Breast Cancer Screening: Lusíadas Individualized Approach

Rastreio Personalizado de Cancro da Mama Lusíadas

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https://doi.org/10.48687/lsj.195

Keywords: Breast Neoplasms/diagnosis; Early Detection of Cancer; Mass Screening

Palavras-Chave: Detecção Precoce de Cancro; Neoplasias da Mama/diagnóstico; Rastreio

Introduction

Breast cancer is the most common cancer in women in our country and the leading cause of death. Globally, throughout the world, and Portugal is no exception, its incidence has been increasing, as has the number of cases at younger ages. The increase in life expectancy and population ageing cannot explain this increase below the age of 50. Still, factors such as an increase in the exogenous intake of hormones and obesity, among others, may be involved.[1]Breast cancer screening with mammography not only reduces breast cancer mortality but also allows for earlier diagnosis and, consequently, less aggressive treatments. The first screening programmes began in the 1960s, and multiple studies have shown a reduction in breast cancer mortality with screening; for example, the Pan Canadian Study, which included almost 2.8 million women screened in Canada between 1990 and 2009, found a 40% reduction. The estimated benefit was given by the number of women participating needed to prevent one death.[2] The UK Age Trial found a significant reduction in mortality at 10-year follow-up, with 83 deaths in the intervention group and 219 in the control group, with the results suggesting a reduction in mortality with annual mammography from age 40-49, with no additional overdiagnosis compared to the group of women aged 50 and over.[3] Breast cancer screening and diagnosis have evolved considerably in recent decades; digital mammography has replaced screen film mammography, and tomosynthesis has emerged, with multiple studies demonstrating an increase in cancer detection rates and a reduction in recall rates. Magnetic resonance imaging (MRI) has established its role, has become more accessible, with abbreviated protocols contributing to this, and has become the standard technique for breast cancer screening in high-risk women and recommended for some women at intermediate risk. Artificial intelligence (AI) has now begun to be introduced into screening programmes, as in Malmo, Sweden, where previous studies have demonstrated its ability to improve the technical quality of screening programmes and to reduce the workload resulting from the increase in work justified by extending screening, especially to other age groups. In addition to detecting lesions and classifying them, AI will play a role in detecting the risk of breast cancer by assessing the breast pattern (texture and density).[4] Since the late 1980s, screening programmes have been introduced in several countries based on the results of randomized studies. However, these programmes have always

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Recebido/Received: 07/12/2023 **– Aceite/Accepted:** 11/12/2023 **– Publicado online/Published online:** 29/12/2023 **Publicado / Published:** 29/12/2023

been based on the "one size fits all" premise, based exclusively on age, typically between 50 and 69. This approach has demonstrated benefits, such as reducing mortality, although it is accompanied by undesirable effects such as false positives, over-diagnosis and even over-treatment. On the other hand, the sensitivity of mammography is not perfect and the impact on reducing mortality is lower than expected.

In the era of personalized medicine, new screening strategies should be adopted based on each woman's individual risk, which depends on various factors such as genetics, lifestyle, or hormones.

What distinguishes screening from diagnosis?

Mammography is the primary imaging method for detecting and diagnosing breast cancer. It can be carried out in two different diagnostic or screening scenarios. In either case, it should always be digital rather than screen film mammography, given the lower radiation dose, better image quality, and possibility of post-processing, among other advantages. If possible, tomosynthesis should be performed, increasing the cancer detection rate, even in dense patterns.

Screening mammography is carried out periodically to detect small cancers before they are clinically evident. Mammography is performed annually, biennially, or triennially, from the age of 40-50 to 70-75, according to each country's national or even regional programme. The European Guidelines currently recommend screening two years apart, starting at age 50 and ending at age 70.[5] In general, and in most screening programmes, the screening mammogram consists of 4 incidences or projections, two for each breast, the cranio-caudal and medio-lateral oblique incidences, which are read independently by two radiologists. If the screening test is positive, i.e., if the mammogram reveals any alterations, the woman is called for a subsequent assessment as part of a check-up appointment, which may include additional views, tomosynthesis, contrast mammography, ultrasound, or biopsy.

Diagnostic mammography is performed in patients with symptoms, such as evidence of a clinical nodule on palpation, breast discharge, nipple retraction or when there has been a previous positive screening test, and in cases of BI-RADS 3 follow-up.[6] The standard mammography images are obtained, as well as any complementary images that the radiologist seems necessary. These may be magnified views, with rotation, or with skin marking of a palpable lesion. The patient is clinically assessed, and, in general, bilateral breast ultrasound is performed. All these imaging and clinical assessment results in a structured report, with reference to the breast pattern, changes following the BI-RADS (Breast Imaging Reporting and Data System) lexicon, conclusion, recommendation, and classification, generally using the BI-RADS classification.

Population-based screening versus personalized screening: what distinguishes them?

A population-based screening programme, in this case, breast screening, is an organized programme whose main aim is to reduce the mortality rate of a highly prevalent disease in the population by detecting it early, i.e., at an early stage of the disease.

In this type of screening, women are identified individually and personally invited to be screened.

The organization and operation of this type of screening presupposes a number of requirements: definition of the target population, capacity for active individualized and personalized invitation of the entire target population, defined and universal screening method for all women (mammography), safety based on quality parameters with recording and control of relevant data, control and monitoring of the incidence of the disease in the target population, organization of screening centers and structured and organized decision-making capacity in the orientation towards health services.

In 2003, the European Council presented recommendations for breast cancer screening in Europe so that each country could implement its own screening programme with quality criteria. In 2006, the European Commission published the 4th edition of guidelines to ensure the quality of screening and promote the articulation of diagnostic units, using various quality criteria, such as the proportion of women who adhere to screening.

Increasing screening in high-risk women and decreasing screening in low-risk women has not been and probably never will be studied in clinical trials due to ethical issues. However, mathematical models show that intensifying screening in higher-risk women and decreasing the frequency of mammograms in lower-risk women would be a cost-effective decision. Individualizing population-based screening is a challenge and a difficult, unachievable process. It requires lengthy discussions between women and health professionals about risks and benefits, the risk of recalls and false positives.

However, a personalized strategy is likely to increase adherence to screening. Providing balanced information doesn't seem to change participation in screening, but it does allow women to make an informed choice. In addition, information about the possibility of a false positive will reduce its psychological impact.

In personalized screening, the starting age will be that at which the risk of breast cancer is equal to the risk of a low-risk woman at the age of 50, and the cut-off age is not defined but depends on the woman's individual characteristics and life expectancy. The frequency with which this screening is carried out is adapted to the individual risk level, as are the adapted imaging screening methods, with the advantage that this screening strategy can be changed regularly and individually. Its main objective will always be to increase the effectiveness of screening in reducing the mortality rate from breast cancer without increasing costs and undesirable effects in the majority of women (low risk).[7]

At what age should the first risk assessment be carried out?

It is essential to determine each woman's individual risk of breast cancer to offer the most appropriate screening.

According to the American College of Radiology (ACR), the American Society of Breast Surgeons (ASBrS) and the Society of Breast Imaging (SBI), it should be carried out between the ages of 25 and 30.[8,9] This risk stratification is usually carried out in the context of a General Practitioner's consultation or a Gynaecologist's consultation.

Risk models for stratification into low, intermediate and high risk

As we advance in precision medicine, more and more use is being made of breast cancer risk models, with the possibility of identifying high-risk women, with an indication for breast MRI screening, an indication for risk reduction measures and calculation of the probability of *BRCA* 1 and 2 mutation, although the indication for genetic testing derives from the criteria of Guidelines, such as the NCCN.

To fully assess each woman's individual risk, it is essential to check other risk factors in addition to age, such as:

Family history of breast cancer, ovarian cancer or syndromes associated with an increased risk of breast and ovarian cancer (pancreatic and prostate cancer), genetic mutations, history of thoracic radiotherapy, previous histological examinations with results of lobular carcinoma in situ, atypical hyperplasia (ductal or lobular) and high breast density patterns.

There are various models available for determining risk, with advantages and disadvantages. The most commonly used are the Gail Model and the Tyrer-Cuzick Risk Model.

The Gail Model has the disadvantages of not being used in women under the age of 35, in women with a family history on the paternal side, with relatives of the second degree or higher, or with a history of ovarian or prostate cancer.

This risk model also does not take into account a history of biopsies resulting in high-risk lesions, with the exception of atypical ductal hyperplasia.

The other model, the Tyrer-Cuzick Risk Model, is more comprehensive, it also includes cases of relatives on the paternal and maternal side, considers cases of more distant relatives and version 8 includes the breast density pattern. It quantifies the risk of developing breast cancer at 5 and 10 years of age, as well as throughout life. It also provides additional screening information with breast magnetic resonance imaging.

Both tools are available online with the following links:

The Tyrer-Cuzick Risk Model (http://www.ems-trials.org/ risk evaluator)

The Gail Model (http://www.cancer.gov/bcrisktool)

As a result, women are subdivided into three distinct groups: low-risk, intermediate-risk and high-risk.

Determining the risk will make it possible to adjust the age at which screening should begin, the frequency with which it should be carried out and the most appropriate imaging method.

There is some disagreement as to how these clinical risk models predict the risk of breast cancer at five years, mainly when the cutoff of 1.67% is used to define high risk and possible indication for chemoprevention.[10] In this sense, new risk models are being developed, some of which already include information on genetic susceptibility variants for breast cancer, and other studies suggest that artificial intelligence algorithms can supplant or complement these clinical models.

A key point for implementing the Polygenic Risk Score in clinical practice lies in understanding its impact at an individual level, communicating the associated risk, and weighing it up in clinical decision-making. There are several ongoing trials incorporating the polygenic risk score to determine individual risk and define personalized screening, including the women informed to screen depending on measures of risk study.[11] In all likelihood, this score will be added to existing models, as was the case with breast density, making it possible to increase accuracy and improve performance.

There are also studies comparing predictive models of breast cancer risk, in which a hybrid model was analyzed that includes

deep learning (DL) for the complete evaluation of digital mammography and clinical risk factors, with the Tyrer Cuzick model, version 8, which only incorporates breast density in addition to clinical factors. The hybrid system showed greater accuracy, with an AUC of 0.70 versus 0.62, most likely because it was able to identify textural changes and risk marker patterns in the mammogram.[12]

Low-risk patient

Low-risk patients are those whose lifetime risk of developing breast cancer is less than 15%.

This group includes women with no symptoms, no personal history of invasive breast cancer, in situ lobular or ductal cancer or atypia, no family history of breast cancer in first-degree relatives, no hereditary genetic syndromes and no history of thoracic radiotherapy.

In this group of women, the recommendations of the various associations vary greatly. The starting age for screening varies between 40, 45 and 50 years, and the frequency ranges between annual, biennial and even triennial in the various organizations. This involves balancing the benefits (reduced mortality and diagnosis of advanced disease) and the risks of screening (false positives and overdiagnosis).

Why screen earlier if the frequency of the disease is much higher from the age of 50? It is a universal concept that the incidence of breast cancer increases with age. Therefore, in the 40-50 age group, for every diagnosis of breast cancer made during screening, more women will have to be screened than in the 50+ age group. However, it should be emphasized that, as young women have a longer life expectancy, the number of years of life gained by women in their 40s during screening is much higher than those in their 50s.

At Lusíadas individual approach for breast cancer screening at average risk, we have considered the risk-benefit balance and Guidelines of different Scientific Societies, such as the America Cancer Society (ACS), American College of Radiology (ACR), National Comprehensive Cancer Network (NCCN), among others.

We recommend the first mammography at the age of 40 to assess breast density, optional but reasonable, in a decision shared with women between 40 and 44, suggested in women aged 45 to 74.

We also recommend regular screening; preferably, the frequency will be annual between the ages of 40 and 54, and biennial after age 55.

At Lusíadas individual approach, the tests recommended as a screening method are tomosynthesis (digital mammography, alternatively) and breast and axillary ultrasound.

Digital mammography is the only method to date that has been proven to reduce the mortality rate from breast cancer by around 30%. However, breast density is one of its most important limitations in terms of diagnostic accuracy. In high breast density patterns, ACR C (heterogeneously dense) and D (extremely dense), diagnostic sensitivity can drop from 70%--85% to 30%.

Several studies have shown that, in screening, tomosynthesis has a higher diagnostic sensitivity than digital mammography, with an increase in sensitivity from 1.2/1000 to 3.0/1000. Most of these studies show an increased diagnosis rate but without statistical significance. However, the TOMMY trial showed that the overall diagnostic sensitivity of tomosynthesis in all breast density categories was 1.34 times higher than that of digital mammography and demonstrated that in ACR C and D categories, this difference was statistically significant (tomosynthesis 93% versus mammography 86%).

Concerning the ultrasound imaging method, in the balance between the benefits and negative effects of ultrasound combined with tomosynthesis, there are no results that favor or oppose its use, so it is considered that it should be an imaging method to think when it is a usual practice already implemented in patients with high breast density (ACR C and D).

Breast density is important for two reasons: because it reduces the diagnostic accuracy of mammography also because a woman with this density pattern has an intrinsic risk (it can be 4 to 6 times higher than that of a woman with an ACR A lipomatous pattern), not only because of the amount of breast parenchyma but also because of her constitution. Underdiagnosis is particularly a problem in screening women with ACR D-type dense breasts.

A study recently published in 2019, with a second phase whose results were published in 2021, the Dense Trial, played a relevant role in assessing women in the context of screening with high breast density. The authors concluded that breast MRI, as an additional screening to mammography in women with ACR D breast density, can increase the detection rate of breast cancer from 2/1000 to 6/1000 and reduce the cancer-interval rate by 84% (5/1000 to 0.8/1000), when compared to biennial mammography.[13]

More recently, in 2023, EUSOBI included in its recommendations that supplementary screening breast MRI should be offered to all women with ACR D breast density, aged between

50 and 70, at least every four years and preferably every 2/3 years. In this context, it can be performed in place of that year's digital tomosynthesis/mammography.

Intermediate risk patients

Intermediate-risk patients are those whose lifetime risk of developing breast cancer is between 15% - 20%. Women at intermediate risk have a slightly higher risk of the disease appearing at younger ages and have a 3% to 8% risk of developing breast cancer between the ages of 40 and 50.

In this group of patients, we recommend starting screening at the age of 30 with an annual frequency.

Women diagnosed with breast cancer before age 50 or with a personal history of breast cancer and dense breasts should have annual supplemental screening with breast MRI.

Women with atypia or LCIS should consider supplemental surveillance with MRI, especially if other risk factors are present.[14]The other women group should have annual tomosynthesis (digital mammography, alternatively) and breast and axillary ultrasound.

High-risk patients

High-risk patients are defined as those whose lifetime risk of having breast cancer is greater than 20%.

Although the definition of high-risk differs somewhat between the various associations, there is a consensus on the definition of high-risk women. Only between 5% and 10% of breast cancer patients have a known genetic risk.

This group includes women with the BRCA 1 and 2 mutations (82% risk of breast cancer), TP53 (93% of breast cancer at 90 years of age) and PTEN (85% at 80 years of age), although there are many other mutations with a lower associated risk (CDH1 with a 53% risk at 80 years of age); women with a history of radiotherapy treatment (who have a 20% risk of developing breast cancer between 40 and 45 years of age) and also women who are first-degree relatives, untested, of BRCA-positive patients.

In this group of women, the recommendations are consensual and agreed upon by the various associations and their respective guidelines (ACR, ASBS and ACS).

Women with genetic mutations (and their untested first--degree relatives) or those with a calculated lifetime risk of 20% or more should have annual DM, with or without DBT, starting at age 30, and yearly MRI, starting at age 25 to 30. Mutation carriers can delay mammographic screening until age 40 if an annual breast MRI is performed as recommended. Women exposed to a cumulative chest RT dose of >/= 10 Gy by age 30 should have annual mammography starting at age 25 or 8 years after RT, whichever is later, and annual breast MRI beginning at age 25-30

At what age should you finish the screening?

The Population-Based Screening programme in Portugal ends at 69; fortunately, in the future, it will start at 45 and end at 74.

The European Commission Initiative on Breast Cancer (ECIBC) also recommends extending screening until age 74.

At Lusíadas individual approach, we recommend carrying out tomosynthesis (digital mammography, alternatively), plus ultrasound, biennial until 74, and biennial or triennial while life expectancy is no less than ten years. However, age alone should not be the basis for discontinuing screening; it should be a shared decision with the woman, and her health status should be considered.[15]

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.
Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio ou bolsa.
Proveniência e Revisão por Pares: Comissionado; sem revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financial Support: This work has not received any contribution, grant or scholarship.
Provenance and Peer Review: Commissioned; without external peer review.

Contributorship Statement

APV, CCB, JMF and PC: Drafting and review of article
All authors approved the final version

Declaração de Contribuição

APV, CCB, JMF e PC: Redação e revisão do artigo
Todos os autores aprovaram a versão final

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