

## Appendix 5. Dense Breasts on Mammography as a Risk Factor for Early Onset Breast Cancer

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### **INTRODUCTION**

Mammographic breast density is a known independent risk factor for breast cancer. Breast density reporting has become subject to legislation and can be a particularly challenging topic for patients and providers. This review summarizes evidence on mammographic dense breasts as a risk factor for early onset breast cancer (EOBC), whether density can contribute to delay in diagnosis in women under age 46, and whether additional screening mitigates risk.

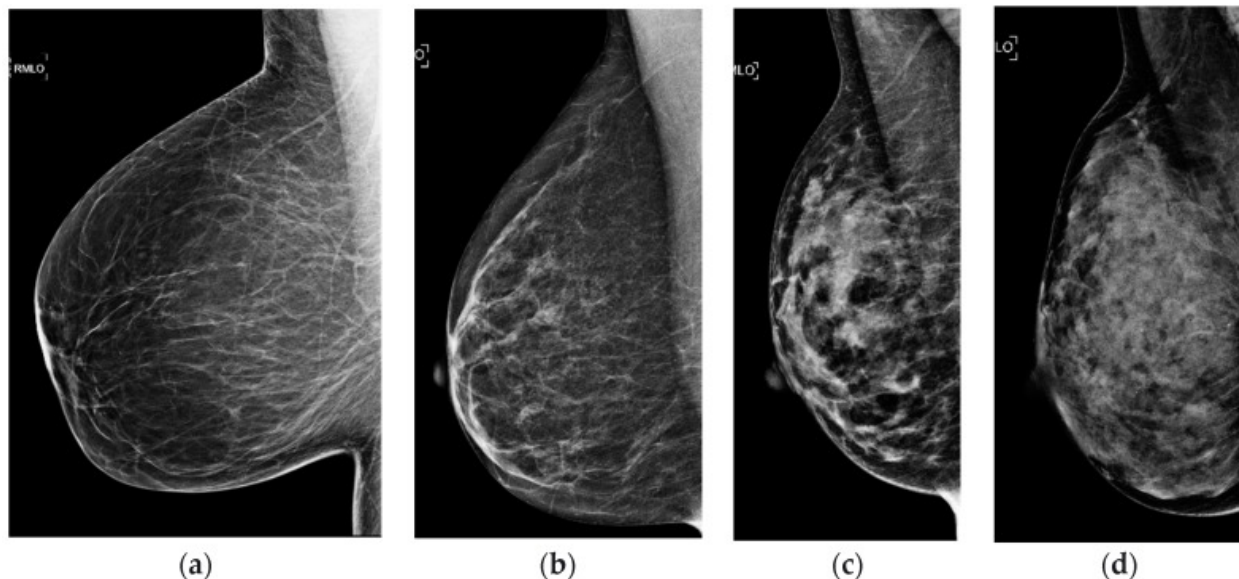
Breast tissue is composed of fibroglandular tissue and fat. The fibroglandular tissue is a mixture of fibrous stroma and the ductal epithelium and appears denser or brighter on mammograms because the X-rays are not able to penetrate this tissue at the same rate as fatty tissue. The Breast Imaging-Reporting and Data System (BI-RADS) developed by American College of Radiology (ACR) includes subjective criteria for how much fibroglandular tissue is present on mammograms (see Table 1, Figure 1).<sup>1</sup> *Breast density* is a subjective radiographic finding. In the past, *percent breast density, range of percent density by quartile, and area density* were used. Many older studies reporting on breast density used these criteria, making comparisons of studies difficult. In the most recent BI-RADS update, even a small area of significant density can result in a film classified as heterogeneously dense.

**Table 1. Based on the ACR Breast Imaging-Reporting and Data System (BI-RADS®)**

<b>Classification of Dense Breasts</b>	<b>Breast Composition Categories</b>
A	The breasts are almost entirely fatty
B	Scattered areas of fibroglandular density
C	Heterogeneously dense, which may obscure small masses
D	Extremely dense, which lowers the sensitivity of mammography

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**Figure 1. Breast density examples.**



Breast density (a) almost entirely fatty, (b) scattered fibroglandular tissue, (c) heterogeneously dense, and (d) extremely dense, as determined by the BI-RADS Atlas 5<sup>th</sup> Edition. Reprinted from Diagnostics (Basel) 2018;8:E38. doi: 10.3390/diagnostics8020038. This figure is from an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

A retrospective review of more than 7,000 mammograms showed that 75% of women aged 40–49 had mammographically dense breasts (combining the heterogeneously dense and the extremely dense group) compared with 44% of women in their 60s.<sup>2</sup> There does not appear to be a correlation between mammographic findings of dense breasts with clinical breast examination. There is an inverse relationship between breast density and age.<sup>3</sup> As women age, breast tissue typically becomes less dense.

*Masking* is a term used to describe the decreasing sensitivity of mammography in women with dense breasts. Since dense breast tissue appears radiopaque, similar to many breast cancers, the decreased sensitivity of mammograms in women with dense breasts is likely due to the lack of visual contrast, especially when the cancer does not have calcifications.<sup>4</sup> In women with extremely dense breasts, mammography has a 62% sensitivity, while the sensitivity is 88% for women with fatty breasts.<sup>5</sup> Advances in screening technology are helping to close this gap. In 2005, the Digital Mammographic Imaging Screening Trial showed a higher diagnostic accuracy of digital mammography over traditional film mammography in women under age 50, with a 27% improved sensitivity (78% vs 51%, 95% confidence interval [CI]: 11–44%,  $P=0.002$ ) over a year of follow-up. Women with dense breasts had a 14% improved sensitivity (70% vs 55%, 95% CI: 3–26%,  $P=0.02$ ).<sup>6</sup> Currently, over 90% of mammography centers in the United States perform digital mammography.

Standard mammography provides a two-dimensional image. These images are obtained with tissue compression and overlap, which may limit cancer detection in women with dense breasts.<sup>7</sup> Many imaging methods and emerging modalities with potential to address these shortcomings are being tested.

Because digital breast tomosynthesis (DBT) creates an image taken from multiple projections over a multiple viewing angles, it has less superimposed breast tissue and allows better imaging when there is dense breast tissue, along with possibly better sensitivity for small tumors.<sup>8</sup> Approximately 30% of mammography centers had DBT in 2018, according to the ACR. The incremental cancer detection was

1.2/1,000 studies in women who underwent digital mammograms in 1 year with digital mammograms and DBT in the subsequent year. The call-back rates decreased by 15%.<sup>9</sup>

## **METHODS**

The following questions were used to direct the literature search.

### **1. Are dense breasts on mammography an independent risk factor for EOBC? How strong is the risk?**

*P – Patient, Problem, or Population. I – Intervention. C – Comparison, Control, or Comparator. O – Outcome(s) (PICO)*

- **P:** Patients aged 18-45 with dense breasts
- **I:** Screening mammography
- **C:** Women with dense breasts on screening mammography vs women who do not have dense breasts on screening mammography
- **O:** Relative risk (RR) or odds ratio (OR) of breast cancer, incidence of breast cancer

### **2. Do dense breasts on mammography result in a delay in diagnosis of EOBC?**

*PICO*

- **P:** Patients aged 18-45 with dense breasts who are diagnosed with breast cancer
- **I:** Screening mammography

- **C:** Women diagnosed with breast cancer with dense breasts on screening mammography vs women who were diagnosed with breast cancer who did not have dense breasts on screening mammography. Also evaluated women with dense breasts diagnosed with breast cancer by screening mammogram vs by interval mammogram.
- **O:** Stage at diagnosis and tumor type

**3. In women with dense breasts, is additional screening beneficial to prevent invasive breast cancer or mitigate its consequences? If so, what are the most effective screening approaches (whole breast ultrasonography, digital mammography, breast tomosynthesis, or magnetic resonance imaging [MRI])?**

*PICO*

- **P:** Patients with dense breasts aged 18-45
- **I:** Whole breast ultrasonography, digital mammogram breast tomosynthesis, MRI
- **C:** Whole breast ultrasonography vs digital screening mammography; digital mammography vs breast tomosynthesis; digital mammography vs MRI
- **O:** Diagnosis of ductal carcinoma in situ (DCIS) vs invasive breast cancer

**4. What are the major society or health services guidelines for screening or management of women with dense breasts before age 46?**

*PICO*

- **P:** Women aged 18-45
- **I:** Guidelines for the management of women with dense breasts
- **C:** Guidelines from one organization to another
- **O:** National Comprehensive Cancer Network (NCCN), U.S. Preventive Services Task Force (USPSTF), American College of Obstetricians and Gynecologists, American Cancer Society, ACR, American Society of Breast Disease, American Society of Breast Surgeons, Society of Surgical Oncology, European School of Oncology, and European Society of Medical Oncologists

Using these PICO questions, a search was conducted for articles available in English from 2010 to January 2019. Systematic reviews, meta-analyses, cohort studies, case-control studies, and randomized controlled trials were reviewed, as well as major U.S. and international professional society and health services guidelines. Guidelines were found via MEDLINE, Google, stakeholder society websites, and bibliographies of other manuscripts found in the literature search. Because specific data about women under age 45 were rare, additional references were included if they addressed substantial proportions of younger women or had data on older women that may be generalizable. Additional resources were obtained by reviewing the references from review articles and systematic reviews. Additionally, websites such as [densebreast-info.org](http://densebreast-info.org) were reviewed. Papers were excluded if they were not available in English, were uncontrolled case series or case reports, if the focus was on breast cancer detection in pregnancy, or if they focused on biomarkers or lifestyle factors associated with breast density. Because most of the studies on breast density were conducted earlier than the originally planned search criteria, making recent data sparse, the search was extended to include earlier studies.

## **RESULTS**

The initial literature search found 127 publications. Of those, 96 were excluded—88 following title and abstract review and 8 after review of the manuscripts—leaving 31 articles for inclusion.

### **Are dense breasts on mammography an independent risk factor for EOBC? How strong is the risk?**

The literature search found no articles that focused on women with dense breasts exclusively in the 18–45 age group. Among other studies, there was heterogeneity resulting from the different classifications of breast density used over time.

Using the BI-RAD classification, a systematic review of studies evaluating risk for breast cancer in women aged 40–49 and meta-analysis of the Breast Cancer Surveillance Consortium (BCSC, a national collaboration of five mammogram registries and two sites that prospectively collects screening data, risk factor information, and cancer outcomes) data identified a single study of over 500,000 women. Of these women, 43% were under age 49. The study reported that extremely dense breasts were associated with an increased risk of breast cancer when compared with fibroglandular breasts (RR: 2.04, 95% CI: 1.84–2.26).<sup>10</sup>

A meta-analysis by McCormack and dos Santos Silva evaluated the risk of breast cancer based on breast density and included 42 studies published before 2005.<sup>11</sup> Some of these studies used different breast density classifications from those currently in use, including the qualitative Wolfe grade, BI-RADS, Tabar



classification, and percent and area of breast density. A total of 14,134 women with breast cancer and 226,871 controls aged 35–80 were included. The pooled RR for the incidence of breast cancer comparing better than or equal to 75% with less than 5% density was 4.64 (95% CI: 3.64–5.91). None of the studies included specific subgroup data on women under age 45.<sup>11</sup>

Two prospective studies in the McCormack review reported the risk of breast cancer diagnosis by density. One study calculated a hazard ratio of 3.5 (95% CI: 1.98–6.21) when comparing the third quartile of density using Wolfe classification with the bottom quartile and a hazard ratio of 3.9 (95% CI: 1.76–8.62) when comparing the fourth quartile (women with most dense breasts) to women with fatty breasts. The median age of cases was 53 years (range: 40.3–79.9).<sup>12</sup> The other study compared dense vs fatty breast tissue using BI-RADS classification and revealed a RR of 4.21 (95% CI: 1.49–11.80) for breast cancer, adjusting for age and premenopausal status. In this study, 25% of the study population was under age 45.<sup>13</sup>

Correlation of screening mammograms performed 5 years prior to diagnosis of breast cancer with the diagnostic mammogram that diagnosed the breast cancer in 231 women, median age of 46 years, found tumors largely arose within the dense breast tissue. The probability of a tumor developing in a particular area increased as the mammographic density increased, suggesting that mammographic density may be directly involved in the development of cancer. There was a 25.5 OR (95% CI: 8.1–80.3) of the cancer developing in the most dense area compared with the least dense area.<sup>14</sup>

In a more recent a case–control study of 213 Korean women with breast cancer, women who had the highest breast density, described as 50% or more density, had a 2.98 increased risk of breast cancer (95% CI: 0.99–9.03), compared with those with the lowest mammographic density after adjusting for multiple variables.<sup>15</sup> Median age in the study was 51.5 years, with 45% of cancers diagnosed before age 50.

In a case–control study of 6,710 women who had other risk factors for developing breast cancer, Assi et al reported that in women aged 40–49 at intermediate risk for breast cancer, greater than 50% density was associated with a higher risk of breast cancer (OR: 4.43, CI: 1.26–15.58) when compared with less than 10% density. Absolute breast density, as opposed to percent density, was found to be an independent risk factor for breast cancer when adjustments were made for other risk factors, including age at menarche, age at first live birth, parity, and past or present hormone therapy (OR: 1.08, 95% CI: 1.00-1.16).<sup>16</sup> The average lifetime risk of breast cancer in this cohort was 23%.

The correlation between breast density and breast cancer has also been demonstrated in postmenopausal women. Yaghjian et al compared 1,044 women with postmenopausal breast cancer from the Nurses' Health Study Cohort with age-matched controls.<sup>17</sup> In this nested case–control study, multivariable analysis demonstrated that women with higher breast density had a higher breast cancer risk (OR: 3.36, 95% CI: 2.44–4.63,  $P<0.0001$ ) and were more likely to be taking postmenopausal hormone therapy.

### **Do dense breasts on mammography result in a delay in diagnosis of EOBC?**

Chelmow D, Pearlman MD, Young A, Bozzuto L, Dayaratna S, Jeudy M, et al. Executive summary of the Early-Onset Breast Cancer Evidence Review Conference. *Obstet Gynecol* 2020;135.  
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The sensitivity of mammography is 62% in women with extremely dense breasts, 69% in women with heterogeneously dense breasts, and over 80% for women with scattered fibroglandular density and fatty breast tissue.<sup>5</sup> Masking of breast cancer because of the decreased visual contrast between dense breasts and cancer is the likely reason for the decreased sensitivity of mammograms in women with dense breasts. Cancers identified between a normal mammogram and the next recommended screening are termed *interval breast cancers* and are one way to assess delay in diagnosis. Interval cancers account for about 15% of breast cancers diagnosed annually.<sup>18</sup> In addition to breast density, other reasons for diagnosis of an interval cancer include a rapidly growing tumor and an incorrect reading of the screening mammogram.

Boyd et al showed in a meta-analysis of three Canadian trials, totaling 1,114 women aged 40–70, that of the 124 cancers that were diagnosed within 1 year of the screening mammogram, the OR for an interval cancer in women with dense breasts (75% or more density; categorization prior to publication of the fifth edition of ACR BI-RADS) was 17.81 compared with those women with less than 10% density.<sup>19</sup> The majority of patients in this meta-analysis were over age 50, but some were in their 40s. The studies included in the meta-analysis preceded the adoption of digital mammography as the primary screening modality.

The BCSC screened a prospective cohort of over 300,000 women aged 40–74 by digital mammography; 29.4% of all patients and 19.1% of those diagnosed with breast cancer were under age 49. To assess risk of interval cancers in high- vs average-risk women, 5-year risk of breast cancer was assessed using the

BCSC risk calculator. The high-risk group included those with a 5-year breast cancer risk greater than or equal to 1.67% and extremely dense breasts and those with a 5-year breast cancer risk of greater than or equal to 2.5% and heterogeneously dense breasts. Twenty-four percent of all women with dense breasts fell into this group and were considered high-risk. Of this high-risk group, those with heterogeneously and extremely dense breasts had a high interval rate of breast cancer, defined as more than one case per 1,000 examinations at or within 1 year of a normal mammogram. This was the cut-off for a high interval cancer detection rate because, in routinely screened women, the incidence of breast cancer is four cases in 1,000 examinations. The investigators felt anything less than a 75% sensitivity would not be acceptable performance for mammography, and one interval cancer per 1,000 examinations would give a 75% sensitivity. For women aged 40–49 at average risk (5-year breast cancer risk of 1–1.66%) and with extremely dense breasts, the interval cancer rate was 0.89 cases per 1,000 mammograms (95% CI: 0.54–1.37). For all women aged 40–49 with extremely dense breasts, the risk of an interval breast cancer was 0.98 per 1,000 examinations (95% CI: 0.67–1.37).<sup>20</sup>

McCarthy et al showed that women aged 40 years or older who had dense breasts and a negative screening mammography had twice the incidence of interval cancers (OR: 2.07, 95% CI: 1.48–2.89,  $P=0.02$ ) compared with women who did not have dense breasts. In this study, over 300,000 women were screened over a 3-year period; approximately one quarter were aged 40–49. Of the women who received a diagnosis of cancer after a negative mammogram, women aged 40–49 years had a worse prognosis compared with those aged 70–89 years (OR: 3.52; 95% CI: 1.15–10.72). Poor prognosis was defined as distant metastases; cancer-positive regional lymph nodes; estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive and hormone epidermal growth factor 2 (HER2)-receptor-

negative invasive cancer 2 cm or more in diameter; ER-negative, PR-negative, HER2-negative (triple negative) invasive cancer 1 cm or more in diameter; or HER2-positive invasive cancer 1 cm or more in diameter.<sup>21</sup> Van der Waal et al showed a similar hazard ratio for death from interval cancers. An interval cancer diagnosed at or before 24 months from a negative screening mammogram had an age-adjusted hazard ratio of 2.06 (95% CI: 1.62–2.61).<sup>22</sup> Women in the study were aged 38–97.

Bertrand and colleagues pooled data from six case–control studies, including 3,414 women with breast cancer and 7,199 women without, all of whom underwent mammography screening. They excluded cancers identified within 6 months of mammography and evaluated tumor type and size and association with percent mammographic density. The mean age at mammography was 57 years. Women who had tumors that were diagnosed at 2.1 cm or greater in size were more likely to have higher mammographic density of 51% compared with 11–25% (mammographic density was divided into 0–10%, 11–25% [the reference group], 26–50% and 51% or more) (OR: 3.12, 95% CI: 2.41–4.04).<sup>23</sup> While there was a statistically significant increased risk of all sizes of tumor in the 51% or higher density compared with the reference group, the increase was largest with the larger tumor size. Compared with the reference group, 51% or higher mammographic density was also associated with a higher risk of node-positive disease (OR: 2.67, 95% CI: 2.07–3.44). The data are mixed about breast cancer tumor subtypes associated with breast density. Detection method was not included in the study and so data were not available as to whether the cancers were detected by screening mammography or mammography done in response to a clinical finding.

**In women with dense breasts, is additional screening beneficial to prevent invasive breast cancer or mitigate its consequences? If so, what are the most effective screening approaches?**

### *Mammography Screening Interval*

A USPSTF evidence review found that women aged 40–49 with dense breasts had a greater risk for advanced stage disease, defined as stage IIB or greater (OR: 2.39, CI: 1.06–3.39) if they had biennial screening compared with annual screening.<sup>24</sup>

### *Adjunctive Screening*

#### ULTRASONOGRAPHY

The literature search found no studies that looked at use of ultrasonography as an adjunct to a negative mammogram in women aged 18–40; some studies included women aged 40–49. The search found no trials studying mortality reduction with supplemental screening.<sup>25</sup>

A systematic review by the USPSTF on supplemental screening for breast cancer in women with dense breasts included studies from 2000 to 2015 using BI-RADS classification for mammographic density.<sup>26</sup>

The sensitivity of handheld ultrasonography (HHUS) for detecting breast cancer was 80–83% (95% CI: 59–96%) in women with dense breasts and a negative mammogram.<sup>26</sup> The one study that was included in this review on automated supplemental breast ultrasonography in women with dense breasts had a

sensitivity of 68% (95% CI: 50–83%).<sup>27</sup> Use of HHUS detected 4.4 cancers per 1,000 examinations after a negative mammogram (95% CI: 2.5–7.2). Screening mammography alone detected 4.7 cancers per 1,000 examinations in the one good quality U.S. study on HHUS<sup>28</sup> and 2.8 cases per 1,000 examinations in a good-quality Italian study.<sup>29</sup> The recall rate for HHUS was reported in only one study; it was 14% (95% CI: 12.7–15.1%) of 3,414 exams.<sup>28</sup>

A systematic review including 10 studies on HHUS and 2 on automated breast ultrasonography from 2000 to 2013 as an adjunct to screening mammography included 53,000 women with dense breasts and an otherwise negative mammogram. It showed additional cancer detection rates of 0.3–12.3 cases per 1,000 examinations, with a median of 4.2 cancers per 1,000 examinations. Mean age of women in the studies ranged from 45 to 65 years. Unlike the USPSTF systematic review, this review included studies using different methods of reporting breast density, in line with the accepted method at the time of the study. Five of the studies were prospective. All of the cancers identified were less than 2 cm and invasive, and 89% were node-negative. While the addition of ultrasonography increased the number of invasive cancers detected in women with dense breasts compared with mammography alone, there was a fivefold increase in biopsies but no data about impact on long-term survival.<sup>30</sup>

A Cochrane review from 2013 evaluating the benefit of adjunctive ultrasonography for screening after a negative mammogram in women of average risk for breast cancer found no studies that met their search criteria other than the Japan Strategic Anti-Cancer Randomized Trial, which was ongoing at the time of the review.<sup>31</sup>

A prospective study of 11,000 women with screening mammography and physical examination followed by ultrasonography in women who had breast density of BI-RADS categories B–D followed from 1995 to 2000 found that breast density was the single most important factor in predicting mammographic sensitivity in all ages.<sup>4</sup> Women in the study had a mean age of 59.6 years (standard deviation, 15.8 years). Initially, women of all breast densities underwent ultrasonography, but after 700 women with fatty or category-A breasts had no cancers detected, ultrasonography was no longer performed on such women. In the subgroup of 5,826 women under age 50, mammographic sensitivity was 50% for those with category-C breasts and 42% for those with category-D breasts ( $P<0.015$ ). In women with dense breasts, the combination of ultrasonography and mammography was 97.3% sensitive for categories B–D, compared with 74.7% for mammography and physical examination alone ( $P<0.001$ ). Additionally, 42% of women with dense breasts and nonpalpable invasive cancer had their cancer detected only on ultrasonography. Seventy percent of the cancers detected only with ultrasonography in women with category-D breast density were less than 1 cm in size, and 89% were node-negative.

A multicenter, randomized trial performed in China compared mammography alone, ultrasonography alone, and mammography and ultrasonography combined in high-risk women.<sup>32</sup> It found that ultrasonography was superior to mammography screening, with 100% sensitivity compared with 57.1% ( $P=0.04$ ). Sixty-four percent of the participants were under age 49 at initial screening, with a mean age at enrollment of 46.4 years. High-risk status was determined by a risk calculator that incorporated many of the factors commonly included in the risk calculators widely used in the United States, as well as “stress anticipation” and combined oral contraceptive use. The authors commented that, in general, Chinese women have dense breasts, but did not state the number of women with dense breasts. They



stated that prior studies suggested that 66% of Chinese women were classified as having heterogeneously or extremely dense breasts. The number of women that needed to be screened per cancer detected was 1,390 for mammography alone, 602 for ultrasonography alone, and 459 for the combined group.

A recent study in Japan randomized 70,000 women aged 40–49 to mammography alone or mammography and ultrasonography combined. The cancer detection rate was higher in women who had ultrasonography, and interval cancers decreased by 50% (0.05% vs 0.10%,  $P=0.034$ ). Seventy-one percent of the cancers detected in the intervention group were detected as DCIS or stage I cancers. In the control group, 52% of the detected cancers were DCIS or stage I ( $P=0.019$ ). While almost 60% of the patients had dense breasts, the detection rates were not reported by breast density.<sup>33</sup>

#### DIGITAL BREAST TOMOGRAPHY

There appears to be no difference between the combination of mammography and DBT compared with mammography alone in cancer detection in women with extremely dense breasts (sensitivity of 63.6% vs 59.1%,  $P=0.64$ , and positive predictive value of 79.2% vs 61.9%;  $P=0.078$ ).<sup>34</sup>

#### MAGNETIC RESONANCE IMAGING

Three studies addressed MRI as a supplemental screening modality in women with dense breasts and a normal mammogram, with a total of 2,162 examinations.<sup>35</sup> The sensitivity of MRI in women with dense

breasts and no additional breast cancer risks after a negative mammogram ranged from 75% (95% CI: 35–97%) to 100% (29–100%), while recall rates ranged from 9% (CI: 4–15.7%) to 23% (CI: 18.9–28.3%), depending on the study. Additional cancer detection rates of supplemental MRI after a negative mammogram in women with dense breasts were 3.5 (95% CI: 1.3–7.6) to 28.6 (CI: 5.9–81.2) per 1,000 examinations, while mammographic cancer detection rates in women with dense breasts in two of these studies were 4.1 and 7.0 per 1,000 examinations.

A prospective observational study evaluated the additional cancer detection rate with supplemental breast MRI in 2,100 average-risk women aged 40–70, with a median age of 53 years. Sixty percent of the study participants had breast density category C or D. Additional breast cancer detection by MRI after a negative screening mammogram was 15.5 per 1,000 examinations (95% CI: 11.9–20). Sixty-seven percent of these cancers were invasive, and 93% of these invasive cancers were diagnosed as stage I. The false-positive rate for MRI was 2.9%. Sixty percent of women in this study had dense breasts (category C or D) and 60% of cancers occurred in this combined group.<sup>36</sup> In another study of high-risk women, Berg et al showed a similar cancer detection rate with MRI, but 58% of women who were offered MRI at no cost to themselves declined.<sup>37</sup>

### **What are the major society or health services guidelines for screening or management of women with dense breasts before age 46?**

*American Cancer Society*

There is not enough evidence to make a recommendation for or against yearly MRI screening for women who have a higher lifetime risk based on certain factors, such as having “extremely” or “heterogeneously” dense breasts as seen on a mammography.<sup>38</sup>

*National Comprehensive Cancer Network*

“For women with mammographically dense breast tissue (heterogeneously or extremely dense tissue), recommend counseling on the risks and benefits of supplemental screening. Dense breasts limit the sensitivity of mammography. Mammographically dense breast tissue is associated with an increased risk of breast cancer. Full-field digital mammography appears to benefit young women and women with dense breasts. Hand-held or automated ultrasonography can increase cancer detection rates in women with dense breast tissue, but may increase recall and benign breast biopsies.”<sup>39</sup>

All recommendations are based on lower level evidence and NCCN consensus, category 2A.

*American College of Radiology*

“For women with dense breast tissue but no additional risk factors, ultrasonography may be useful as an adjunct to mammography for incremental cancer detection, but the balance between increased cancer detection and the increased risk of a false-positive examination should be considered in the decision.”<sup>40</sup>

*Society of Breast Imaging*

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“Dense breast tissue increases the risk of breast cancer and impairs detection of non-calcified cancers on mammography, which can result in later stage at diagnosis. Digital mammography is better than film mammography in women with dense breasts. Digital breast tomosynthesis improves cancer detection compared to standard digital mammography in women with heterogeneously dense breasts but may be less effective in women with extremely dense breasts due to lower internal contrast. Magnetic resonance imaging is recommended for supplemental screening in women at high risk of breast cancer regardless of breast density, but cost and availability limit its use for general screening. Ultrasound improves detection of early stage invasive breast cancer and is the most frequently used supplemental screening modality. It appears that screening ultrasonography is of benefit even after DBT provided the woman is willing to accept an increased risk of false-positives. Surrogate endpoints of stage shift, reduced node-positive disease, and reduced interval cancer rates should be accepted as proof of benefit of supplemental screening.”<sup>41</sup>

*American College of Obstetricians and Gynecologists*

The American College of Obstetricians and Gynecologists does not recommend routine use of alternate or adjunctive tests to screening mammography in women with dense breasts who are asymptomatic and have no additional risk factors.<sup>5</sup>

*U.S. Preventive Services Task Force*

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, MRI, DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram.<sup>42</sup>

*European School of Oncology and European Society of Medical Oncologists*

There is no clear role for routine screening by imaging of any kind in healthy young women under age 40. In the presence of significant family history, a history of chest wall radiation or a germline mutation in a gene known to increase breast cancer risk, the consensus panel recommended considering MRI screening. It also suggested considering breast MRI and ultrasonography in the setting of very dense breast tissue or other high-risk conditions, based on observational studies and case series.<sup>25</sup>

**SUMMARY**

The literature review found no studies specific to breast density in EOBC. General evidence across all age groups suggests a relationship between mammographically dense breasts and increased risk of breast cancer. The risk appears to increase as breast density increases and may reflect a combination of independent risk and impaired diagnosis caused by masking. In its 2016 update, the USPSTF noted that while breast density is a common and independent risk factor for developing cancer, there is no evidence about the impact of breast density on cancer-related deaths.

Studies of adjunctive screening with ultrasonography and MRI generally noted higher cancer detection rates and earlier diagnosis, but no study showed differences in mortality. These studies are limited by short follow-up time, which may not be adequate to show an effect on mortality. Studies in the review that included women of all ages found that the addition of screening ultrasonography to mammography in women with dense breasts significantly increases the detection of nonpalpable cancers and node-negative disease. One randomized controlled trial showed a 50% decrease in interval cancers with adjunctive ultrasonography.<sup>28</sup> Screen-detected cancers may be smaller and less aggressive than clinically detected interval cancers. Adjunctive modalities to mammography, such as ultrasonography, may compensate for the masking effect of dense breasts. The addition of ultrasonography may be beneficial if surrogate markers of effectiveness such as node-negative disease and early stage identification rather than impact on mortality are considered. However, the literature review found no direct evidence of these benefits on outcome in the specified age group.

In addition, MRI has had limited evaluation as a supplemental test after negative screening mammography in average-risk women with dense breasts. The tolerability, cost, lack of widespread availability, and need for renal function testing in selected women may limit its use.

The relative risk of cancer in women with extremely or heterogeneously dense breasts depends on the chosen comparison group, with the highest risks expressed if the most dense breasts are compared with the least dense. In general, the relative risk is similar to having a first-degree family member with breast cancer and greater than having had a prior breast biopsy, both factors currently used to assess individual patient risk for breast cancer.<sup>24</sup>

Currently, 36 states mandate some form of notification to patients about their breast density. Some states also require language that adjunctive tests should be considered. In February 2019, Congress directed the U.S. Food and Drug Administration to develop language to be included in patient letters and health care provider reports to describe the breast density seen on mammograms.

None of the organizations producing major relevant guidelines, particularly the American Cancer Society and USPSTF, make specific recommendations for management of women with mammographic breast density on screening mammography. Several acknowledge the increased risk with dense breasts and allow for counseling and shared decision making about adjunctive screening. General awareness of the associated increased risk in conjunction with state-mandated reporting frequently places providers in situations where they need to answer questions and provide guidance to patients. Provision of guidance is further complicated in younger women, as none of the risk data effectively look at this group separately, and mammographic breast density is common enough in premenopausal women (>75%) that it can, in some senses, be considered normal. Some major guidelines, such as those from USPSTF, do not include recommendations for screening average women before age 50; if these recommendations are followed, women with dense breasts in this age group would not be identified.

In approaching younger women with mammographically dense breasts, some general guidance seems appropriate:

- Women can be counseled that women with mammographic breast density are at slightly higher risk for breast cancer than women without. In the absence of other risk factors, the absolute risk

remains small. Increased mammographic breast density is extremely common in premenopausal women.

- Risk assessment can be performed with a validated risk calculator that includes mammographic breast density.
- When mammographic density in combination with other risk factors places the patient at intermediate risk, additional screening with ultrasonography may be warranted and a shared decision making model should be applied. Patients at high risk should undergo additional screening or prophylaxis according to established recommendations.
- Screening recommendations for average-risk women under age 50 vary between major societies; several involve shared decision making for age at initiation and interval. Once mammographic breast density has been identified, it is reasonable to continue annual (as opposed to biennial) screening.
- Additional screening in young women whose only risk factor is mammographic breast density is controversial. While some guidelines (eg, SBI and NCCN) allow for adjunctive screening after counseling, none specifically recommend it. For women who have no other risk factors but still desire adjunctive screening after counseling, ultrasonography combines lower cost with some evidence of increased and earlier detection, which could theoretically translate into improved outcomes. Patients should be counseled that this remains unproven. Potential harms include an increased numbers of biopsies, many of which will be negative. In addition, diagnosis and overtreatment of indolent lesions should be discussed. The psychological stress of false-positives can also be reviewed with the patient in reaching a shared decision about supplemental screening.



The literature review was most impressive for the knowledge gaps it revealed. Mammographic breast density is present in most women under 50. It appears to be associated with increased cancer risk. Studies to confirm and quantify this risk in younger women are necessary, as is better integration of this risk assessment into risk calculators. The role of adjunctive screening should be defined, including whether it is beneficial, which test is most appropriate, the risks and benefits of adjunctive screening in this age group, and the interval with which it should be repeated. Studies about racial variation and impact of hormonal contraceptives would also be useful.

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