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Breast Cancer Risk assessed by Mammography, US and MRI

INTRODUCTION

When looking at those factors that increase the risk for breast cancer, we find that there are specific factors that one can modify and others that are not modifiable.

Non-modifiable risk factors:

1. Female gender
2. Old age
3. Inheriting certain gene changes (such as BRCA1 and BRCA2)
4. Family or personal history of breast cancer
5. Race and ethnicity
6. Being taller
7. Having dense breasts
8. Having certain benign conditions e.g. atypical hyperplasia
9. Starting menstrual periods early or late menopause
10. Exposure to chest radiation
11. Exposure to DES (diethylstilbestrol) in utero.

Modifiable risk factors:

1. Drinking alcohol
2. Being overweight/obese
3. Not being physically active
4. Being nulliparous
5. Never breastfed
6. Hormonal contraception – very rare
7. Postmenopausal hormone therapy – rare
8. Breast Implant-Associated Anaplastic Large Cell Lymphoma – very rare

All these factors need to be considered when tailoring breast cancer screening programs to the patient's specific needs. They have been incorporated into the Tyrer-Cuzick Risk Calculator, which calculates the 10-year and lifetime risk score for developing breast cancer based on the above criteria.[1] The performance of these epidemiologically based risk models is improved by incorporating findings detected during breast imaging.

The primary aim of breast cancer screening studies is to detect breast cancer early to allow early treatment and improved treatment outcomes. However, they also have the potential to identify those individuals who are at increased risk of developing breast cancer.

This article describes the range of imaging features associated with breast cancer risk using digital mammography (DM), digital breast tomosynthesis (DBT or 3D mammography), breast ultrasound (breast US), and MRI.

IMAGING CRITERIA THAT INDICATE A HIGHER RISK OF BREAST CANCER

Breast density detected on mammography is an independent risk factor for breast cancer. Breast density is assessed on a four-category scale developed by the American College of Radiology (ACR). The scale forms part of the Breast Imaging Reporting and Data System (BI-RADS). Thus, individuals who have dense breasts on DM or DBT, have an increased risk for developing breast cancer.[2] In addition, dense breast tissue may obscure a cancer resulting in delayed diagnosis and potentially a poorer therapeutic outcome.[3]

Besides breast density, increased parenchymal complexity of the breast has been shown to correlate with a higher risk for cancer.[4]

Unlike mammography, breast US is capable of distinguishing glandular (ductal and lobular) from fibrous (stromal) elements of the breast. A higher glandular component that can be detected on breast US correlates with a higher incidence of breast cancer.

Finally, a higher background parenchymal contrast enhancement on breast MRI is also indicative of a higher breast cancer risk. Contrast enhanced mammography and molecular breast imaging are both capable of demonstrating background parenchymal enhancement. However, to date, these latter techniques are not widely used.

BREAST DENSITY ON MAMMOGRAPHY

Approximately 44% of women aged 20-74 have dense breasts.[5] The stromal (fibrous) and glandular components of the breast are the fibroglandular tissues that contribute towards breast density (whiteness) on DM and DBT. Adipose tissue is darker than fibroglandular tissue. Breast cancer most commonly occurs in the fibroglandular components. In addition, fibroglandular tissue may obscure breast cancer on mammography since both tissues have similar density.

Figure 1. BI-RADS classification of breast density is based on four categories that are assessed on medio-lateral oblique (MLO) mammograms:
A. Breast is almost entirely fatty.
B. Scattered areas of fibroglandular density.
C. Heterogeneously dense breast, which may obscure small cancers.
D. Extremely dense breast, which lowers sensitivity for detecting cancer.

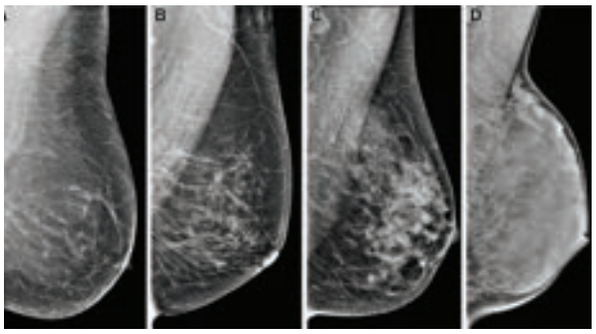
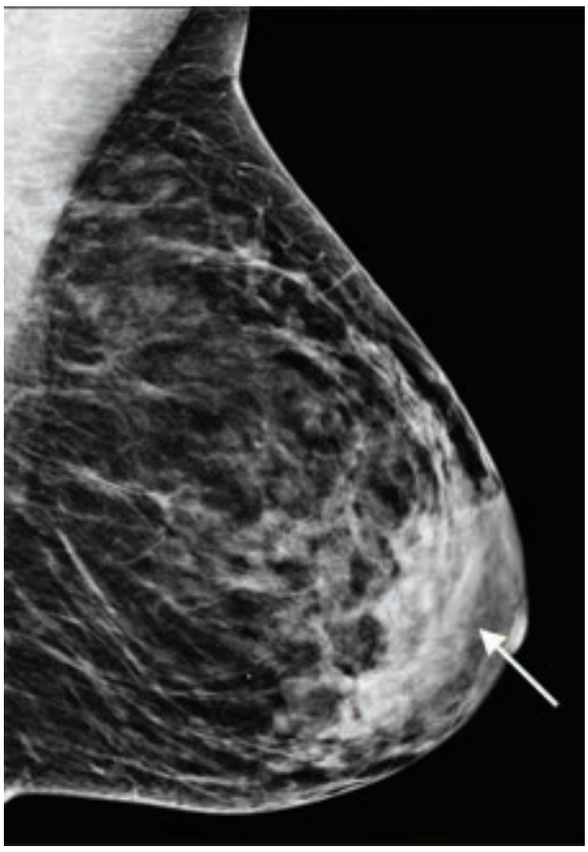


Figure 2. Note that the retroareolar density (arrow) shown in this left MLO mammogram could potentially obscure breast cancer. Therefore, even though most of the breast contains fatty tissue, this breast would still be classified as category C.



The BI-RADS classification method for breast density is based on a scale of four categories (Fig 1). Note that the classification is not based on the size of the area of increased density. It is based on the likelihood that the dense tissue might obscure a cancer (Fig 2).

Considerable inter-reader variability has been shown when using BI-RADS breast density assessment.[6] Several research groups have consequently attempted to use deep learning to mitigate this issue. There are currently at least nine U.S. Food and Drug Administration approved breast density assessment methods for DM, DBT and synthetic mammography (SM) using artificial intelligence.[7]

Using DBT, breast density can be assessed three-dimensionally in two ways: either as total dense breast volume or by measuring dense breast as a percentage total breast volume. Volumetric percental density has been shown to be more accurate for predicting breast cancer risk.[8]

BREAST PARENCHYMAL COMPLEXITY ON MAMMOGRAMS

Breast parenchymal complexity that is evident on mammograms can be quantified using computer analytical methods. Radiomic features are extracted using computer analysis of DM and can be displayed as heat maps[9] (Fig 3).

Figure 3. Radiomic analysis of the complexity of breast parenchymal texture that is then displayed in heat maps. The skewness map (A) shows the difference in textural complexity between one area and that adjacent to it, while the entropy map (b) shows the extent of disorder within the tissues. Red areas are those with high complexity and high disorder levels, while blue areas correlate with low complexity and low disorder levels.

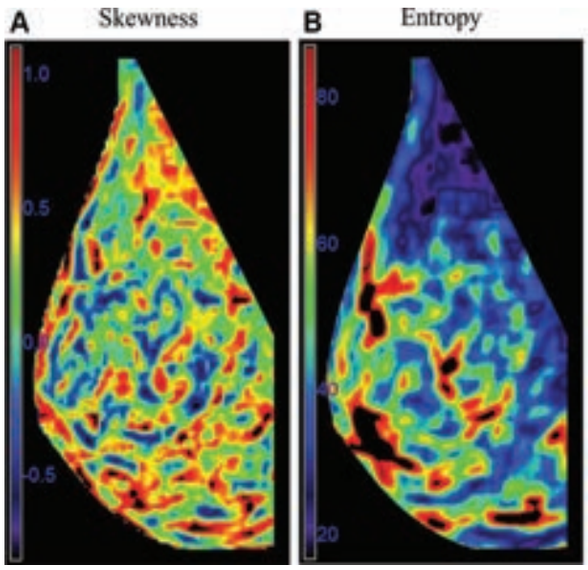
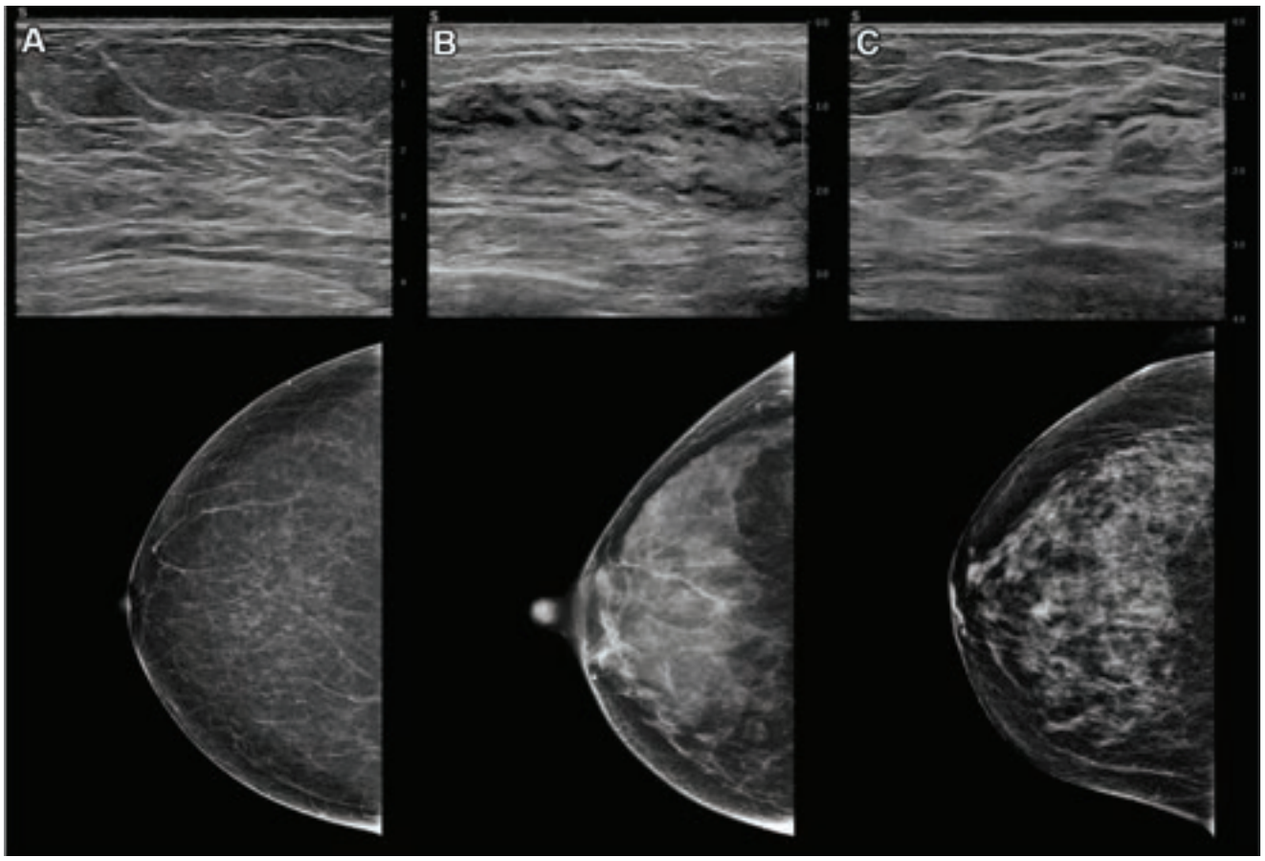


Figure 4. A. US category homogeneous background (fat) correlates with a fatty breast on mammography. B. US category homogeneous background (fibroglandular) corresponds to a dense breast. C. US category heterogeneous background correlates with a scattered fibroglandular elements on mammography.



Similar to increased breast density, increased parenchymal complexity is also associated with an increased risk for breast cancer.[4]

DEEP LEARNING IN BREAST CANCER RISK ASSESSMENT

Recent advances in deep learning have resulted in the computer being able to "learn" the features associated with cancer risk.[6]

Early studies that compared the results from the Tyrer-Cuzick calculator alone, DM features alone, and a deep learning model combining Tyrer-Cuzick and DM features, showed that the deep learning model delivered higher accuracy for diagnosing breast cancer. The same research group subsequently developed a mammography-based deep learning model that delivered an accuracy that surpassed the earlier one.[10] This is probably due to the improvement of deep learning technology with time and training.

One research group obtained the highest accuracy achieved so far by combining deep learning features (density, calcifications, masses) with familial, demographic, lifestyle, and polygenic risk scores that surpassed the Tyrer-Cuzick risk model.[11]

BREAST US

As discussed, the BI-RADS classification method for breast density is based on a scale of four categories (Fig 1). On the other hand, tissue composition on US is classified into three categories according to the BI-RADs classification: Homogeneous background (Fat), homogeneous background (fibroglandular), and heterogeneous background which is a combination of both fat and fibroglandular tissue (Fig 4). These categories correspond loosely with the four categories seen on mammography. Breast US can further distinguish stromal from glandular tissue within the

fibroglandular components of the breast; a higher proportion of glandular elements reflects a higher risk for breast cancer.

Internal echogenicity patterns of fibroglandular tissue on breast US may contribute to cancer risk assessment. However, standardisation of methods of evaluation and quantification as well as deep learning models will be required to develop a robust assessment method. In keeping with this, an international study that will evaluate the implications of sonographic glandular features on breast cancer risk is currently recruiting patients [ClinicalTrials.gov Identifier: NCT05460975].

BREAST MRI

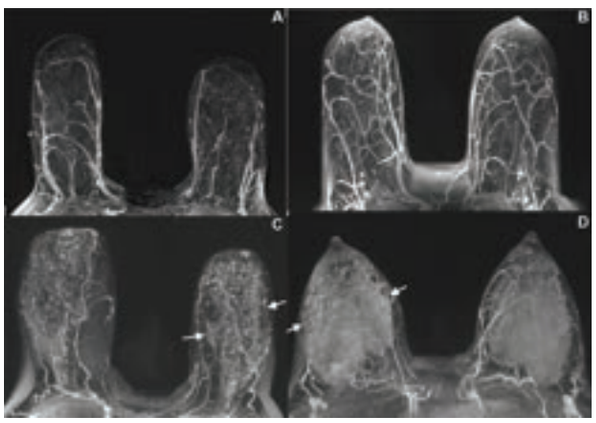
MRI is the most sensitive imaging modality for detecting breast cancer. Breast MRI features may be used to evaluate breast cancer risk.

Fibroglandular tissue is enhanced after administration of gadolinium-based contrast material; this enhancement is known as background parenchymal enhancement (BPE). BPE parallels the breast density categories seen on mammography: almost entirely fat, scattered fibroglandular elements, heterogeneous fibroglandular tissue, and extreme fibroglandular tissue (Fig 5).

BPE can be assessed visually (qualitatively) or using software (quantitatively). BPE is an independent risk factor for breast cancer, with high degrees of enhancement corresponding to a higher risk.

It is uncertain whether the degree of BPE is due to hormonal stimulation or glandular proliferation. Women with dense breasts who show a low BPE do not have a higher risk for breast cancer.[12] On the other hand BRCA1 and BRCA2 variant carriers who have had risk-reducing salpingo-oophorectomy, but in whom BPE remains high, still have an increased breast cancer risk.[13]

Figure 5. Qualitative BPE assessment according to the BI-RADS lexicon. Axial subtracted postcontrast, maximum intensity projection images of four different patients showing (A) minimal, (B) mild, (C) moderate, and (D) marked BPE (arrows).



Further evaluation of BPE for breast cancer risk prediction is required with the development of reproducible prediction models including deep learning models.

CONCLUSION

In addition to mammographic density, the above article describes a number of breast cancer risk assessment techniques which have shown promising results. However, these technologies require further evaluation and validation based on large prospective multinational studies. The ultimate goal is to deliver a tailored breast cancer screening strategy that is based on the level of breast cancer risk.

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