Impact of Breast Density on Breast Cancer Risk Stratification

By Dr. S Destounis

INTRODUCTION

Breast cancer is the most common cancer diagnosis in US women. With over 40,000 women dying of the disease in 2019 [1], breast cancer is the second leading cause of death after lung cancer. While screening mammography has demonstrated its value in breast cancer detection by decreasing mortality from the disease by up to 30% [2-6], the fact remains that one in eight women will still be diagnosed with breast cancer [1]. For those women, the risk of death remains uncertain.

Mammography remains the gold standard for breast cancer detection but does have limitations. One well-known limitation of the technology is the imaging of dense breast tissue [7]. The highest categories of mammographic breast density (MBD) are reported to confer increased relative risks of developing breast cancer by 4- to 6-fold compared to the lowest MBD categories, or 2-fold compared to the population average breast density [8]. In addition, high breast density can be responsible for a masking effect in mammography, due to the similar X-ray attenuation properties of dense tissue and breast tumors, both appearing white on a mammogram. Results from large scale studies and screening populations have suggested that up to 50% of cancers may be missed by mammography in women whose breasts are in the highest density categories [9]. Such women are six-fold more likely of being diagnosed with an interval cancer compared to those in the lowest two density categories [9]. For these reasons, MBD has become an important consideration in the screening for breast cancer.

Research related to breast density and cancer risk dates back to 1976, when Wolfe *et al.* published a seminal study showing a stepwise increase in the risk of breast cancer development risk in women with varying breast parenchymal patterns [10]. Wolfe divided the breast patterns into four categories, with the lowest being composed mainly of fat (BIRADS correlate, category A - mostly fatty), and the most extreme category being composed mainly of tissue that hides any ducts and with almost no fat (BIRADS correlate category D - extremely dense). This early study found that the most extreme category had a 37 - fold increased chance of developing breast cancer than the lowest, most fatty category. Similar research followed Wolfe's initial publication, and while the results were not able to be precisely replicated, research did continue to find a correlation between increased breast density and breast cancer risk [11-15]. Despite this, the implication of having dense breasts was not widely acknowledged by medical professionals, nor were women themselves aware of breast density. In the United States this changed when grassroots advocacy groups pushed for women to be informed of their breast density and the resulting implications, leading to legislation being adopted which mandated that the density of a woman's breasts should be reported to her in the mammography report after a screening mammogram [16]. The goal of the legislation was to bring awareness to the increased risks associated with having dense breast tissue, so allowing women to make informed decisions about their own healthcare, to understand the risk of dense breast tissue and to consider seeking supplemental screening. Because of the risk associated with increased breast density, MBD has been viewed to have clinical utility for identifying women at increased risk of developing breast cancer and/or having a breast cancer missed. These women can thus benefit from supplemental screening, risk assessment, and potentially preventative therapies. Identifying women with dense breasts is of prime importance to provide them optimal screening outcomes.

RISK ASSESSMENT MODELS

Risk assessment through use of a suitable risk assessment model is the primary method of identifying women at increased risk. There are two main types of risk assessment: the chances of developing breast cancer over a given timespan, including the lifetime; and the chances of there being a mutation in a known high-risk gene such as *BRCA 1* or *BRCA 2*. Most available models utilize traditional risk factors such as first-degree and second-degree relatives on the maternal and paternal side; also, hormonal, and reproductive factors such as menopausal status, age at menses, use of hormone replacement therapy, and age at first pregnancy. What started as early investigation with these models for research purposes has recently become commonplace in many clinical settings as providers seek to identify high-risk women.

The earliest models for risk stratification used basic and obvious markers for higher risk in women such as family history of breast cancer, meaning a genetic predisposition,

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and the chance of having a strong genetic marker like *BRCA1* or *BRCA2*. A variety of models exist, such as the Gail model, the Breast Cancer Surveillance Consortium (BCSC) model, the Claus model, and the Tyrer-Cuzick (TC) model, and all incorporate a variety of risk factors to determine a woman's risk. The choice of which model to use is not standardized and is based on the purpose of the risk assessment. The models all perform differently depending on the patient population being assessed. Most recently, several models were updated to include breast density in the risk calculation, in an effort to improve risk assessment and thus identification of those at high risk.

INCLUSION OF BREAST DENSITY IN RISK ASSESSMENT

A literature review by Vilmun and colleagues showed that, overall, the inclusion of breast density has the potential to improve breast cancer risk prediction models [17]. The review evaluated eleven eligible studies and investigated the overall impact of adding breast density to breast cancer risk models. Four studies included in the review modified the Gail model, four modified the Tyrer-Cuzick model, and five studies developed new models. Several methods were used to measure breast density, including visual, semi- and fully automated methods. Eleven studies reported discriminatory accuracy and one study reported calibration. Seven studies found a statistically significantly increased discriminatory accuracy when including density in the model. The increase in AUC ranged from 0.03 to 0.14. Four studies did not report on statistical significance, but reported an increased AUC ranging from 0.01 to 0.06. The study authors determined from the review that the discriminatory accuracy remains limited on an individual level, and that most breast cancer risk models yield poor to fair discrimination. Further evaluation is still needed.

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Brentnall *et al.* showed that adding mammographic density to the classic risk factors in the Tyrer–Cuzick (TC) model improves risk stratification [18, 19]. Similarly, a prospective study showed that the addition of mammographic density to the TC or Gail model added accuracy to the risk assessment [20]. Work with the BCSC model has similarly provided validation to adding breast density to the risk calculation [21]. Lee *et al.* retrospectively compared the traditional Gail model to modified versions of the model to include breast density and genetic variants for 24,161 women undergoing screening in Singapore [22]. The study compared the risk scores of women when only traditional risk factors were input, compared to the level of risk once breast density and BMI were added into the model. The authors found that, when breast density and BMI were added to the model, increased breast density amplified the risk of breast cancer two- to four- fold compared to less dense breasts. The addition of breast density increased the AUC of the risk prediction model by 3%, showing improved performance. Similarly, Keller *et al.* [23] investigated the effect of breast density on the Gail model, but added a further aspect to the study by comparing various calculations of breast density: absolute dense area, percent dense area, percent dense volume and absolute dense area. The study found that all four measures of density strengthened the risk prediction by a significant factor ($P < 0.003$) relative to the model including only traditional risk factors.

FUTURE OF DEEP LEARNING AND AUTOMATED INTELLIGENCE

Deep learning models have been developed in various aspects of breast imaging, including in cancer risk assessment. While the models that are currently being utilized in clinical practice have been well validated, limitations still exist. Yala *et al.* retrospectively assessed a hybrid deep learning model that incorporates both mammographic features and traditional risk factors from screening mammograms [24]. The authors hypothesized that there is subtle, yet informative information contained within the mammogram images that while not discernible by the human eye, could be utilized by a deep learning model to further improve risk assessment. The hybrid deep learning model was found to be significantly more accurate than the TC model (0.70 vs 0.62, respectively). The model was better at identifying high-risk cohorts, categorizing a greater percentage of patients with cancer in the top risk decile, compared with the original TC model. Utilizing the mammography images themselves is where we will see further development of risk assessment. For example, a publication by Dembrower and colleagues described the use of deep learning with convolutional neural networks to determine individual breast cancer risk scores based on mammogram images [25]. The output of the model was the DL risk score, which reflects the likelihood of developing breast cancer based on a single mammographic image. Results found that the area of dense breast at mammography was higher among women diagnosed with breast cancer than in those without a breast cancer diagnosis, along with older age at mammography and percentage density at mammography, with a high association for breast cancer. The study authors report that the performance of their model trained on mammography images was better than that of density-based models. These promising findings support the proposition that an all-inclusive approach to risk prediction is imperative to best identify those at risk of the development of breast cancer. Further development and training of risk models is needed, across institutions and geographic locations.

CONCLUSIONS

MBD has been proven to be an important risk factor for breast cancer. Utilization of density in risk assessment provides a more accurate method for assessing a woman's risk of breast cancer, guiding more informed decision-making, including personalized screening with supplemental screening tools, as well as potential prevention strategies.

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BOOK REVIEW

MRI Physics: Tech to Tech Explanations

By Stephen J. Powers

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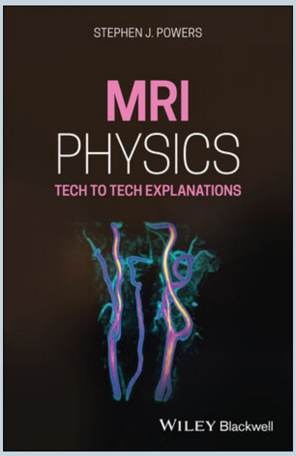

Technologists must have a solid understanding of the physics behind Magnetic Resonance Imaging (MRI), including safety, the hows and whys of the quantum physics of the MR phenomenon, and how to competently operate MRI scanners. Generating the highest quality images of the human body involves thorough knowledge of scanner hardware, pulse sequences, image contrast, geometric parameters, and tissue suppression techniques.

MRI Physics: Tech to Tech Explanations is designed to help student MRI technologists and radiotherapists preparing for Advanced MRI certification examinations to better understand difficult concepts and topics in a quick and easy manner.

Written by a highly experienced technologist, this useful guide provides clear and reader-friendly coverage of what every MR Technologist needs to know. Topics include safety considerations associated with the magnetic field and RF, pulse sequences, artifacts, MRI math, the much-feared gradients, and I.V. contrast.