Examining the Effectiveness of Supplementary Imaging Modalities for Breast Cancer Screening in Women with Dense Breasts: A Systematic Review and Meta-analysis

Deborah Mizzi, **Clare Allely**, Francis Zarb, Judith Kelly, Peter Hogg, Mark McEntee, Andrew England, **Claire Mercer**

Abstract

Purpose: To systematically review studies on the effectiveness of supplementary imaging for breast cancer screening in women with dense breasts.

Materials and methods: A systematic search of peer-reviewed publications in English (January 2000 to March 2021) was carried out. Eight databases were used to retrieve the studies: MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, PubMed, and Web of Science. Two radiographers and an academic independently reviewed the articles to determine if the studies met inclusion criteria. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Summary estimates of diagnostic accuracy were obtained by using proportion and diagnostic metanalysis.

Results: From 3764 studies that underwent title and abstract screening, 221 studies underwent full-text screening. Of these 42 were included in the qualitative and quantitative synthesis. Results for sensitivity, specificity, positive and negative predictive values, cancer detection rates, recall and biopsy rates in women with dense breasts undergoing supplementary imaging were reported. Studies included in this review were heterogeneous, as was the proportion of women undergoing prevalence and incidence screening rounds.

Conclusions: Supplementary screening among women with dense breasts who had recent negative mammograms can consistently identify additional cancers and lead to further recalls and biopsies.

Keywords

Breast Density, Ultrasound, Tomosynthesis, Magnetic Resonance Imaging, Molecular Breast Imaging, Contrast-Enhanced Digital Mammography

Introduction

Many countries have implemented mammography screening programs to decrease breast cancer mortality via early diagnosis (1,2). In mammography screening, identifying breast cancer in the denser breast has been highlighted as an area of concern for several years (3). The American College of Radiology Breast Imaging-Reporting and Data System [BI-RADS] (4) categorises levels of breast density. It employs the letters ‘a’ to ‘d’, where ‘a’ refers to breasts which are almost entirely fatty, ‘b’ refers to breasts which have scattered areas of fibro-glandular density, ‘c’ is defined as breasts that are heterogeneously dense and ‘d’ refers to extremely dense breasts. Recently the European Society of Breast Imaging (EUSOBI) guidelines recommend women should be appropriately informed about their breast density and that supplemental screening should be in place for women with extremely dense breasts (Mann et al, 2022).

Women with either heterogeneously or extremely dense breast tissue can be classified as having high mammographic density. High mammographic breast density decreases the sensitivity of full-field digital mammography [FFDM] to around 47% due to its masking effect. It can increase false positives owing to the superimposition of the dense parenchymal patterns (5). Given that women with dense breasts experience reduced sensitivity with FFDM, imaging modalities, namely Digital Breast Tomosynthesis [DBT], Magnetic Resonance Imaging [MRI], Hand-held Ultrasound [HHUS], Automated Breast Ultrasound [ABUS], Contrast-enhanced Digital Mammography [CEDM] and Molecular Breast Imaging [MBI], have been introduced as supplemental screening to FFDM (6–8). Published results within the last ten years [2011-2021] have demonstrated improved breast cancer detection and decreased interval cancer rates associated with the introduction of supplemental screening for dense breasts (9–11).

Systematic reviews have examined the role of individual supplementary imaging modalities such as HHUS or DBT (12,13). In addition, Melnikow and colleagues (14) evaluated the diagnostic test performance and clinical results of supplementary screening with HHUS, ABUS, MRI and DBT (14). Another systematic review and meta-analysis by Scaranelo and colleagues (15) was ‘ongoing’ at the time of writing. Furthermore, the revised European Breast Guidelines (16) was informed by systematic reviews of the evidence conducted between March 2016 and December 2018.

Since previous systematic reviews (14,16) did not include CEDM or MBI as supplementary screening, the purpose of the current systematic review was to build on existing systematic reviews and include CEDM and MBI. The current systematic review also builds on the existing knowledge gained from previous systematic reviews as it includes both prevalent screens and incident screens. Moreover, the field of breast imaging is a rapidly evolving one with new imaging modalities such as CEDM, MBI and ABUS which supports the need for an updated systematic review of the literature in the field with the aim to evaluate supplementary imaging modalities for breast cancer screening in women with dense breasts.

Methods

Protocol Registration

The review protocol was registered in PROSPERO (17) [registration number CRD42019145308].

Eligibility Criteria

A set of criteria for inclusion and exclusion of studies were set beforehand on the understanding of the literature as per PRISMA guidelines [Table 1] (18).

For retrieved studies to be included in the systematic review, the studies had to include asymptomatic women with dense breasts BI-RADS c or d; prospective or retrospective observational studies, randomised controlled trials or diagnostic test accuracy studies; studies published in English; studies published from 1st January 2000 up to end of March 2021, and peer-reviewed studies. Cancers detected by supplementary testing only were included in the sensitivity calculation, and no limit was set on the minimal number of patients per cohort.

For retrieved studies to be excluded from this systematic review, studies were prior systematic reviews, meta-analyses, editorials and opinions; studies not published in English; studies published before 1st January 2000 and after March 2021 and non-peer-reviewed studies. Cancers detected by mammography were not included in the calculation of sensitivity values.

Information Sources and Search

Eight data sources were used to retrieve the studies, namely Medical Literature Analysis and Retrieval System Online Complete [MEDLINE], Cumulative Index of Nursing and Allied Health Literature Complete [CINAHL], the Cochrane Central Register of Controlled Trials, Cochrane Clinical Answers, Cochrane Database of Systematic Reviews and Cochrane Methodology Register through EBSCO; PubMed and Web of Science [All databases]. These data sources were selected to minimise database selection bias. The reference lists of the studies and retrieved systematic reviews were screened for any potentially relevant articles that were not identified in the database searches. Articles suggested by experts were also retrieved (19). This was done by contacting a key organisation in breast density for recently published studies related to the research question (20).

All searches were performed in the English language, and the dates of coverage were from 1st January 2000 up to the end of March 2021. Studies published before 1st January 2000 were not considered for this review since FFDM was only approved by the U.S. Food and Drug Administration in 2000 (21) and since studies have shown that the implementation of FFDM has led to significantly higher cancer detection when compared with film (22). The PICOS concepts were determined and translated into search terms using Medical Subject Headings [MeSH]. A list of synonyms, abbreviations and spelling variants was then produced. Table 2 presents the complete electronic search method for one database, comprising the restrictions utilised.

Study Selection

Articles identified from the search were loaded into Mendeley Reference Management Software [Elsevier, London, UK], and duplicates were removed (23). To manage and conduct the systematic review, a review team was established. The review team was composed of two radiographers [DM & NM] who specialised in breast imaging and an academic [FZ] proficient in systematic reviews and statistics. Having three reviewers minimised bias and error at all stages of the review (19). The review team followed a predetermined review protocol based on the PRISMA guidelines (18). Two reviewers [DM & NM] independently reviewed the titles and abstracts of identified articles to determine if studies met the inclusion criteria [Table 1]. Discordant publications were reviewed by the third reviewer [FZ]. Finally, two reviewers [DM & NM] independently evaluated the full-text articles to determine which would be included in

the analysis. Disagreements in the full-text review were resolved by discussion between the review team, and the final decision was reached with a majority vote.

For screened women to be included in the diagnostic performance characteristics analysis [sensitivity, specificity, PPV and NPV], studies were required to report a reference standard [biopsy - the gold standard to diagnose breast cancer; or one-year follow-up for negative results]. For such studies, the interval cancer rate could be determined. On the other hand, the cancer detection rate, recall rate and biopsy rate could be calculated even in studies that did not report a reference standard. Studies were required to report outcomes from two or more radiologists to ensure accuracy in the study findings.

Data Collection Process and Data Items

A predefined validated form was developed and used to extract information from the studies that met the review's inclusion and exclusion criteria. Authors of primary studies were contacted to provide missing or additional data, with some of the authors providing the needed data (24). The information extracted comprised population aspects, namely breast density, demographics and personal or family history of breast cancer; information on study design, namely inclusion/exclusion criteria, follow-up, and rounds of screening; information on screening test aspects, namely number of readers, their experience and the reference standard. The diagnostic performance characteristics extracted included sensitivity, specificity, NPV, PPV, true positives, true negatives, false positives, and false negatives. Moreover, the breast cancer detection rates, recall rates and biopsy rates were abstracted.

Risk of Bias in Individual Studies and across Studies

The quality of the included studies in the review was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The assessment of bias and applicability in QUADAS-2 across four domains reflects the typical test accuracy study design stages. This

tool is recommended for systematic reviews to evaluate the risk of bias and applicability of primary diagnostic accuracy studies (25).

Summary Measures and Quantitative Synthesis of Results

Summary evidence tables were created to synthesise data separately for sensitivity and specificity, cancer detection rates, recall rates and biopsy rates. These tables were the basis of the qualitative synthesis. To conduct the qualitative synthesis, the range of results was examined in the context of study quality and looked for possible associations between study results and population or modality characteristics. When required, sensitivity, specificity, PPV, NPV, cancer detection rates, recall and biopsy rates were calculated for women with dense breasts subgroups. 95% confidence intervals were calculated for each study estimate of sensitivity, specificity, PPV, NPV, cancer detection rates, recall and biopsy rates. Confidence intervals for sensitivity and specificity were Clopper-Pearson confidence intervals. Confidence intervals for the predictive values were the standard logit confidence intervals (26).

Meta-analysis was performed to estimate the proportion of cancers detected, recalls and biopsies and to calculate sensitivity and specificity for all the imaging modalities using random-effects models using the OpenMetaAnalyst software. Subgroup meta-analysis was performed for each supplementary imaging modality to plot summary data in comparison. By doing so the difference and heterogeneity of studies in comparison was illustrated. Under the fixed effects model, it was assumed that all studies came from a standard population and that the effect size (the proportions) was not significantly different among the different studies. This assumption was tested by the Heterogeneity test (Cohran's Q). Q is the weighted sum of squares on a standardised scale. It was reported with a P-value with low P-values indicating the presence of heterogeneity (27). The random-effects model was more appropriate if this test

yielded a low P-value (P<0.05). The random variation within the studies and the variation between the different studies were incorporated.

Heterogeneity across studies was quantified with the I^2 measure. I^2 is the percentage of observed total variation across studies due to real heterogeneity rather than chance. It is calculated as:

$$I^2 = \frac{100\% \times (Q - df)}{Q}$$

Where Q is Cochran's heterogeneity statistic, and df is the degrees of freedom. Negative values of I^2 were put equal to zero so that I^2 was between 0% and 100%. A value of 0% indicated no observed heterogeneity, and larger values showed increasing heterogeneity (27).

Subgroup analysis was also undertaken for breast cancer detection, recall and biopsy rates as described by Viechtbauer (28). In all analyses, p-values <0.05 were considered statistically significant.

Results

Search Results

A total of 3764 studies were eligible for a title and abstract screening, and 221 studies were checked at full-text reading [Figure 1]. Forty-two met the predefined inclusion criteria and were included in the qualitative synthesis; study inclusion with reasons for exclusion are described in Figure 1.

The review team identified and reviewed studies of diagnostic test characteristics with HHUS, ABUS, MRI, DBT, MBI and CEDM among women with dense breasts and negative screening mammography. Twenty-one studies reported HHUS (29,30,39–48,31,49,32–38), five studies reported ABUS (50–54), five studies reported MRI (9,55–58), six studies reported DBT (11,59–63), one study reported CEDM (64) and two studies MBI (65,66). There were also two studies reporting HHUS and DBT (67,68). Tables 3-8 represent the information extracted, including the population characteristics [baseline demographics, breast density, family or personal history of breast cancer], study design [inclusion/exclusion criteria, follow-up, screening rounds], and screening test characteristics [reference standard, number of readers, radiological experience] for the different supplementary imaging modalities.

Sensitivity, Specificity, PPV and NPV

There is limited evidence on the diagnostic test performance of potential supplementary screening modalities for women identified as having dense breasts. Seven studies of HHUS (32,33,38,40,44,49,67) were relatively consistent in estimates of sensitivity and NPV. However, the specificity of HHUS studies varied considerably, and the PPV was generally low, resulting in many false-positive recalls and biopsies. The studies for DBT (63,67), MRI (9,69), CEDM (64) and MBI (65) were consistent in estimates of sensitivity, specificity, and NPV. Nevertheless, the PPV for MBI and CEDM was low, resulting in many false-positive recalls and biopsies. Although the specificity and NPV for the two studies of ABUS (52,54) were similar, being high for both studies, the sensitivity and PPV varied considerably.

Seventeen studies were included in the meta-analysis of performance characteristics and sensitivity and specificity [Figure 2], but a degree of heterogeneity was noted (I^2 = 45.97%). Based on a fixed effects model (p=0.020), the sensitivity of supplementary imaging examinations would likely be 89% (95% CI: 81% to 94%), while the specificity of supplementary imaging examinations would likely be 91% (95% CI: 79% to 96%).

Subgroup meta-analysis by individual supplementary imaging modalities resulted in:

- HHUS having no heterogeneity (I2 = 0.09%) and based on a fixed effects model (p=0.433), the sensitivity of supplementary HHUS would likely be 86% (95% CI: 77% to 92%), while the specificity of supplementary HHUS would likely be 86% (95% CI: 75% to 93%).
- ABUS having high heterogeneity (I2 = 86.9%) and based on a fixed effects model (p=0.006), the sensitivity of supplementary ABUS would likely be 90% (95% CI: 30% to 100%), while the specificity of supplementary ABUS would likely be 99% (95% CI: 97% to 100%).
- MRI having no heterogeneity (I2 = 0%) and based on a fixed effects model (p=0.516), the sensitivity of supplementary MRI would likely be 95% (95% CI: 87% to 98%), while the specificity of supplementary MRI would likely be 53% (95% CI: 7% to 100%).

- DBT having moderate heterogeneity (I2 = 72.8%) and based on a fixed effects model (p=0.055), the sensitivity of supplementary DBT would likely be 84% (95% CI: 23% to 99%), while the specificity of DBT would likely be 99% (95% CI: 78% to 100%).
- For MBI and CEDM subgroup analysis by individual supplementary imaging modalities was not applicable since only one study was included in each subgroup metanalysis.

Breast Cancer Detection, Recall and Biopsy Rates

Supplementary imaging consistently detected additional breast cancers not identified by mammography [Appendix A]. Only two studies did not detect any additional breast cancers (41,50). The highest breast cancer detection rate was with MRI [33.5 per 1000 women] (Appendix A) (55). In terms of the proportion of breast cancers detected, 43 studies were included in the meta-analysis. Again, high heterogeneity was noted (I^2 = 91.85%) [Figure 3]. Based on a random-effects model (p< 0.001), 304,713 supplementary imaging examinations in women with negative mammograms would likely lead to a detection of an additional 4 per 1,000 women cancer cases (95% CI: 4.0 to 5.0 per 1,000 women) [Figure 3].

Subgroup meta-analysis by individual supplementary imaging modalities resulted in:

- HHUS having high heterogeneity (I^2 = 91.42%) and based on the random effects model (p< 0.001), 237,085 supplementary HHUS examinations in mammography negative women would likely lead to a detection of an additional 3 per 1,000 women cancer cases (95% CI: 2.0 to 4.0 per 1,000 women).
- ABUS having high heterogeneity (I^2 = 92.59%) and based on the random effects model (p< 0.001), 23,008 supplementary ABUS examinations in mammography negative women would likely lead to a detection of an additional 6 per 1,000 women cancer cases (95% CI: 2.0 to 10.0 per 1,000 women).
- MRI having high heterogeneity (I^2 = 91.88%) and based on the random effects model (p< 0.001), 10,044 supplementary MRI examinations in mammography negative women would likely lead to a detection of an additional 20 per 1,000 women cancer cases (95% CI: 10.0 to 30.0 per 1,000 women).
- DBT having high heterogeneity (I^2 = 84.69%) and based on the random effects model (p< 0.001), 30,890 supplementary DBT examinations in mammography negative

women would likely lead to a detection of an additional 4 per 1,000 women cancer cases (95% CI: 2.0 to 6.0 per 1,000 women).

- MBI having no heterogeneity (I^2 = 0%) and based on the fixed effects model (p= 0.516), 3117 supplementary MBI examinations in mammography negative women would likely lead to a detection of an additional 9 per 1,000 women cancer cases (95% CI: 5.0 to 12.0 per 1,000 women).
- For CEDM subgroup analysis by individual supplementary imaging modalities was not applicable since only one study was included in the systematic review for CEDM.

Additionally, sub-analysis by individual supplementary imaging modalities (Chi-Squared test) did not identify any statistically significant differences (p>0.05) concerning cancer detection rates.

Recall rates and biopsy rates were increased by supplementary screening, with the highest recall rate reported by HHUS [370 per 1000 women] (33) and the highest biopsy rate reported by MRI [146 per 1000 women] (Appendix A) (55). Thirty-three studies were included in the meta-analysis for 'recalls'. Again, the included studies had high heterogeneity in reporting the proportion of breast cancer detection (I^2 = 99.7%) [Figure 4]. The proportion of recall across all modalities as per the random-effects model (p<0.001) was 109 per 1,000 women (95% CI: 94 to 125 per 1,000 women), based on 154,422 supplementary imaging examinations (Figure 4).

Subgroup meta-analysis by individual supplementary imaging modalities resulted in:

- HHUS having high heterogeneity (I^2 = 99.71%) and the proportion of recall with HHUS as per the random effects model (p< 0.001), was 134 per 1,000 women (95% CI: 111 to 157 per 1,000 women), based on 99,841 supplementary imaging examinations.
- ABUS having high heterogeneity (I^2 = 99.81%) and the proportion of recall with ABUS as per the random effects model (p< 0.001), was 132 per 1,000 women (95% CI: 4 to 259 per 1,000 women), based on 15,243 supplementary imaging examinations.
- MRI having high heterogeneity (I^2 = 98.04%) and the proportion of recall with MRI as per the random effects model (p< 0.001), was 73 per 1,000 women (95% CI: 30 to 117 per 1,000 women), based on 8762 supplementary imaging examinations.

- DBT having high heterogeneity (I^2 = 99.59%) and the proportion of recall with DBT as per the random effects model (p< 0.001), was 60 per 1,000 women (95% CI: 26 to 95 per 1,000 women), based on 26,890 supplementary imaging examinations.
- MBI having no heterogeneity (I^2 = 0%) and the proportion of recall with MRI as per the fixed effects model (p=0.777), was 82 per 1,000 women (95% CI: 73 to 92 per 1,000 women), based on 8762 supplementary imaging examinations.
- For CEDM subgroup analysis by individual supplementary imaging modalities was not applicable since only one study was included in the systematic review for CEDM.

Additionally, sub-analysis by individual supplementary imaging modalities (Chi-Squared test) did identify a statistically significant difference in recall rates between HHUS and MBI (p=0.039) and HHUS and CEDM (p=0.016).

Twenty-five studies were included in the meta-analysis of biopsy rates. Studies had a high heterogeneity in reporting the proportion of breast cancer detection (I^2 = 98.91%) [Figure 5]. The proportion of biopsies in all modalities as per the random-effects model (p<0.001) was 36 per 1,000 women (95% CI: 29 to 43 per 1,000 women), based on 122,059 supplementary imaging examinations (Figure 5).

Subgroup meta-analysis by individual supplementary imaging modalities resulted in:

- HHUS having high heterogeneity (I^2 = 98.76%) and the proportion of biopsies with HHUS as per the random effects model (p< 0.001), was 33 per 1,000 women (95% CI: 25 to 41 per 1,000 women), based on 95,299 supplementary imaging examinations.
- ABUS having high heterogeneity (I^2 = 98.44%) and the proportion of recall with ABUS as per the random effects model (p< 0.001), was 24 per 1,000 women (95% CI: 4 to 43 per 1,000 women), based on 18,103 supplementary imaging examinations.
- MRI having high heterogeneity (I^2 = 98.33%) and the proportion of recall with MRI as per the random effects model (p< 0.001), was 73 per 1,000 women (95% CI: 35 to 112 per 1,000 women), based on 8657 supplementary imaging examinations.
- For DBT, MBI and CEDM subgroup analysis by individual supplementary imaging modalities was not applicable since no study was included in the respective meta-analysis of biopsy rates.

Additionally, sub-analysis by individual supplementary imaging modalities (Chi-Squared test) did not identify any statistically significant differences ($p>0.05$) in terms of biopsy rates.

Although the current systematic review examined subsets of women without specific risk factors, the authors suspect that, in general, these women were at higher risk. This is due to the wide range of cancer prevalence in these additional examinations [Appendix A]. This implies that the populations were not asymptomatic screening cohorts. For this reason, the results of this systematic review cannot be generalised to the general screening population of women with dense breasts.

Quality of Studies

An evaluation of the quality of the studies using the QUADAS–2 framework revealed a potential risk for bias in terms of patient selection, the index tests, reference standard and flow and timing [Figure 6a]. The QUADAS-2 tool also revealed some potential issues with the applicability of the findings, mainly due to patient selection [Figure 6b]; the overview of the risk of bias and applicability is presented in Appendix B.

Out of the 42 included studies, eighteen studies were at high risk of bias, and nine studies had applicability concerns regarding patient selection. The reasons for the increased risk of bias were; namely, supplementary imaging was performed self-financed or self-referred by the women themselves; supplementary imaging was offered to women who had dense breasts but also feared breast cancer or wanted a thorough examination of the breasts; heterogeneous dense breasts [BI-RADS c] were excluded, and only dense breasts [BI-RADS d] were included; supplementary imaging was performed based on availability; some women also had additional risk factors such as family or personal history of breast cancer (35,60,70); in retrospective studies, not all consecutive exams were included.

Eleven of 42 studies were at high risk of bias in terms of index tests since mammogram and index tests were not performed independently, and the reader was not blinded to clinical data. Thus, the conduct or interpretation of the index test could have introduced bias in these eleven studies. This was not the case for the applicability concern since all the 42 studies had a low risk of applicability concern related to the index test. Therefore, there was no concern that the index test, its conduct, or interpretation differed from the review question.

Out of the 42 studies, seventeen were at high risk of bias in terms of a reference standard. Only a biopsy was performed, and there was no follow-up of normal results. In one of the eleven studies by (51), biopsy and one-year follow-up were performed, but only 88% of follow-up was completed when the article was published. This means that the reference standard, its conduct, or its interpretation would have introduced bias.

There were concerns about one study related to the reference standard used (66). This is because 966 out of 1696 women were lost to follow-up after one year. Thus, the target condition as defined by the reference standard does not match the review question. The other studies had the appropriate target condition investigated.

Thirteen studies were at high risk of bias regarding flow and timing domain because not all patients received a reference standard. Thus, the patient flow in these 13 studies could have introduced bias.

Discussion

Main Findings

The findings from this systematic review are consistent with previous studies (7,12,13) that indicate that supplementary screening among women with dense breasts and recent negative mammography can consistently identify additional cancers and lead to further recalls and biopsies. Based on the meta-analysis, the sensitivity of supplementary imaging examinations was 89% and specificity 91%. The highest breast cancer detection rate was with MRI [33.5 per 1000 women] (Appendix A) (55). Recall rates and biopsy rates were increased by supplementary screening, with the highest recall rate reported by HHUS [370 per 1000 women] (33) and the highest biopsy rate reported by MRI [146 per 1000 women] (Appendix A) (55). Also, supplementary imaging examinations in women with negative mammograms would lead to a detection of an additional 4 per 1,000 women cancer cases ($p<0.001$). The additional women who would need to be recalled for further investigations would be 109 per 1,000 women ($p<0.001$), and the additional women who would need a biopsy would be 36 per 1,000 women ($p<0.001$). Since 34 studies reported on only a single round of screening [only one study reported on six screening rounds (71)], the cumulative effect of recall for additional imaging and biopsy is likely to be more significant over time.

The high risk of bias and applicability in the included studies resulted in very heterogeneous studies. There are problems in the data quality of the included studies. Poor-quality studies had important limitations (inadequate reference standard; population including high-risk women) that could limit the generalisability of this systematic review and meta-analysis.

Review novelty

A gap existed in the literature when considering the additional cancers detected with the supplementary screening of women with dense breasts and the additional women recalled for additional imaging and biopsies, leading to high false-positive rates. The current systematic review started to bridge the gap in the literature by systematically reviewing all available studies on supplementary imaging procedures when used to screen women with dense breasts for cancer.

Although limited studies [n=2] were randomised trials (9,58), both mammography and supplementary imaging in the selected studies were undertaken sequentially in the same women. All women acted as their own controls, thereby accounting for between-patient variability. Also, most of the included studies defined women with dense breasts as per BI-RADS breast density c and d, with only three studies, (9,55,58) including women with BI-RADS density d, and one study (52) used the Wolfe Classification (Wolfe, 1976). This ensured that there were minimal differences in the study designs.

Critical synthesis of results

Twenty-four studies (9,11,42,45,51,52,56,58,59,61,62,65,30,67,68,72,73,31–34,36,40,41) focused exclusively on women with BI-RADS c and d density, while others reported on mixed populations (29,35,53,54,60,64,66,71,74,75,37–39,44,46–48,50). These studies reporting on mixed populations included women with elevated risk due to BRCA1 and BRCA2 mutations, women with a personal history of breast cancer, women with a family history of breast cancer, women with previous benign biopsies or women with a history of uterine cancers. Only the studies in which most women had a risk factor of dense breasts were included. In some cases, it was possible to represent women with dense breasts as a sole risk factor for breast cancer to

isolate the subgroup of women with dense breasts without any of the other risk factors. Nevertheless, the current review is limited because some study populations were at higher risk of breast cancer than would be presented by increased breast density alone. This limitation of the study raises questions about the generalisability of findings to the broad population of women with dense breasts. Future work should include RCTs or well-designed comparative observational studies to provide stronger evidence about sensitivity, specificity, PPV and NPV of supplementary screening for women with dense breasts as the only known risk factor.

Other sources of variation may relate to variability in competency among interpreting radiologists, with some radiologists reporting only one year of experience (40) while others have a 41 years' experience (62). Also, studies had variations in technology used for supplementary imaging and the skill of health care professionals using supplementary imaging, leading to intra- and inter-operator variability. Another difference among studies was the outcome definitions that may contribute to some observed heterogeneity. Studies performed in the United States (35,36,65,66,70,76,38,41,45,48,50,51,60,61) used the BI-RADS system for reporting recall whereas the European studies (9,11,62,67,68,71,77,30,31,34,37,47,54,58,59) used a simplified 'recall or no recall' reporting for screen-readings. Another factor that may have affected the heterogeneity between the studies is the proportion of studied women undergoing prevalence [first] and incidence [any subsequent] screening rounds.

Moreover, to facilitate comparison, an assumption of independent screens was made, which might not be the case in the eight studies that included more than one screening round (9,34,38,49,56–58,61) or where study populations might overlap. Also, the studies differed in the degree to which image interpretation of supplementary screening could be influenced by knowledge of mammography imaging and vice versa [although this detail was not consistently reported] and in how the studies selected their study populations [e.g., by whether screening was organised or opportunistic]. All these factors may have led to slightly different selections of women in terms of their risk profile. Thus, the studies included in this review were heterogeneous in several aspects, and due to this, the meta-analysis results should be interpreted with caution.

A limitation of the studies identified in this systematic review is that the current evidence suggests that the number, quality, and rigour of studies on diagnostic test performance were

quite limited. Only three studies (64–66) included MBI and CEDM as supplementary imaging modalities for women with dense breasts following a negative mammogram. The limited number of studies indicates the need for further studies on these modalities.

Several studies lacked a complete reference standard or a clear follow-up description, so they could not calculate sensitivity, specificity, PPV and NPV. Moreover, some studies did not provide data for women with dense breasts only, and it was not possible to calculate the diagnostic test performance for this subgroup of women. Most studies assessed short-term incremental impact among women undergoing screening mammography and supplementary screening. Eighteen studies included mixtures of women at increased breast cancer risk due to risk factors other than breast density, limiting the generalisability of findings in these studies to the general screening population of women with dense breasts. Studies of breast MRI focused on women with multiple risk factors; very little data were available for women with dense breasts and no other major risk factors for breast cancer. The quality of the literature on HHUS, ABUS, DBT, MRI, CEDM and MBI for women with dense breasts was minimal and more studies are needed before any firm conclusions can be reached.

Other limitations are due to the evidence base. Many studies had short follow-ups in most studies. Due to the recent introduction of the supplementary imaging modalities, the lack of extended follow-up [although the optimum follow-up period is unknown] makes it impossible to assess whether the improved cancer detection rate and sensitivity of supplementary screening further reduce breast cancer mortality through screening compared to screening with FFDM alone. Very little data were available for women with dense breasts and no other major risk factors for breast cancer. This is because there is limited published evidence which meets the eligibility and quality criteria for this review.

Clinical Implications

The included studies were predominately designed to estimate the incremental impact of additional testing on cancer detection rates and diagnostic testing. Eighteen studies lacked sufficient follow-up (minimum one year) to identify false negatives (11,29,58–61,66–68,74,30,36,45–48,51,55). Given the importance of identifying false negatives to estimate the impact of supplementary imaging modalities in women with dense breasts, these studies provide limited value to this systematic review. None of these studies compared potential

surrogates for breast cancer mortality among two groups of women with dense breasts undergoing mammography screening versus supplementary imaging.

Moreover, from the metanalysis results, it can be determined that while more women with dense breasts would be diagnosed with breast cancer, an even more significant proportion of these women would have undergone further imaging and biopsies, leading to potential additional anxiety and the need for more resources.

In summary, evidence suggests that supplementary imaging examinations' sensitivity would likely be 89% and specificity 91%. More breast cancers will be detected (4 per 1,000 women) by supplementary HHUS, ABUS, MRI, DBT, CEDM and MBI screening of women with dense breasts, but this is associated with increased recall (109 per 1,000 women) and biopsy rates (36 per 1,000 women) for diagnostic investigation among women who do not have breast cancer,

Conclusion

While further research is required to focus on women with dense breasts as their only risk factor, supplementary imaging is beneficial for women with dense breasts. The highest breast cancer detection rate and biopsy rate in women with dense breasts were associated with supplemental MRI. The highest recall rate was associated with HHUS.

Declarations of Interest Statement

Declarations of interest: None

Funding Sources

This work is part of a PhD programme which is part-financed by the Tertiary Education Scholarship Scheme [TESS], Government of Malta [TESS Contract MEDE 417/2018/61]. The primary author would like to thank the TESS for the financial support covering the University of Salford fees. The funding source was not involved in the review.

5573 Words

References

1. Duffy S, Mackay J, Thomas S, Anderson E, Chen T, Ellis I, et al. Evaluation of mammographic surveillance services in women aged 40-49 years with a moderate family history of breast cancer: a single-arm cohort study. Health Technol Assess (Rockv) [Internet]. 2013 Jan;17(32):1–95.

2. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. Breast-cancer screening--viewpoint of the IARC Working Group. N Engl J Med. 2015 Jun;372(24):2353–8.

3. Thigpen D, Kappler A, Brem R. The Role of Ultrasound in Screening Dense Breasts-A Review of the Literature and Practical Solutions for Implementation. Diagnostics (Basel, Switzerland) [Internet]. 2018 Mar 16;8(1):20.

4. ACR. 2013 ACR BI-RADS Atlas: Breast Imaging Reporting and Data System. 5th ed. D'Orsi CJ, editor. American College of Radiology, 2014; 2013.

5. Wengert GJ, Helbich TH, Kapetas P, Baltzer PAT, Pinker K. Density and tailored breast cancer screening: practice and prediction - an overview. ACTA Radiol OPEN. 2018 Sep;7(9).

6. Yaffe MJ, Mittmann N, Lee P, Tosteson ANA, Trentham-Dietz A, Alagoz O, et al. Clinical outcomes of modelling mammography screening strategies. Heal REPORTS. 2015 Dec;26(12):9–15.

7. Berg WA. Supplemental Breast Cancer Screening in Women With Dense Breasts Should Be Offered With Simultaneous Collection of Outcomes Data. [Internet]. Vol. 164, Annals of Internal Medicine. Magee-Womens Hospital of UPMC and University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.: American College of Physicians; 2016. p. 299–300.

8. Vourtsis A, Berg W. Breast density implications and supplemental screening. Vol. 29, European Radiology. Springer Verlag; 2019. p. 1762–77.

9. Bakker MF, de Lange S V, Pijnappel RM, Mann RM, Peeters PHM, Monninkhof EM, et al. Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. N Engl J Med [Internet]. 2019;381(22):2091–102. Available from: https://doi.org/10.1056/NEJMoa1903986

10. Gilbert FJ, Tucker L, Gillan MGC, Willsher P, Cooke J, Duncan KA, et al. The TOMMY trial: a comparison of TOMosynthesis with digital MammographY in the UK NHS Breast Screening Programme a multicentre retrospective reading study comparing the diagnostic performance of digital breast tomosynthesis and digital mammography with di. Health Technol Assess (Rockv). 2015 Jan;19(4):1+.

11. 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 [Internet]. 2013 Jun;14(7):583–9.

12. Phi X-A, Tagliafico A, Houssami N, Greuter MJW, de Bock GH. Digital breast tomosynthesis for breast cancer screening and diagnosis in women with dense breasts - a systematic review and meta-analysis. BMC Cancer. 2018 Apr;18.

13. Rebolj M, Assi V, Brentnall A, Parmar D, Duffy SW. Addition of ultrasound to mammography in the case of dense breast tissue: systematic review and meta-analysis. Br J Cancer. 2018 Jun;118(12):1559–70.

14. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: A systematic review

for the U.S. Preventive services task force. Vol. 164, Annals of Internal Medicine. American College of Physicians; 2016. p. 268–78.

15. Scaranelo, A. Fazelzad, R. Menezes, R. Kulkarni S. Supplemental screening modality in patients with intermediate risk of breast cancer based on breast density with negative mammogram - what is the most effective modality? Systematic review; meta-analysis and cost effectiveness analysis. 2018. Report No.: PROSPERO 2018 CRD42018080402.

16. European Commission Initiative on Breast Cancer. Screening in women with high breast density [Internet]. 2020. Available from: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/dense-breast

17. PROSPERO [Internet]. 2019 [cited 2020 Jan 7]. Available from: https://www.crd.york.ac.uk/PROSPERO/

18. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Vol. 6, PLoS Medicine. 2009.

19. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training [Internet]. 2019 [cited 2020 Jan 7]. Available from: https://training.cochrane.org/handbook/current

20. DenseBreast-info Inc. DenseBreast-info.org [Internet]. 2021. Available from: https://densebreast-info.org/

21. Vinnicombe S, Pinto Pereira SM, McCormack VA, Shiel S, Perry N, Dos Santos Silva IM. Full-field digital versus screen-film mammography: Comparison within the UK breast screening program and systematic review of published data. Radiology. 2009 May;251(2):347–58.

22. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: Follow-up and final results of Oslo II study. Radiology. 2007 Sep;244(3):708–17.

23. Free Reference Manager & Citation Generator - Mendeley [Internet]. 2019 [cited 2020 Jan 7]. Available from: https://www.mendeley.com/reference-management/mendeley-desktop

24. Systematic Reviews: CRD"s guidance for undertaking reviews in health care [Internet]. 2009 [cited 2020 Jan 7]. Available from: www.york.ac.uk/inst/crd

25. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. Vol. 155, Annals of Internal Medicine. American College of Physicians; 2011. p. 529–36.

26. Mercaldo ND, Lau KF, Zhou XH. Confidence intervals for predictive values with an emphasis to case-control studies. Stat Med. 2007 May 10;26(10):2170–83.

27. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Vol. 327, British Medical Journal. 2003. p. 557–60.

28. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1–48.

29. Bae MS, Moon WK, Chang JM, Koo HR, Kim WH, Cho N, et al. Breast cancer detected with screening US: reasons for nondetection at mammography. Radiology [Internet]. 2014 Feb;270(2):369–77.

30. Brancato B, Bonardi R, Catarzi S, Iacconi C, Risso G, Taschini R, et al. Negligible advantages and excess costs of routine addition of breast ultrasonography to mammography in dense

breasts. Tumori. 2007;93(6):562–6.

31. Buchberger W, Geiger-Gritsch S, Knapp R, Gautsch K, Oberaigner W. Combined screening with mammography and ultrasound in a population-based screening program. Eur J Radiol [Internet]. 2018 Apr;101:24–9.

32. Chae EY, Kim HH, Cha JH, Shin HJ, Kim H. Evaluation of screening whole-breast sonography as a supplemental tool in conjunction with mammography in women with dense breasts. J Ultrasound Med [Internet]. 2013 Sep;32(9):1573–8.

33. Chang JM, Koo HR, Moon WK. Radiologist-performed hand-held ultrasound screening at average risk of breast cancer: results from a single health screening center. Acta radiol [Internet]. 2015 Jun;56(6):652–8.

34. Corsetti V, Houssami N, Ghirardi M, Ferrari A, Speziani M, Bellarosa S, et al. Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: Interval breast cancers at 1year follow-up. Eur J Cancer [Internet]. 2011 May;47(7):1021–6.

35. Destounis S, Arieno A, Morgan R. New York State Breast Density Mandate: Follow-up Data With Screening Sonography. J Ultrasound Med [Internet]. 2017 Dec;36(12):2511–7.

36. Dibble EH, Singer TM, Jimoh N, Baird GL, Lourenco AP. Dense Breast Ultrasound Screening After Digital Mammography Versus After Digital Breast Tomosynthesis. AJR Am J Roentgenol. 2019 Dec;213(6):1397–402.

37. Girardi V, Tonegutti M, Ciatto S, Bonetti F. Breast ultrasound in 22,131 asymptomatic women with negative mammography. Breast [Internet]. 2013 Oct;22(5):806–9.

38. Hooley, Greenberg, Stackhouse, Geisel, Butler, Philpotts, et al. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. Radiology. 2012 Oct;265(1):59–69.

39. Hwang J-Y, Han B-K, Ko EY, Shin JH, Hahn SY, Nam MY. Screening Ultrasound in Women with Negative Mammography: Outcome Analysis. YONSEI Med J. 2015 Sep;56(5):1352–8.

40. Kim S-Y, Kim MJ, Moon HJ, Yoon JH, Kim E-K. Application of the downgrade criteria to supplemental screening ultrasound for women with negative mammography but dense breasts. Medicine (Baltimore) [Internet]. 2016 Nov;95(44):e5279–e5279.

41. Klevos GA, Collado-Mesa F, Net JM, Yepes MM. Utility of supplemental screening with breast ultrasound in asymptomatic women with dense breast tissue who are not at high risk for breast cancer. Indian J Radiol Imaging [Internet]. 2017 Jan;27(1):52–6.

42. Korpraphong P, Limsuwarn P, Tangcharoensathien W, Ansusingha T, Thephamongkhol K, Chuthapisith S. Improving breast cancer detection using ultrasonography in asymptomatic women with non-fatty breast density. Acta Radiol [Internet]. 2014 Oct;55(8):903–8.

43. Lee, Yi A, Jang M, Chang J, Cho N, Moon W. Supplemental Screening Breast US in Women with Negative Mammographic Findings: Effect of Routine Axillary Scanning. Radiology [Internet]. 2018 Mar;286(3):830–7.

44. Leong LCH, Gogna A, Pant R, Ng FC, Sim LSJ. Supplementary breast ultrasound screening in Asian women with negative but dense mammograms-a pilot study. Ann Acad Med Singapore. 2012 Oct;41(10):432–9.

45. Parris T, Wakefield D, Frimmer H. Real World Performance of Screening Breast Ultrasound Following Enactment of Connecticut Bill 458. Breast J. 2013;19(1):64–70.

46. Pishdad P, Moosavi A, Jalli R, Zarei F, Saeedi-Moghadam M, Zeinali-Rafsanjani B. How can additional ultrasonography screening improve the detection of occult breast cancer in women with dense breasts? POLISH J Radiol. 2020 Jul;85:E353–60.

47. Venturini E, Losio C, Panizza P, Rodighiero MG, Fedele I, Tacchini S, et al. Tailored breast cancer screening program with microdose mammography, US, and MR Imaging: short-term results of a pilot study in 40-49-year-old women. Radiology [Internet]. 2013 Aug;268(2):347–55.

48. Weigert JM. The Connecticut Experiment; The Third Installment: 4 Years of Screening Women with Dense Breasts with Bilateral Ultrasound. Breast J [Internet]. 2017 Jan;23(1):34–9.

49. JH Y, EK K, MJ K, JY K, EJ S, Youk JH, et al. Performance of hand-held whole-breast ultrasound based on BI-RADS in women with mammographically negative dense breast. Eur Radiol [Internet]. 2011 Apr;21(4):667–75.

50. Arleo EK, Saleh M, Ionescu D, Drotman M, Min RJ, Hentel K. Recall rate of screening ultrasound with automated breast volumetric scanning (ABVS) in women with dense breasts: a first quarter experience. Clin Imaging [Internet]. 2014;38(4):439–44.

51. Brem RF, Tabár L, Duffy SW, Inciardi MF, Guingrich JA, Hashimoto BE, et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology [Internet]. 2015 Mar;274(3):663–73.

52. Giuliano V, Giuliano C. Improved breast cancer detection in asymptomatic women using 3D-automated breast ultrasound in mammographically dense breasts. Clin Imaging [Internet]. 2013;37(3):480–6.

53. Kelly KM, Dean J, Lee S, Comulada WS. Breast cancer detection: radiologists' performance using mammography with and without automated whole-breast ultrasound. Eur Radiol [Internet]. 2010 Nov;20(11):2557–64.

54. Wilczek B, Wilczek HE, Rasouliyan L, Leifland K. Adding 3D automated breast ultrasound to mammography screening in women with heterogeneously and extremely dense breasts: Report from a hospital-based, high-volume, single-center breast cancer screening program. Eur J Radiol [Internet]. 2016 Sep;85(9):1554–63.

55. Chen S-Q, Huang M, Shen Y-Y, Liu C-L, Xu C-X. Abbreviated MRI Protocols for Detecting Breast Cancer in Women with Dense Breasts. Korean J Radiol [Internet]. 2017;18(3):470–5.

56. Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers R-D, Bieling HB. Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum-Intensity Projection-A Novel Approach to Breast Cancer Screening With MRI. J Clin Oncol [Internet]. 2014 Aug;32(22):2304–10. A

57. Kuhl CK. Abbreviated breast MRI for screening women with dense breast: the EA1141 trial. Br J Radiol [Internet]. 2018 Oct;91(1090):20170441.

58. Veenhuizen SGA, de Lange S V., Bakker MF, Pijnappel RM, Mann RM, Monninkhof EM, et al. Supplemental Breast MRI for Women with Extremely Dense Breasts: Results of the Second Screening Round of the DENSE Trial. Radiology. 2021 Mar 16;203633.

59. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostillio L, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. Lancet Oncol [Internet]. 2016;17(8):1105–13.

60. Haas BM, Kalra V, Geisel J, Raghu M, Durand M, Philpotts LE. Comparison of tomosynthesis plus digital mammography and digital mammography alone for breast cancer screening. Radiology [Internet]. 2013 Dec;269(3):694–700.

61. McCarthy AM, Kontos D, Synnestvedt M, Tan KS, Heitjan DF, Schnall M, et al. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. JNCI J Natl Cancer Inst [Internet]. 2014 Nov;106(11):dju316–dju316.

62. Zackrisson S, Lång K, Rosso A, Johnson K, Dustler M, Förnvik D, et al. One-view breast tomosynthesis versus two-view mammography in the Malmö Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study. Lancet Oncol [Internet]. 2018;19(11):1493–503.

63. Houssami N. Evidence on Synthesized Two-dimensional Mammography Versus Digital Mammography When Using Tomosynthesis (Three-dimensional Mammography) for Population Breast Cancer Screening. Clin Breast Cancer. 2018 Aug;18(4):255+.

64. Sorin V, Yagil Y, Yosepovich A, Shalmon A, Gotlieb M, Neiman OH, et al. Contrast-Enhanced Spectral Mammography in Women With Intermediate Breast Cancer Risk and Dense Breasts. Am J Roentgenol. 2018 Nov;211(5):W267–74.

65. Rhodes DJ, Hruska CB, Conners AL, Tortorelli CL, Maxwell RW, Jones KN, et al. JOURNAL CLUB: Molecular Breast Imaging at Reduced Radiation Dose for Supplemental Screening in Mammographically Dense Breasts. Am J Roentgenol [Internet]. 2015 Feb;204(2):241–51.

66. Shermis RB, Wilson KD, Doyle MT, Martin TS, Merryman D, Kudrolli H, et al. Supplemental Breast Cancer Screening With Molecular Breast Imaging for Women With Dense Breast Tissue. AJR Am J Roentgenol [Internet]. 2016 Aug;207(2):450–7.

67. Tagliafico AS, Mariscotti G, Valdora F, Durando M, Nori J, La Forgia D, et al. A prospective comparative trial of adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts (ASTOUND-2). Eur J Cancer [Internet]. 2018 Nov 15;104:39–46.

68. Tagliafico AS, Calabrese M, Mariscotti G, Durando M, Tosto S, Monetti F, et al. Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts: Interim Report of a Prospective Comparative Trial. J Clin Oncol [Internet]. 2016 Jun;34(16):1882–8.

69. Kuhl CK. Abbreviated Magnetic Resonance Imaging (MRI) for Breast Cancer Screening: Rationale, Concept, and Transfer to Clinical Practice. Annu Rev Med. 2019 Jan;70:501–19.

70. Kelly, Dean, Comulada, Lee, Kelly, Dean, et al. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol [Internet]. 2010 Mar;20(3):734–42.

71. Kuhl CK, Keulers A, Strobel K, Schneider H, Gaisa N, Schrading S. Not all false positive diagnoses are equal: On the prognostic implications of false-positive diagnoses made in breast MRI versus in mammography / digital tomosynthesis screening. Breast Cancer Res. 2018 Feb;20(1):13.

72. Houssami N, Lang K, Hofvind S, Zackrisson S, Bernardi D, Hunter K, et al. Effectiveness of digital breast tomosynthesis (3D-mammography) in population breast cancer screening: a protocol for a collaborative individual participant data (IPD) meta-analysis. Transl Cancer Res. 2017 Aug;6(4):869–77.

73. Chen S-Q, Huang M, Shen Y-Y, Liu C-L, Xu C-X. Application of Abbreviat d Protocol of Magnetic

Resonance imaging for Breast Cancer Screening in Dense Breast Tissue. Acad Radiol [Internet]. 2017 Mar;24(3):316–20.

74. Lee J, Nishikawa RM, Rohde GK. Detecting mammographically-occult cancer in women with dense breasts using Radon Cumulative Distribution Transform: a preliminary analysis. In: Petrick, N and Mori, K, editor. MEDICAL IMAGING 2018: COMPUTER-AIDED DIAGNOSIS. 2018. (Proceedings of SPIE; vol. 10575).

75. Youk J, Kim E, Kim M, Kwak J, Son E. Performance of hand-held whole-breast ultrasound based on BI-RADS in women with mammographically negative dense breast. Eur Radiol [Internet]. 2011;21(4):667–75. Available from: http://dx.doi.org/10.1007/s00330-010-1955-8

76. Giuliano V, Giuliano C. Using Automated Breast Sonography as Part of a Multimodality Approach to Dense Breast Screening. J Diagnostic Med Sonogr [Internet]. 2012 Jul;28(4):159–65.

77. Houssami N, Bernardi D, Caumo F, Brunelli S, Fantò C, Valentini M, et al. Interval breast cancers in the "screening with tomosynthesis or standard mammography" (STORM) population-based trial. Breast. 2018 Apr;38:150–3.

78. Ritse M. Mann, Alexandra Athanasiou, Pascal A. T. Baltzer, Julia Camps-Herrero, Paola Clauser, Eva M. Fallenberg, Gabor Forrai, Michael H. Fuchsjäger, Thomas H. Helbich, Fleur Killburn-Toppin, Mihai Lesaru, Pietro Panizza, Federica Pediconi, Ruud M. Pijnappel, Katja Pinker, Francesco Sardanelli, Tamar Sella, Isabelle Thomassin-Naggara, Sophia Zackrisson, Fiona J. Gilbert & Christiane K. Kuhl On behalf of the European Society of Breast Imaging (EUSOBI). Breast cancer screening in women with extremely dense breasts recommendations of the European Society of Breast Imaging (EUSOBI) Eur Radiol (2022). https://doi.org/10.1007/s00330-022-08617-6

79. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer. 1976;37:2486–2492. - PubMed