

## Use of mammography with contrast for the diagnosis of breast cancer

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### Abstract

Breast cancer is a heterogeneous disease, caused by the progressive accumulation of mutations and chromosomal abnormalities. Currently, breast cancer is considered the neoplasm with the highest incidence and mortality in women worldwide, so much so that every year in the world, one million breast cancers are discovered and around 400,000 women die from it. The search for diagnostic techniques that allow the detection of this pathology in an effective way has become essential and that is where mammography emerges, as a screening method, which has been shown to reduce mortality by detecting breast cancer early; however, in very dense breasts detection is difficult, so they have been modified, and thus generating new screening and diagnostic methods such as contrast-enhanced mammography, which is the newest and most promising imaging technique based on neovascularization of breast tumors in a similar way and may even be better than MRI.

**Keywords:** Breast Cancer; Diagnosis; Mammography; Contrast

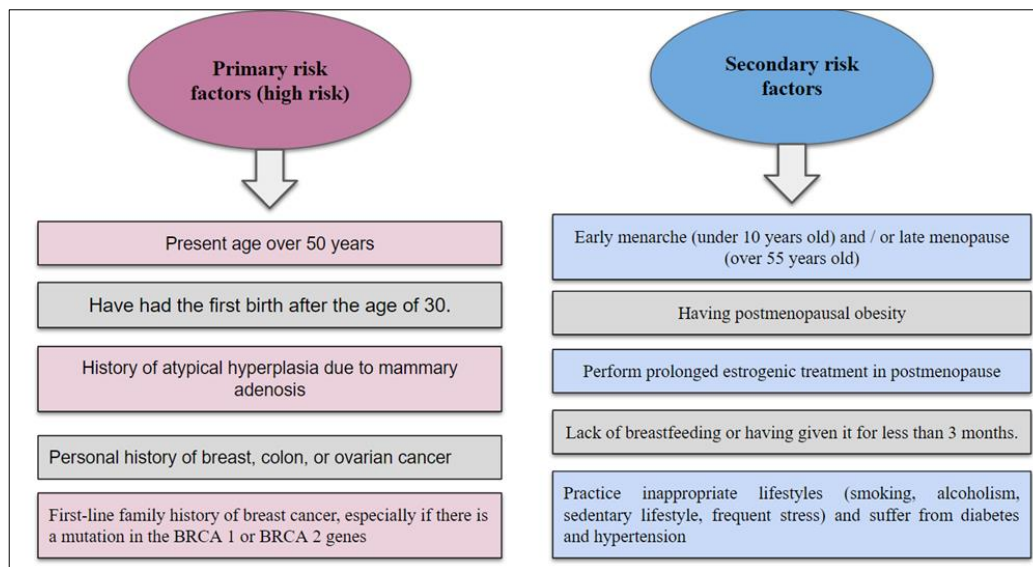
### 1. Introduction

One of the most frequent types of cancer in women is breast cancer, this pathology is nothing more than the accelerated, disordered and uncontrolled proliferation of cells with mutated genes, which normally act by suppressing or stimulating the continuity of the cell cycle belonging to different tissues of a mammary gland, in fact, at present, breast cancer is considered the neoplasm with the highest incidence and mortality in women worldwide, so much so that Every year in the world, one million breast cancers are discovered and about 400,000 women die. It has been estimated that a woman dies of breast cancer every 53 minutes, and every 30 minutes she is diagnosed. In Colombia, it is a public health concern due to the fact that it presents an age-adjusted incidence rate of 44.1 per 100,000 people, which translates into 13,380 new cases diagnosed per year, for this reason, emergency care is necessary. This neoplasm under precepts of efficiency, quality and opportunity [1, 2, 3].

There are multiple risk factors that may be in favor of causing breast cancer, these are usually divided into primary and secondary factors, among these genetic, hormonal and environmental factors have been described that are linked to the development of this neoplasm, in addition to age and breed (Figure 1). Among the genetic factors, familial breast cancer

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constitutes around 10% of all breast tumors, associated with the presence of mutations in the germ line of the p53, PTEN, BRCA1 and BRCA2 genes, fundamentally [4,5].



Taken from Risk factors for breast cancer in a Primary Health Care office by Emilio Rivera Ledesma et al

**Figure 1** Risk factors for breast cancer

It is important to recognize the risk factors for this pathology because, at the time of taking the anamnesis, the presence of one or several factors mentioned above can guide a correct diagnosis. In addition to searching for key points of the pathology in the patient, if breast cancer is suspected there are different tests that can facilitate its detection, such as contrast mammography, which is one of the methods radiography most used in medical diagnostic techniques, being one of the most reliable procedures for the detection and diagnosis of breast lesions [6].

It is clear that one of the most important advances in science and technology in recent decades has been the advancement in medical imaging technologies. These advances have undoubtedly greatly facilitated the detection, diagnosis, and study of conditions in the human body due to its usefulness with respect to deeper inspection of the breast, as shown in Table 1. Mammography is considered a method of diagnostic screening that enables early detection of breast cancer and has been shown to reduce breast cancer mortality by 30%. Since mammography was introduced as a specific radiological examination, significant efforts have been made to increase its diagnostic capacity by adapting the design of x-ray equipment and image detectors to the particular characteristics of the anatomy and morphology of the breast, as well as to the characteristics of the lesions of diagnostic interest, such as cancer, which is one of the most frequent alterations present in the breast [6, 7].

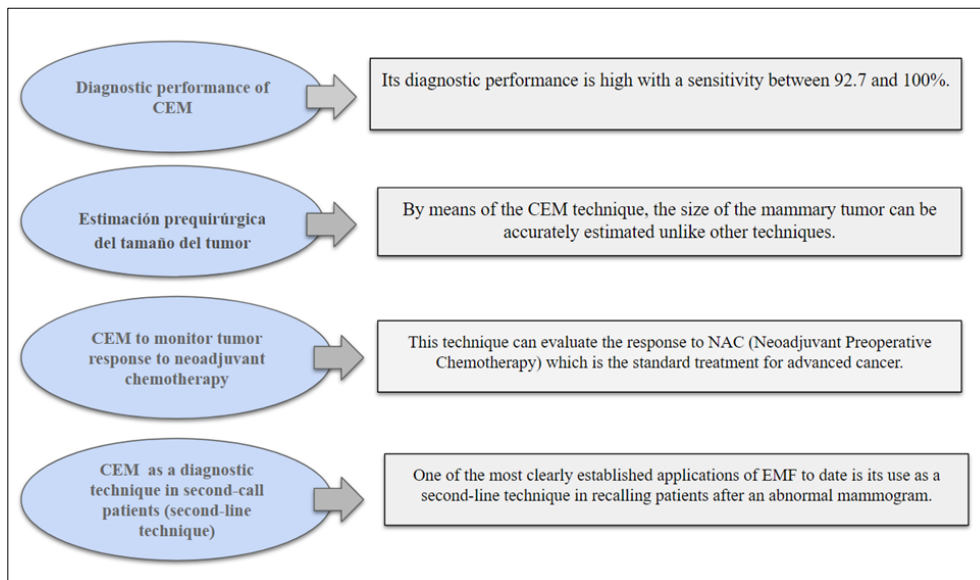
**Table 1** Usefulness of tomography to detect abnormalities in the breast

It allows the detection and characterization of lesions with mitigating properties very similar to those of the healthy tissues that make up the breast.
It allows observing small calcifications (microcalcifications)
It allows to detect and confirm asymmetries in the breasts
thanks to this technique the distortions of the breast tissue can be better appreciated

Taken from Martínez Aguila, Damaris, et al "Comparison of image quality in Phase Contrast Mammography vs. Digital Mammography

There are different types of mammography, however, contrast-enhanced mammography (CEM) is the newest and most promising imaging technique based on neovascularization of tumors in a similar way to breast MRI, in fact, some results of the Clinical studies show that the diagnostic performance of this type of mammography is significantly better than that of digital or conventional mammography, and ensure that its sensitivity and specificity values make it comparable to magnetic resonance imaging. It is a new and alternative method to magnetic resonance imaging (MRI), whose objectives are to evaluate the formation of new blood vessels (angiogenesis) and to increase the permeability of tumor tissues that are metabolically active and require a large amount of nutrients. Although breast magnetic resonance imaging (MRI) is the gold standard method, CEM, in a diagnostic context, has similar sensitivity to MRI and higher specificity [8].

The technique itself has two objectives, the first is the neovascularization of tumors that allows the diffusion of the contrast medium towards the tumor tissue, and the second, the attenuation suffered by X-rays when they pass through materials of different composition, in this case, iodine and soft tissues, without a doubt this is a better diagnostic proposal because, due to the contrast and sharpness of the images, false positives are reduced, among other advantages present in Figure 2 [9].



Taken from Maria and Octavio Pérez-Luzardo. Clinical utility of contrast-enhanced mammography (CEM): a review of the literature

**Figure 2** Advantages of using contrast tomography for the diagnosis of breast cancer

## 2. Material and methods

A detailed bibliographic search of the most relevant published information is carried out in the databases pubmed, scielo, medline, national and international libraries specialized in the topics covered in this review article. The following descriptors were used: Breast cancer, Diagnosis, Mammography, contrast. The data obtained range between 5 and 30 records after the use of the different keywords. The search for articles was conducted in Spanish and English, limited by year of publication, and studies published from 2010 to the present were used.

## 3. Results

After applying the search strategies in the different databases, the articles that were selected were obtained, therefore, we found that over the years the development of early detection programs for breast cancer has increased the proportion of cases that are diagnosed in stages 0 and 1, becoming a curable and preventable cancer. Early diagnosis plays an important role in reducing mortality, which is why, without a doubt, mammography for active screening together with the correct treatment of cases are decisive [9]. Mammography is used in asymptomatic patients as a screening procedure and in symptomatic patients, basically 2 projections are made (craniocaudal and external oblique at 60 degrees). With this diagnostic tool, signs of malignancy can be detected, such as a dense, spiculated nodule with irregular contours, fine and irregular grouped microcalcifications in number greater than six and not disseminated, and tissue breakdown breast with loss of its architecture. Even the BI-RADS mammographic classification categorizes the risk of cancer according to the lesions found [10]. For example, BIRADS 1 is a negative study with 0% risk. In BIRADS 2

there is a 0% probability of cancer but intramammary lymph nodes, hyalinized fibroadenoma and benign calcifications are detected. If they find lesions with well-circumscribed nodules, focal asymmetries and punctate or rounded microcalcifications, they are facing a BIRADS 3 with a risk of less than 2% of developing cancer. But we will have a risk of 25-90% when we have typical lesions of nodules with poorly defined contours and pleomorphic microcalcifications, here we are talking about BIRADS 4. Lastly, we will have a BIRADS 5 in cases of stellate nodules and vermicular microcalcifications where there is a greater risk of 90% risk for cancer [11].

The suspicion of the existence of breast cancer in imaging tests (mammography, ultrasound, nuclear magnetic resonance) requires histological confirmation. If discovered in the symptomatic period, breast cancer can still be cured, although it will generally require more treatments than if it is discovered by mammography in the asymptomatic period. Ideally, breast cancer is discovered before it produces signs or symptoms, and this can be achieved by routine screening mammograms (and in selected cases, by other tests (such as magnetic resonance imaging for women in families with hereditary breast/ovarian cancer) [12].

For this reason, mammography remains the imaging modality of choice for the study of breast lesions in symptomatic patients over 40 years of age, as well as the only technique admitted nowadays for population screening. However, contrast mammography is a totally new and promising imaging technique based on neovascularization of tumors in the same way as breast MRI, with an average sensitivity calculated between 92.7 and 100%. In a study conducted by Santo da Anunciação Zage it is shown that phase contrast mammography using synchrotron beams is a technique feasible for the detection of lesions since it produces improvements in image contrast and increases the visibility of the smallest details [13].

Contrast-enhanced digital mammography is one of the most recent developments that has helped improve the sensitivity and specificity of mammography. This technique reduces the negative impact of anatomical noise inherent in conventional mammography, has the potential to clarify questionable lesions in dense breasts, supports therapeutic planning, and may allow the identification of multifocal lesions [14]. To perform contrast mammography, the screening of high-risk patients is taken into account: dense breasts, carriers of BCRA1 and BCRA2 mutations, a history of breast cancer in a female first-degree relative, clinical or imaging suspicion of breast cancer: perform CEMS and not 2D mammography, assessment of multicentricity and multifocality, contraindications for performing MRI, which include: ferromagnetic materials, pacemakers, allergy to gadolinium, claustrophobia, obesity, evaluation of response to neoadjuvant therapy, occult primary investigation, and characterization of inconclusive findings by mammography and ultrasound [15]. Although breast MRI is the gold standard method, contrast-enhanced mammography, in a diagnostic context, has similar sensitivity to MRI and higher specificity, as well as good agreement on tumor size when compared to MRI. Magnetic [16].

Mokhtar et al. Between 2012 and 2013, they evaluated 60 patients with dense breasts and inconclusive mammographic and ultrasound findings, or with significant findings. They performed contrast-enhanced mammography on these patients. They found a lower rate of erroneous negatives who underwent contrast-enhanced mammography, compared with regular mammography [17]. Sorin, V. et al. compared the diagnostic performance of contrast-enhanced spectral mammography with that of usual digital mammography in women with intermediate risk and dense breasts. They found improvements in sensitivity, compared with usual mammography, however specificity has been lower with the use of contrast-enhanced mammography [18]. Thus, contrast-enhanced digital mammography and molecular breast imaging improve cancer detection, but require further validation for screening, and direct biopsy guidance should be implemented for any screening modality [19]. In turn, contrast-enhanced mammography (CEM) has matured and provides excellent diagnostic accuracy. To reduce the total radiation dose, evaluation of single-view (1 V) CEM exams instead of dual-view (2 V) readings may be considered as an alternative reading strategy in women who cannot undergo MRI [twenty]. In Navarro's report, 465 contrast-enhanced mammograms were analyzed. The most frequent clinical indications were suspicion of cancer and previous inconclusive studies. Mass-type lesions were detected in 33% of the studies. Non-mass-like lesions were observed in 10% of cases and findings compatible with papillomatosis in 2%. Fifty-five percent of the studies had no visible lesions. In the 85 patients with a pathological study of the biopsy, the sensitivity of contrast tomography was 100%, with a diagnostic accuracy of 85%, positive and negative predictive values of 82 and 100%, respectively [21]. Stage-contrast mammography with synchrotron radiation is an innovative imaging procedure, where synchrotrons produce x-lightning that is essentially monochromatic, allowing for dose optimization and an overall reduction in scattered radiation. Instead of the detector being positioned rapidly behind the sample, in the same way as in classical x-lightning techniques, the detector is at a defined distance, which is an independent propagation locus that transforms the stage modulation of the transmitted beam into an amplitude modulation. Unlike ordinary or digital mammography, in synchrotron radiation mammography stage contrast and image diffraction generate enhancements in image contrast and increase the visibility of small details.

#### 4. Discussion

The results of the studies analyzed in this systematic review reveal the enormous benefit of using contrast-enhanced mammography for the diagnosis of breast cancer, as this is the most frequent neoplasm in women and the main cause of death in this group. Contrast-enhanced spectral mammography combines an iodinated contrast agent with standard mammographic technique to enhance lesion visibility and tumor growth is accompanied by angiogenesis. This technique uses a dual-energy exposure performed during a single breast compression, after injection of an iodinated contrast agent (1.5 mL/kg body weight). Two minutes after injection, standard mediolateral oblique (MLO) and craniocaudal (CC) views are performed on each breast [22]. Therefore, contrast-enhanced digital mammography (CEDM) is a new technique in which full-field digital mammography (FFDM) is supplemented by the use of intravenous iodinated contrast administration. In this technique, digitally contrast-subtracted images are used to assess tumor neo-angiogenesis, in a similar manner as in contrast-enhanced magnetic resonance imaging (MRI), with near complete subtraction of background parenchyma [23]. Thus, mammography is the only imaging modality that has been shown to reduce mortality from breast cancer through early detection. However, mammography has low sensitivity in dense breasts, which is consistent with our results. When used as an adjunct to a standard FFDM analysis, CEDM was shown to significantly increase diagnostic sensitivity (0.71-0.78;  $p = 0.006$ ). Since low-energy CEDM imaging has the potential to be used instead of FFDM imaging without losing visibility of lesion calcification, obtaining FFDM imaging in addition to CEDM imaging confers little sensitivity benefit compared to obtaining CEDM. CEDM images alone (sensitivity of FFDM and CEDM versus sensitivity of CEDM alone, 95% versus 94.7%) [24]. Therefore, CEDM may be a suitable low-cost alternative in women with dense breasts or among those who have a higher-than-average lifetime risk of breast cancer, especially when MRI is not available or cannot be performed. While this technique may be useful for indications previously reserved for MRI, such as problem solving, determining the extent of disease in newly diagnosed cancer patients, monitoring response to neoadjuvant therapy, evaluating post-treatment breast screening to detect residual or recurrent disease and potentially screening women at intermediate or high risk for breast cancer [25].

Most international organizations consistently recommend screening, at least between 45-50 and 75 years of age. The American Cancer Society recommends that women at average risk of breast cancer get regular mammograms starting at age 45, whereas ages 45 to 54 should get annual mammograms. For those over 55 years of age, screening is recommended every year or every two years, depending on personal choice. Between the ages of 40 and 44 they should have the opportunity to start annual screening if they so wish, and should continue to do so as long as their health status is good and their life expectancy is greater than 10 years [26,27]. Our results coincide with previous works that after 40 years of age this disease is more frequent, so it is appropriate to start screening at this age, however, positive cases have also been found in increasingly younger women.

The most important challenge of contrast mammography is related to the administration of contrast material. Iodinated contrast material is associated with risks of allergic reactions and extravasation events. Additional staff training is required for the administration of contrast material and for the management of contrast-related complications. Additionally, it is not sensitive enough to account for all breast cancers and may miss cancers that show little associated enhancement, such as low-grade ILC or DCIS. In addition, cancers may be obscured by background parenchymal enhancement or may not be included in the field of view, such as cancers that are close to the chest wall [28].

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#### 5. Conclusion

Since years ago, several studies have been available on the different aspects, pros and cons of CEM. However, there are more positive impacts with results that are really promising, showing a significantly better diagnostic performance of this type of mammography than that of digital or conventional mammography in the case of patients with breast cancer, due to its way of show better results in image contrast and detection of small details compared to the other two digital techniques, in fact, it can be very useful for the evaluation of patients with altered conventional mammography, before indicating an MRI or a percutaneous biopsy or in advanced stages of cancer. Research continues at an exponential rate, with several publications each year on this topic, both in diagnostic aspects and in improvements to the technique that are being implemented in patients with breast cancer [29].

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#### Compliance with ethical standards

##### *Disclosure of conflict of interest*

The authors declare no conflicts of interest.

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