BJR

Received: 20 August 2013 | Revised: 14 October 2013 | Accepted: 23 October 2013

doi: 10.1259/bjr.20130528

Cite this article as:
Tagliafico A, Tagliafico G, Houssami N. Differences in breast density assessment using mammography, tomosynthesis and MRI and their implications for practice. Br J Radiol 2013;86:20130528.

INVITED COMMENTARY

Differences in breast density assessment using mammography, tomosynthesis and MRI and their implications for practice

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Literature searching of PubMed highlights, through the number of articles related to breast density and also to digital breast tomosynthesis (DBT), that there is an increasing interest in breast density assessment and DBT. Indeed, searching at first the term "breast density" and then "digital breast tomosynthesis", it is possible to note a positive trend on these topics (http://www.ncbi.nlm.nih.gov). The question then arises as to why there is an interest in breast density assessment and how this relates to new modalities for breast cancer detection?

The answer may be that modern medicine is rapidly moving towards a personalised or tailored approach based on predefined risks of a particular disease, a concept that is particularly applicable to breast cancer. Identifying females with an increased risk of developing breast cancer is possible and is important because they may benefit from modified screening and diagnostic protocols [1].

The inclusion of breast density assessment in statistical models such as the Gail et al [2] and Claus et al [3] models may improve their accuracy or use because these methods include non-modifiable risk factors, such as age at inclusion, age at menarche, age at first full-term pregnancy, number of previous biopsies with a benign result and number of first-degree relatives with breast cancer. By contrast, breast density is considered to be an independent risk factor [4], and it is also indicative of changes in modifiable risk factors [5–9]. Moreover, breast density may be particularly suitable for individualised breast cancer risk estimation and not for population-level brief estimation only [10].

Breast density assessment may be carried out using different imaging modalities used in clinical practice, such as mammography, DBT and MRI. These commonly used imaging techniques may give similar results for density assessment, but they may not always be interchangeable for an individualised purpose [11]. Therefore, the purpose of this article is to give a brief overview on breast density percentage assessment with these imaging techniques, highlighting our perspectives on the differences and limitations of each technique.

MAMMOGRAPHY

In mammography, the traditional imaging modality that defined the concept of tissue density, breast density is quantified as percent density (PD), the percentage of the mammogram area occupied by non-fatty "dense" tissue relative to the fatty "non-dense" tissue. A reliable method for semi-quantitative PD measurement is possible using the Breast Imaging Reporting and Data System® (BI-RADS) lexicon, developed by the American College of Radiology, Reston, VA, but this method was not originally intended to serve as a method of measuring breast density. Other classifications for density exist (some of which were developed decades ago and are still in use), including Wolfe's parenchymal patterns, Tabar's classification, quantitative assessment using computer-aided techniques for measuring PD and some systems that obtain a volumetric breast density measurement [12,13].

Quantitative assessment of breast density is important for performing epidemiological studies, including the estimation of breast cancer risk, radiation dose monitoring, and the effects of hormone replacement therapy and of different endocrine treatments [14,15]. To evaluate breast density on mammograms quantitatively, it is possible to use either film-screen or full-field digital mammograms [11,13,16]. As visual assessment is invariably subjective and associated with suboptimal reproducibility, its replacement with reproducible computerised density assessment has been suggested [5–11]. Using a semi-automated or fully automated software for PD measurement may be the best solution; however, it is important to consider that the software performance on digitalised film-screen mammograms is worse than the performance of the software on digital mammograms. The main reasons are artefacts in the edge recognition algorithms and different contrast and windows during printing. These problems are greatly reduced with full-field digital mammograms, although some artefacts occur in the upper and lower part of the 0–100 percentage measure. For example, a "non-dense" mammogram may be artefactually considered "dense" because of a failure to recognise background pixels as fatty tissue and vice-versa. A limitation of the mammographic breast density assessment is that the reference standard, also for software evaluations, is usually calibrated on the basis of the radiologists' visual estimation. Furthermore, differences between breast PD evaluation obtained using a software and visual classifications for the same mammograms have been reported: software-based measurements provide systematically lower PD values with a cut-off ranging from 13% to 22% [16,17].

DIGITAL BREAST TOMOSYNTHESIS

DBT is a relatively new, promising and emerging modality for breast cancer detection and characterisation. DBT is based on a full-field digital mammography (FFDM) platform, and the DBT images for clinical use are usually obtained by the same projections (craniocaudal and mediolateral oblique views) as conventional mammography. The tomographic images or "slices" are usually reconstructed at defined intervals and visualised on dedicated work stations. As for CT, DBT images may also be viewed as "slabs". DBT should reduce or eliminate overlapping tissues, with the intent to distinguish superimposed normal breast tissue from breast lesions better than conventional mammography. In dense breasts, the elimination of superimposed breast tissue should theoretically improve the detection of lesions that are otherwise occult on standard mammograms. Very promising results have been obtained for DBT so far [18,19]; therefore, the use of DBT in clinical practice is anticipated to rapidly increase. It seems reasonable to expect that, in future, many females will obtain their mammograms using DBT, and it will become inevitably necessary to evaluate breast density using DBT examinations. One of the first studies comparing breast density on digital mammograms and on the central projection of DBT reported a high correlation between breast density estimates on digital mammograms and those on central DBT projections, suggesting that the latter could be used to estimate breast density on three-dimensional (3D) reconstructed images with a lower radiation dose [20]. Further research compared breast density on FFDM and DBT using fully automated software, and it has been demonstrated that breast density may be significantly underestimated on DBT by up to 16% (relative to FFDM) [21]. Moreover, the authors suggest that automated estimation with software was more accurate than BI-RADS quantitative evaluation [21]. It is possible that differences between breast density assessment on DBT and FFDM could be attributed to differences in positioning, compression, dose to the detector and to software algorithms. Probably, patient positioning and compression are not sufficient to fully explain the differences. We agree with previous studies that DBT projections would be useful since they are not dependent on DBT reconstruction algorithms [20]. However, this concept may be explored further through research. To date, there are no sufficient data to support the use of DBT projection or reconstructed images for breast density assessment. It seems intuitive that the use of fully automated software should be preferred for measuring density with DBT, as it eliminates the problem of training, performs image analysis with no need for superiority control and saves time in large epidemiological studies. The problem of image artefacts is very limited when using fully digital images on automated software. Moreover, a good integration of breast density into risk assessment and risk management, including tailored screening and primary prevention, will be possible with future software development [22].

A relatively counterintuitive concept is that, using DBT, breast density values were underestimated in comparison to FFDM in a non-linear relationship across the BI-RADS categories [23]. This means that it will be difficult to find a correction factor to compare breast density evaluated on DBT and on FFDM. In one study, for BI-RADS Categories 2 and 3, there were relatively lower differences for density measures between FFDM and DBT, whereas for BI-RADS Categories 1 and 4, there were relatively higher differences for density measurements. The implication of this for breast cancer risk prediction is that the difference between DBT-based and FFDM-based density measures related to BI-RADS Category 4 may be a concern owing to an underestimation of the breast density percentage in patients undergoing DBT [23]. For this reason, a patient with a dense breast (on conventional FFDM) may potentially have an underestimated breast cancer risk if only DBT images are considered.

MRI TECHNIQUE

MRI has been used to calculate the water content of a human breast via slices or slabs and with segmentation of 3D images with tailored sequences [24–30]. It has been shown that percent MRI-density correlates strongly with mammographic PD; however, MRI, as also discussed above for DBT, has been shown to underestimate breast density compared with conventional mammography.

To date (and to the best of our knowledge), only one study directly compared breast tissue density estimates evaluated on digital mammograms with DBT and on MRI within the same patients [11]. In this study, the MRI sequence used as a reference standard was an iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) sequence. This sequence was developed to separate the fatty non-glandular tissue from the water content of the true glandular tissue, taking advantage of the biochemical features of the breast tissue more than the proton density. This sequence may therefore be considered a quasi-histological proof of the difference between "dense" and "non-dense" breast tissue. To date, different sequences have been used in several studies to assess breast density on MRI, but no definite consensus has been reached about the optimal sequence to be used. Further research should clarify which MRI sequence best fits the purpose of breast density evaluation considering that IDEAL sequences are time consuming and difficult to integrate into normal protocols.

On MRI, some artefacts were registered because of the high field strength; therefore, the use of the fully automated software was

Table 1. Comparison among mammography, digital breast tomosynthesis (DBT), MRI and ultrasound for breast density assessment: general advantages and disadvantages are reported.

Technique	Advantages	Disadvantages
Mammography	Widely used	Ionising
Digital breast tomosynthesis	Three dimensional and similar values to MRI	Ionising and not widely used so far
MRI	Non-ionising similar to histology	Not used for non-dense breast costs
Ultrasound	Non-ionising, wide-availability, repeatable and cost	Operator dependent, not used for non-dense breasts and lack of comparison among ultrasound/MRI and DBT

See text for more details.

difficult [11]. Both MRI and DBT underestimated breast density in comparison to FFDM, but all three methods were well correlated. No significant differences between MRI and DBT percent densities were observed, suggesting that these modalities may be suitable techniques to obtain PD assessment similar to the quasi-histological IDEAL sequence. Moreover, measuring breast density on DBT and MRI, the entire volume of the breast is considered in a true 3D fashion, which is theoretically preferable to two-dimensional imaging for the purpose of estimating tissue density.

ULTRASOUND

The radiological techniques described above have the disadvantage of using ionising radiations (mammography and tomosynthesis) and are very expensive (MRI). Given the physical features of an ultrasound beam, in clinical practice, ultrasound assessment of breast density has the potential to provide a non-ionising method suitable for young females and those who need repetitive measurements in longitudinal studies [31,32]. Several research groups found that mammographic breast density has a significant correlation with ultrasound assessments of breast density [33]. In addition, recently, it has been demonstrated that ultrasound, which is operator dependent for data acquisition, has a substantial intermodality and interobserver agreement for assessment of breast density [33]. Different authors have added elastography to B-mode ultrasound evaluation of the breast. It was found that only the grey levels correlated positively with mammographic breast density and the elastographic data [34]. To date, the use of ultrasound in large case-control studies has not been validated as a breast cancer risk predictor. The use of ultrasound for breast tissue characterisation could be considered in young and pregnant women [34]. Further researches may compare breast percentage density evaluated on ultrasound with the data derived from MRI and DBT.

FUTURE RESEARCH

Much of what we know about breast tissue density has been based on knowledge acquired from conventional mammography. We have outlined the emerging information about the potential of using DBT or MRI for defining breast tissue density, while being cognisant that the evidence is still limited. In this regard, studies comparing mammographic breast density measurements with those obtained on DBT or MRI would be valuable especially where the screening of breast cancer is personalised and starts at an early age with MRI (*e.g.* high-risk females). Future research on tissue density should further explore methods to obtain and compare estimates of breast density for the different modalities available today in clinical practice, including ultrasound. Future research should in particular investigate which of the currently available imaging modalities used to measure density best predicts the risk of breast cancer.

REFERENCES

1. Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. Cancer 2005;103: 1898–905. doi: 10.1002/cncr.20971
2. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989; 81:1879–86.
3. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer 1996;77: 2318–24. doi: 10.1002/(SICI)1097-0142(19960601)77: 11<2318::AID-CNCR21>3.0.CO;2-Z
4. Martin LJ, Boyd NF. Mammographic density: potential mechanisms of breast cancer risk associated with mammographic density—hypotheses based on epidemiological evidence. Breast Cancer Res 2008;10:201–14. doi: 10.1186/bcr1831
5. Vachon CM, Sellers TA, Vierkant RA, Wu FF, Brandt KR. Case-control study of increased mammographic breast density response to hormone replacement therapy. Cancer Epidemiol Biomarkers Prev 2002;11:1382–8.
6. Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Byng J, et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. J Natl Cancer Inst 1997; 89:488–96.
7. Ursin G, Sun CL, Koh WP, Khoo KS, Gao F, Wu AH, et al. Association between soy, diet, reproductive factors, and mammographic density in Singapore Chinese women. Nutr Cancer 2006;56:128–35. doi: 10.1207/s15327914nc5602_2
8. Chow CK, Venzon D, Jones EC, Premkumar A, O'Shaughnessy J, Zujewski J. Effect of tamoxifen on mammographic density. Cancer Epidemiol Biomarkers Prev 2000;9: 917–21.

9. Cuzick J, Warwick J, Pinney E, Warren RM, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst 2004;96:621–8.
10. Bakic P, Carton AK, Kontos D, Zhang C, Troxel A, Maidment A. Estimation on digital mammograms and central tomosynthesis projections. Radiology 2009;252:40–8. doi: 10.1148/radiol.2521081621
11. Tagliafico A, Tagliafico G, Astengo D, Airaldi S, Calabrese M, Houssami N. Comparative estimation of percentage breast tissue density for digital mammography, digital breast tomosynthesis, and magnetic resonance imaging. Breast Cancer Res Treat 2013;138: 311–7. doi: 10.1007/s10549-013-2419-z
12. Jeffreys M, Warren R, Highnam R, Smith GD. Breast cancer risk factors and a novel measure of volumetric breast density: cross-sectional study. Br J Cancer 2008;98:210–6. doi: 10.1038/sj.bjc.6604122
13. Tagliafico A, Tagliafico G, Tosto S, Chiesa F, Martinoli C, Derchi LE, et al. Mammographic density estimation: comparison among BI-RADS categories, a semi-automated software and a fully automated one. Breast 2009;18:35–40. doi: 10.1016/j.breast.2008.09.005
14. Highnam R, Jeffreys M, McCormack V, Warren R, Davey Smith G, Brady M. Comparing measurements of breast density. Phys Med Biol 2007;52:5881–95. doi: 10.1088/0031-9155/52/19/010
15. Diorio C, Pollak M, Byrne C, Mâsse B, Hébert-Croteau N, Yaffe M, et al. Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. Cancer Epidemiol Biomarkers Prev 2005;14:1065–73. doi: 10.1158/1055-9965.EPI-04-0706
16. Ciatto S, Bernardi D, Calabrese M, Durando M, Gentilini A, Mariscotti G, et al. A first evaluation of breast radiological density assessment by QUANTRA software as compared to visual classification. Breast 2012; 21: 503–6. doi: 10.1016/j.breast.2012.01.005
17. Rafferty E, Smith A, Niklason L. Comparison of three methods of estimating breast density: BI-RADS density scores using full field digital mammography, breast tomosynthesis, and volumetric breast density. Proffered paper. Chicago, IL: Radiological Society of North America; 2009. p. SsM01.
18. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol 2013;14:583–9. doi: 10.1016/S1470-2045(13)70134-7
19. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology 2013;267:47–56.
20. Bakic PR, Carton AK, Kontos D, Zhang C, Troxel AB, Maidment AD. Breast percent density: estimation on digital mammograms and central tomosynthesis projections. Radiology 2009;252:40–9. doi: 10.1148/radiol.2521081621
21. Tagliafico A, Tagliafico G, Astengo D, Cavagnetto F, Rosasco R, Rescinito G, et al. Mammographic density estimation: one-to-one comparison of digital mammography and digital breast tomosynthesis using fully automated software. Eur Radiol 2012; 22:1265–70. doi: 10.1007/s00330-012-2380-y
22. Houssami N, Kerlikowske K. The impact of breast density on breast cancer risk and breast screening. Curr Breast Cancer Rep 2012; 4: 161–8. doi:10.1007/s12609-012-0070-z
23. Tagliafico AS, Tagliafico G, Cavagnetto F, Calabrese M, Houssami N. Estimation of percentage breast tissue density: comparison between digital mammography (2D full field digital mammography) and digital breast tomosynthesis according to different BI-RADS categories. Br J Radiol 2013; 86: 20130255. doi: 10.1259/bjr.20130255
24. Poon CS, Bronskill MJ, Henkelman RM, Boyd NF. Quantitative magnetic resonance imaging parameters and their relationship to mammographic pattern. J Natl Cancer Inst 1992;84:777–81.
25. Graham SJ, Bronskill MJ, Byng JW, Yaffe MJ, Boyd NF. Quantitative correlation of breast tissue parameters using magnetic resonance and X-ray mammography. Br J Cancer 1996; 73:162–8.
26. Lee NA, Rusinek H, Weinreb J, Chandra R, Toth H, Singer C, et al. Fatty and fibroglandular tissue volumes in the breasts of women 20–83 years old: comparison of X-ray mammography and computer-assisted MR imaging. AJR Am J Roentgenol 1997;168: 501–6. doi: 10.2214/ajr.168.2.9016235
27. Klifa C, Carballido-Gamio J, Wilmes L, Laprie A, Lobo C, Demicco E, et al. Quantification of breast tissue index from MR data using fuzzy clustering. Conf Proc IEEE Eng Med Biol Soc 2004;3:1667–70. doi: 10.1109/IEMBS.2004.1403503
28. Wei J, Chan HP, Helvie MA, Roubidoux MA, Sahiner B, Hadjiiski LM, et al. Correlation between mammographic density and volumetric fibroglandular tissue estimated on breast MR images. Med Phys 2004; 31: 933–42.
29. Reeder SB, McKenzie CA, Pineda AR, Yu H, Shimakawa A, Brau AC, et al. Water-fat separation with IDEAL gradient-echo imaging. J Magn Reson Imaging 2007; 25:644–52. doi: 10.1002/jmri.20831
30. Clendenen TV, Kim S, Moy L, Wan L, Rusinek H, Stanczyk FZ, et al. Magnetic resonance imaging (MRI) of hormone-induced breast changes in young premenopausal women. Magn Reson Imaging 2013; 31:1–9. doi: 10.1016/j.mri.2012.06.022.
31. Kaizer L, Fishell EK, Hunt JW, Foster FS, Boyd NF. Ultrasonographically defined parenchymal patterns of the breast: relationship to mammographic patterns and other risk factors for breast cancer. Br J Radiol 1988;61: 118–24.
32. Malini S, Smith EO, Goldzieher JW. Measurement of breast volume by ultrasound during normal menstrual cycles and with oral contraceptive use. Obstet Gynecol 1985;66: 538–41.
33. Kim WH, Moon WK, Kim SJ, Yi A, Yun BL, Cho N, et al. Ultrasonographic assessment of breast density. Breast Cancer Res Treat. 2013; 138:851–9. doi: 10.1007/s10549-013-2506-1
34. Jud SM, Häberle L, Fasching PA, Heusinger K, Hack C, Faschingbauer F, et al. Correlates of mammographic density in B-mode ultrasound and real time elastography. Eur J Cancer Prev 2012;21:343–9. doi: 10.1097/CEJ.0b013e32834e3214