detección Precóz del Câncer; Tamizaje Masivo; Mamografia; Guias de Prática Clínica como Asunto

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