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Short Review

Imaging and clinicopathologic characteristics in a contemporary cohort of younger women with newly diagnosed breast cancer

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ABSTRACT

Background: Younger women tend to have dense breasts and early detection of breast cancer in this population remains challenging. Although MRI is more sensitive than mammography, MRI is associated with a greater false positive rate. The purpose of this study is to evaluate the relationship of MR imaging and clinical characteristics in young women with breast cancer.

Methods: The Breast Cancer Database at our medical center was queried for all women who had a mammogram and MRI from 2010–2014. Variables included demographics, risk factors, tumor characteristics, mammographic breast density (MBD), background parenchymal enhancement (BPE), and assessment of fibroglandular tissue (FGT) with contiguous MR images. Statistical analyses included Pearson's Chi Square Tests.

Results: Of 1829 women, 111 (6%) were <40 years at the time of breast cancer diagnosis. When compared to women ≥ 40 years, younger women more often presented with palpable masses ($p<0.0001$), a higher proportion of BRCA1 mutations ($p=0.02$), stage II–III tumors ($p<0.0001$), invasive ductal carcinomas ($p=0.006$), HER2-positive tumors ($p=0.005$) and higher Ki-67 scores ($p=0.02$). Younger women had increased MBD ($p<0.0001$) and increased FGT ($p<0.0001$) when compared to older women, however, BPE was not significantly different ($p=0.70$).

Conclusions: Younger women had more palpable lesions and increased MBD and FGT. However, BPE was not significantly different between age groups. This suggests that BPE may not contribute to the increase in false positives associated with MRI in premenopausal women. These results underscore the importance of the clinical breast exam and breast self-awareness in young women who do not undergo routine screening.

Microabstract: Younger women with breast cancer often present with palpable lesions and more advanced breast disease. Younger women tend to have increased breast density, but there is a dearth of literature on MRI characteristics in this population. Since younger women have increased breast density and are not routinely screened, improved monitoring with clinical breast exams and breast self-awareness may be important.

1. Introduction

In 2015, approximately 10,500 new cases of invasive breast cancer in the United States were diagnosed in women younger than 40 years old [1,2]. Breast cancer in this population accounts for 5% of all newly diagnosed invasive breast cancers in the United States with approximately 1.8% of breast cancer occurring in women less than 35 years old [1–3].

Recently, various breast cancer screening guidelines for women above the age of 40 have been revised and the American Cancer Society now offers a qualified recommendation for annual screening mammography in women aged 40–44 [4,5]. Screening recommendations for women younger than 40 years old are less clearly defined [6,7]. This ambiguity along with lower awareness, suspicion and perceived risk of breast cancer in younger women contributes to delays in diagnosis [7–9]. As such, breast cancer in younger women is often symptomatic at presentation [10–13], and diagnosed at a later stage compared to older women [10,12,14–16]. Furthermore, their cancers are thought to be biologically more aggressive [17], with possibly

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worse prognosis, although younger age as a predictor of worse prognosis has been questioned [18].

To facilitate earlier detection of these cancers, the American Cancer Society (ACS) recommends annual screening with mammography and breast MRI as early as age 30 in women at high risk of developing breast cancer [19]. High-risk women include those with a known *BRCA1* or *BRCA2* gene mutation, a history of radiation to the chest between age 10–30 years, and women with a lifetime risk of $\geq$20–25% using risk assessment tools largely dependent on family history [19].

Although mammography is the primary modality for breast cancer screening, younger women are more likely to have dense breast tissue, which decreases the sensitivity of mammography [14,20,21]. Screening breast MRI has been found to be more sensitive than mammography (77–91% and 33–40%, respectively) [22–24], particularly in pre-menopausal women, and women with dense breast tissue [25–27]. Breast MRI has also demonstrated cost-effectiveness and superior sensitivity in high-risk women [19,28].

However, a major limitation in the use of MRI is the increased false positive rate compared to screening mammography. This has been partly attributed to features such as background parenchymal enhancement (BPE), which can affect the interpretation of dynamic contrast-enhanced breast MRI [29]. BPE represents the amount of enhancement of normal breast on MRI and is described as minimal, mild, moderate or marked, per the American College of Radiology BI-RADS reporting system [30]. Though BPE is known to be hormonally sensitive, decreasing in post-menopausal women [31], one study found no difference in BPE in women ages $<$35 years old compared to $\geq$35 years old [32]. Since elevated BPE has been found to increase false-positive interpretations of breast MRI [33,34], BPE in younger women deserves further evaluation.

The purpose of this study is to assess the presentation of breast cancer in a contemporary cohort of women $<$40 years old compared to women $\geq$40 years old, with regards to both clinicopathologic and imaging characteristics; imaging characteristics of interest include BPE and FGT on MRI, in addition to mammographic breast density.

2. Patients and methods

2.1. Study participants

The Breast Cancer Database at our medical center is a longitudinal study that was established in January 2010. All patients undergoing definitive breast cancer surgery for a new breast cancer diagnosis at our institution are eligible to enroll in the Breast Cancer Database. All clinical data were obtained from comprehensive questionnaires filled out at the time of surgery and review of the electronic medical records. Variables collected include information on demographics, risk factors, tumor characteristics, and imaging characteristics, such as mammographic breast density (MBD), BPE, and fibroglandular tissue (FGT); a three dimensional assessment of breast density on MRI. Patients included in this study were enrolled in the Breast Cancer Database between January 2010 and May 2014. Men were excluded from this study. This retrospective study was approved by the Institutional Review Board.

2.2. Diagnostic imaging

2.2.1. Mammography imaging technique

All mammograms were performed with digital technique and were acquired using MAMMOMAT® Novation DR software (version V8.3, Siemens Healthcare). Based on routine institutional practice, the images were further analyzed by iCAD computer-aided detection software (iCAD, version VA20E, Nashua, NHiCAD, Inc.).

2.2.2. MR imaging technique

Bilateral dynamic contrast enhanced breast MRI examinations for pre-menopausal women are scheduled during the second week (days 8–14) of their menstrual cycle. All breast MRI examinations were performed on a 3.0-T (TIM Trio, Siemens Medical Solutions) with the patient in prone positioning using a dedicated surface breast coil (7-Channel Breast Biopsy Array, InVivo Research). The standard imaging protocol includes a localizing sequence followed by a sagittal T2-weighted sequence (TR/TE, 7220/84); a sagittal T1-weighted non-fat-suppressed 3D fast spoiled gradient-recalled echo sequence (4.01/1.52; flip angle, 12°; matrix, 384 $\times$ 384; field of view, 270 mm; section thickness, 1mm) followed by the same sagittal T1-weighted fat-suppressed 3D fast spoiled gradient-recalled echo sequence performed before and four times after a rapid bolus injection of 0.1 mmol/L of gadopentetate dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals) per kilogram of body weight at an injection rate of 2.0 mL/s via an intravenous catheter. Image acquisition began immediately after administration of the contrast material and saline bolus. The first contrast-enhanced dynamic sequence was obtained at approximately 100 s, followed by four additional consecutive sequences (three sagittal followed by one delayed axial). The delayed axial images were obtained so that subtle asymmetric background parenchymal enhancement could be appreciated. Post-processing included subtraction images and MIP images. Images were reviewed on high resolution PACS monitors.

2.3. Image assessment

Mammographic breast density was categorized according to the American College of Radiology as entirely fatty, scattered fibroglandular, heterogeneously dense breasts or extremely dense [30]. All mammograms were assessed for breast density by two fellowship-trained breast radiologists in consensus.

All breast MRI examinations were assessed for BPE, in consensus, by two fellowship-trained breast radiologists who had up to 12 years of experience in reading breast MRI. Both readers were blinded to mammographic density, clinical data of the patients and to pathology results. The level of global BPE, rather than the highest BPE in a single quadrant, was assessed using a combination of pre- and the first post-contrast T1-weighted fat saturated and subtracted images and was recorded on a 4-point scale (a. minimal; b. mild; c. moderate; d. marked) in accordance with latest BI-RADS categories [30]. Both intensity and volume were considered in the assessment. Furthermore, the amount of FGT was evaluated using the scale based on American College of Radiology BI-RADS criteria: entirely fatty, scattered fibroglandular, heterogeneously fibroglandular and extreme fibroglandular tissue [30]. In cases of asymmetry of the breasts, the higher level of mammographic density, BPE and FGT was recorded. All information on mammographic breast density, BPE and FGT were collected from the IRB approved database and electronic medical records.

2.4. Statistical analyses

Descriptive statistics were used to summarize the data and to see the distribution of the variables between women $<$40 and women $\geq$40 years of age. Pearson's chi-square was used to test for any associations between the variables of interest and age group with a significance level of 0.05. When the expected value in at least one of the cells was less than 5, Pearson's Chi Square was