

Breast Density

A literature review to inform BreastScreen Australia's position statement on breast density and screening

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CONTENTS

ΚΕΥ Τ	ERMS		4
GUID	ANCE ON	HOW TO READ THIS REPORT	4
KEY F	INDINGS		5
1.	INTRODU	JCTION	14
	1.1.	About breast density	14
	1.2.	BreastScreen Australia's current position on breast density and screening	15
	1.3.	Purpose and scope of this literature review	16
	1.4.	Ongoing research	17
2.	METHOD	OLOGY	18
	2.1.	Objectives	18
	2.2.	Research questions	18
	2.3.	Literature search	21
	2.4.	Limitations and interpretation	23
3.	ASSESSM	IENT OF EVIDENCE AND PRESENTATION OF RESULTS: DENSITY CLASSIFICATION A	AND
	THE IMP	ACT OF BREAST DENSITY ON THE RISK AND MASKING OF BREAST CANCER	25
	3.1.	Classifying and validating breast density	26
	3.2.	Risk of breast cancer: the association with breast density	37
	3.3.	Masking	71
	3.4.	The role of supplemental testing	76
4.	ASSESSI	IENT OF EVIDENCE AND PRESENTATION OF RESULTS: THE IMPACT OF BREAST	
	DENSITY	ON CLINICAL OUTCOMES	96
	4.1.	Physical health outcomes	96
	4.2.	Mental health outcomes	98
5.	NOTIFIC	ATION AND REPORTING	109
	5.1.	Notification and reporting in other jurisdictions	109
	5.2.	Information that women want and acceptability of reporting	114
REFE	RENCES		116
APPE	NDIX A: O	UALITY ASSESSMENT FOR EACH INCLUDED STUDY	127

KEY TERMS

BSA	BreastScreen Australia
BSGI	Breast-specific gamma imaging
BIRADS	Breast Imaging Reporting and Data System
CDR	Cancer detection rate
CI	Confidence interval
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
ER	Oestrogen receptor
FFDM	Full-field digital mammography
MBI	Molecular breast imaging
MRI	Magnetic resonance imaging
OR	Odds ratio
PD	Percent density
PPV	Positive predictive value
RR	Relative risk

GUIDANCE ON HOW TO READ THIS REPORT

This report contains two parts:

- 1. The Key Findings section provides a summary of the findings of this literature review presented by the research questions. A summary of the evidence and quality assessment is also provided.
- 2. The main report provides detailed findings on to inform the research questions. Relevant data from all primary studies is included in evidence tables.

Appendix A includes the quality assessment tables (based on AMSTAR2 and the Scottish Intercollegiate Guidelines Network tools) for included systematic and narrative reviews, and RCTs.

KEY FINDINGS

The BreastScreen Australia (BSA) program currently uses bilateral full-field digital mammography (FFDM) as the "gold standard" screening test for the early detection of breast cancer in all asymptomatic, average-risk women (including those with more dense breasts). Breast density (also known as mammographic or parenchymal density) is not routinely assessed or reported to women participating in the BSA program (except in the Western Australia BSA program); however, consumer requests for consistent individualised data about breast density to inform choices about breast cancer screening are increasing.

The Department of Health (Australia) contracted *Allen + Clarke* to undertake a literature review (not systematic review) of the evidence base informing the BSA position statement on breast density and screening in asymptomatic women aged over 40 years. We want to know:

- the best (and validated) ways to measure breast density
- the established increase in risk of breast cancer for women with more dense breasts, the relative risk of breast cancer by age and by breast density and how (or if) the association between breast density and risk changes with adjustment for age
- the degree to which breast density masks breast cancer in modern digital mammography
- the role of supplemental testing in breast cancer screening for asymptomatic women with more dense breasts
- if there have been any changes in screening participation or health and psychosocial outcomes for women who have received information about their breast density, and
- notification and reporting of breast density to women and health practitioners.

Included study types were epidemiological studies including systematic reviews, randomised controlled trials and prospective cohort or case-control studies.

This literature review will support the Breast Screening Technical Reference Group's consideration of what updates (if any) are needed to BSA's position statement on breast density. Further updates to the BSA position statement may be required as recruiting or active studies report interim or final findings.

Although a range of classification systems exist to describe breast density, much of the research discussed in this report used the Breast Imaging Reporting and Data System (BIRADS) classification system. Under BIRADS, women with more dense breasts are classified as 3/c or 4/d; women with more fatty/less dense breasts are classified as 1/a or 2/b. Other classification systems are also used. This complicates the reporting of results as there is no consensus on or widely preferred system used to classify mammographic density.

Methodology

Allen + Clarke completed a systematic search of the Ovid Medline, CINAHL, Embase, ProQuest and Scopus databases as well as searches of health technology assessment, NICE, Cochrane and clinical trial databases and other key websites relating to breast cancer screening. We used combinations of subject/index terms as appropriate to the search functionality of each database (eg, exploded term 'mammography' or exploded 'breast neoplasm' in combination with key words, or key words alone). Articles were included if they were epidemiological in nature and met the PICO(T) criteria.

For three research questions (related to classification, risk and masking), our inclusion criteria were originally limited to systematic reviews and RCTs as previously agreed with the Technical

Reference Group. Due to the limited number of systematic reviews or meta-analyses available, we also included some narrative and non-systematic reviews (although these lack some essential components like clear eligibility criteria, search strategies, study selection processes, outcomes, and assessment of bias in individual studies). This initial search identified 42 articles that met the inclusion criteria.

It was decided that for specific research questions, including those relating to the measurement of breast density, risk, and masking, the search criteria would be extended to ensure that emerging evidence was included in the literature review. For information related to these questions, the literature search was repeated using the same parameters and methodology outlined above, but inclusion criteria were expanded to include prospective cohort and case-control studies. An additional 26 articles were identified that met the extended inclusion criteria. An additional narrative review was also identified from responses to the consumer survey on breast density.

While we understand that while inclusion of narrative literature reviews and prospective studies may introduce reporting bias and evidence that is less robust than RCTs or systematic reviews, their inclusion is warranted as this provides a bigger picture view and a wider look at the current evidence available related to breast density.

A total of 69 studies were identified that met final inclusion criteria.

The Department of Health has commissioned two other literature reviews: one investigating digital breast tomosynthesis' (DBT) role in breast cancer screening for all women (including those with more dense breasts) and the other underpinning a horizon scan of incremental improvements to imaging modalities or new imaging techniques, which included a focus on screening outcomes for women with more dense breasts. Additional information about the role of DBT, ultrasound, magnetic resonance imaging (MRI) and molecular breast imaging (MBI) in the early detection of cancer in asymptomatic women with more dense breasts and the role in primary screening is also available in these literature reviews.

This is not a systematic review but an assessment of the quality of each systematic review, narrative review and RCT included in the report was completed. An overall summary table provides an indication of the strength of findings.

Results

Classifying and validating breast density

Breast tissue comprises skin, blood vessels, ductal and stromal elements of the glands (which appear radio-opaque or white on mammography) and fat (which appears radiolucent or black on mammography). Mammographic breast density is defined as the relative amount of radio-opaque (white) elements to radiolucent (black) fat on the image. Increase in the proportion of radio-opaque elements leads to greater mammographic breast density.

High mammographic density is relatively common. One of the most common methods currently used to report breast density is the American College of Radiologists' BIRADS system. BIRADS estimates indicate that approximately 10% of women have almost entirely fatty breasts (BIRADS 1), 40% of women have scattered fibroglandular densities (BIRADS 2), another 40% have heterogeneously dense breasts (BIRADS 3), and 10% have extremely dense breasts (BIRADS 4). Dense breasts are defined as either heterogeneously dense (BIRADS 3) or extremely dense (BIRADS 4). Thus, approximately 50% of the population undergoing mammography could be categorised as having dense breasts. In addition, the same women can be classified as having dense or fatty breasts depending on how the results are read or interpreted. This can then affect clinical

decision making around the information women receive on whether they should undergo supplementary screening.

There are six common systems used to classify breast density: BIRADS, Wolfe, Tabár, semiautomated visual estimation (eg, Cumulus), automated area-based methods, and volumetric estimation (eg, Volpara). The BSA position statement on breast density states that there is no consensus on the best measure of breast density. The evidence reported in this literature review still finds no consensus about which method is the most accurate. All classification systems have been shown to have high sensitivity in detecting density. All systems have been shown to have inter- and intra- report variability, particularly when categorising less dense breasts. This is because even though each system is underpinned by semi-objective measures, assessment still requires a reader's subjective assessment. Newer technologies such as fully-automated assessment methods (eg, Volpara) reduce this variability and have been found to have a strong association with breast cancer risk, but further work to develop consistent algorithms is still required.

Evaluating the impact of breast density on cancer risk and clinical outcome for screen-detected cancers requires thorough studies with consistent mammographic procedures, standardised methods of density measurement and breast density classification, as well as a standardised definition of high breast density; however, there is currently no consensus on any of these factors. This results in variations in estimates of the association between breast density and breast cancer risk, depending on the screening procedures and assessment methods used. These findings are consistent with the 2016 BSA position statement on the measurement and classification of breast density. The uncertainty described in the BSA program's 2016 position statement remains.

Breast density and cancer risk

Breast density is an established risk factor for breast cancer through cumulative exposure over the lifetime, but the extent to which breast density affects risk for breast cancer is not absolutely established. Many (but not all) studies compare women with a percent density of more than 75% compared to women with a percent density of <5%, with the former group having four to six times higher risk for breast cancer. These studies inflate the breast cancer risk because this risk does not represent that posed to the average women (as these categories are at the extreme ends of the population continuum). When risk is compared between women with heterogeneously or extremely dense breast tissue and women with average breast density, the relative risk decreases to approximately 1.2 to 2.1.

Despite the lack in standardisation of breast density thresholds, there is still an association between breast density and breast cancer regardless of how breast density is defined. When mammographic phenotypes are examined, percent density area (calculated by dividing the dense area by the total breast area) is generally found to have a stronger association to breast cancer than absolute dense area (i.e., the amount of fibroglandular tissue per mm² or cm²). That said, one large cohort study found that combining information on both absolute dense area and percent density significantly improved risk prediction compared to using the information independently.

The relative risk conferred by breast density in part depends on a woman's other risk factors for breast cancer. Many studies investigating breast density and breast cancer risk (and screening) comprise women with an elevated risk of breast cancer, independent of their breast density (eg, familial risk). Therefore, it is difficult to conclude what the risk and screening options for women with dense breasts and other moderate or strong risk factors would be and much of the research is silent on this issue. That said, most studies that control for these potential confounding factors find that they do not have a significant impact on the association between breast density and breast cancer risk. This suggests that breast density is an independent predictor of breast cancer risk.

Kerlikowske et al. (2015) reported that breast density should not be the sole criterion for deciding whether supplemental imaging is justified because not all women with dense breasts have high interval cancer rates. Age and breast cancer risk influence cancer incidence and tumour stage at diagnosis (and therefore screening performance). These factors should be considered along with breast density to optimise identification of women with high interval cancer rates or high rates of false-positive results who may benefit from supplemental testing or alternative screening tests.

There is some evidence that breast density differs due to genetic variation and ethnicity, and that breast density is associated with different biological factors such as receptor subtypes. Increased breast density was found to be a risk factor for most breast cancer subtypes; however, the particular association for each subtype needs to be further explored, as current evidence is mixed regarding the association between breast density and specific subtypes of breast cancer. Similarly, high breast density was found to be associated with gene variation in a number of genes. It is likely that breast density will be affected by several genes that are largely unknown at the present time.

A number of studies were identified that reported women of Asian ethnicity have a lower risk of breast cancer related to breast density than that reported for European women. The reason for these findings are unknown. Further research is needed in women of different ethnicities.

There were limited studies focusing on the relationship between age and breast density. Findings from those studies suggest that the association between breast density (and screening performance) and breast cancer risk may be stronger for younger women. Even taking this into consideration, the risk of breast cancer remains low and the harms of screening (listed below in this review) are likely to outweigh the small benefits of screening for this population.

Masking

The proportion of women aged over 40 years who have dense breasts is estimated to be between 30-60%. This is inversely proportional with age: a higher proportion of women in their 40s have more dense breasts compared to those in their 70s.

It is well accepted that mammography is the primary screening tool for breast cancer and has been shown in multiple RCTs to reduce the death rate from breast cancer. However, even in the best circumstances, mammography may miss up to 20 percent of breast cancers. The sensitivity of mammography reduces further with increasing breast density, resulting in the potential for masking of cancer and non-detection; current evidence suggests that the sensitivity of mammography reduces from around 85-90% for women with average breast density to around 60-65% for women with dense breasts.

The increased risk of interval cancer attributed to masking cannot easily be separated from the potentially rapid growth of tumours in dense tissue, although there is preliminary evidence that higher density is related to increased risk of interval cancers after controlling for fast-growing tumours. One study found lower rates of mortality reduction from screening for women with dense breasts compared to those with fatty breasts, although this difference was not statistically significant.

The number of studies specifically assessing the masking effect of breast density (eg, reduced sensitivity and higher interval cancer rates) is relatively small, and further evidence is needed to gain a clear understanding of this relationship. That said, the growing recognition of the likely negative impact of breast density on the performance of mammography screening has resulted in an increasing focus on the potential of supplemental testing as a method that could reduce the masking effect of breast density.

The role of supplemental testing

Approximately one-half of women undergoing screening mammography have dense breasts. As discussed in previous sections, there is evidence to suggest that increased breast density is associated with higher breast cancer risk and a decrease in mammography performance. This suggests that supplemental imaging could be beneficial for women with dense breasts; however, there is no direct, robust evidence that supplemental imaging reduces mortality from breast cancer.

Furthermore, there are a number of potential harms associated with supplemental imaging following a negative mammography, including increased false-positive screening results, recall rates and unnecessary breast biopsies, and potential increases in screening-related anxiety. These potential harms become more pertinent when one considers the variability of breast density classification. The classification of breast density for individual women has been found to vary between readers, and across time due to several factors, including age and weight changes. It is therefore possible to receive incorrect or outdated information about breast density, which could unduly influence clinical or personal decision-making regarding screening.

Evidence and expert consensus remains unclear as to the risk-benefit balance of supplemental imaging using DBT, ultrasound, MRI, and MBI for women whose <u>only</u> risk factor is mammographic density and who have an average lifetime risk of developing breast cancer. Each of these adjunct modalities has advantages and disadvantages related to factors such as accuracy, cost, radiation dose, acceptability, and availability. Not surprisingly, there is therefore no one measure that is best at overcoming the masking issues seen with mammography for women with more dense breasts. For this reason, there are also no guidelines or consensus established in Australia or other jurisdictions as to which screening modality women should undergo if they have the denser breasts (as the only risk factor).

The Connecticut Experiment suggested that supplementary screening with ultrasound benefits all women through improved CDR (even those with fatty breasts). There are still gaps regarding whether women with more dense breasts benefit more from different screening strategies compared to women with less dense breasts, or if their screening-related clinical outcomes differ.

Some cancers are mammographically occult and can be detected only by other (non-mammography based) breast imaging. Whether performing supplemental imaging to identify mammographically occult cancers provides more benefit in terms of reduced cancer mortality than harm is not established.

Physical health outcomes associated with breast density reporting

A total of 31 states in the United States and Western Australia have adopted legislation and/or recommendations that women be informed of their breast density, that dense breast tissue may be a risk factor for breast cancer, and that dense breast tissue may interfere with early cancer detection by mammography screening.

When women are informed about mammographically identified increased breast density, it is recommended that clinicians discuss the risks and benefits of supplemental imaging with women prior to initiating such screening. Topics for discussion include: the risk of a false-negative mammogram, the risk of a false-positive ultrasound finding leading to unnecessary breast biopsy, and the risk of overdiagnosis (or, perhaps more accurately, over-treatment) if breast cancer is detected. Few studies have investigated if, when and how information is delivered and the related outcomes for the women.

Our literature review found insufficient evidence to draw conclusions on the impact of breast density notification on physical health outcomes. No studies reported on outcomes such as mortality or interval cancer rates in asymptomatic women with dense breasts who have been notified of their density. Other early research reported that breast density notification may drive an increase in demand for supplemental testing and as a result, it may be associated with an increased detection of breast cancer. However, it is unclear if this association indicates earlier or improved detection of cancers or an over-diagnosis (over-treatment) of cancers.

Mental health outcomes associated with receiving advice on breast density

While there is some association between notifying women about their breast density and negative mental health outcomes (eg, knowing that she has extremely dense breasts may increase a woman's anxiety about developing breast cancer) in women, the identified studies do not indicate a consistent and significant relationship. However, this could also signal that women generally have a poor understanding of the summary letter or a lack of knowledge of the relationship between breast density and cancer risk. There is also a limited body of evidence in this area, including a lack of studies that assess mental health outcomes associated with notification in women with more dense breasts only, and cohort studies following women before and after the implementation of legislation (with a long-term follow up) to understand how the notifications impact on screening behaviour.

Two American studies reported on ethnic differences in emotional responses to breast density notification. Both studies found African American women to have more breast density-related anxiety compared to European women, however socioeconomic status and knowledge partially accounted for the effect of ethnicity on psychological response.

A small number of studies examined the association between breast density awareness or knowledge (as a result of breast density notification) and women's responses to breast cancer screening. The studies indicate that breast density notification may increase women's engagement in screening but further research to determine this relationship is needed.

Notification and reporting

No studies identified what information women need in (or additional to) a breast density notification letter. Legislation has been implemented at an individual state level in the United States (as opposed to federal legislation), which has resulted in variations in the language of the notifications and can impact on the quality of care delivered (for example, inconsistent referral for supplemental testing) and women's understanding.

Studies highlight that where breast density notification occurs, it is critical for women and providers to be informed of the meaning of the information in the notification, and how it should influence their approach to breast screening. This relies on providers being confident in communicating the complexity around breast density, risk and screening and emphasises the need for physician education and evidence-based guidelines for the management of women with more dense breasts.

The developing evidence base

Breast density is a mammographic finding. Multiple factors contribute to breast density in women, including age, genetics, and BMI. Dense breasts are found in approximately 50 percent of women undergoing mammography (depending on the classification system used). For most purposes, the term "dense breasts" refers to either heterogeneously dense or extremely dense breasts (categories 3/c or 4/d of BIRADS). There is variability in classification of breast density with 13 to 19% of women re-categorised between "dense" and "non-dense" breasts on sequential screenings in some

American settings. Computer-aided methodologies (which may allow more consistent and objective breast density assessment) are currently not widely used to determine density classification. Studies are needed to provide consensus on mammographic procedures, methods of density measurement, breast density classification as well as a standardised definition of high breast density. Until this occurs, it will be hard to gain conclusive evidence on the preferred screening and clinical pathways for women with more dense breasts. These findings are consistent with the 2016 BSA position statement on breast density.

The presence of dense breast tissue on mammography both decreases the sensitivity of mammography and increases the risk of breast cancer, as most cancers develop in the glandular parenchyma. However, increased breast density has not been associated with increased mortality from breast cancer. To date, there have been no RCTs comparing screening with a combination of ultrasound and mammography and screening with mammography alone in average-risk women. The addition of ultrasonography, DBT, MRI, and MBI to mammography increases sensitivity for small cancers, but often greatly decreases specificity. In studies of supplemental testing with ultrasound, greater than 90 percent of positive test results were false-positive. Supplemental testing with MRI is also limited by high false-positives and additionally by higher cost, lack of wide availability, and increased radiation.

There are no major guidelines for breast cancer screening that advise breast density as the sole factor in determining the need for supplemental testing. There is accumulating medical evidence and expert consensus guidelines to support risk stratification as a means to determine strategies for supplemental breast cancer testing. Breast density may be one of several risk factors considered. To be able to define meaningful clinical outcomes for women with dense breasts, well-designed, long-term prospective, comparative studies of supplemental tests are needed. Active trials are currently underway (eg, the DENSE trial), which will help answer these questions.

Notification of breast density has been implemented in many regions however there is no standard method or information provided to women across jurisdictions. Further research is needed to determine the best methods for the delivery of the information and the benefits and/or harms associated with notification of breast density to women, clinicians and the health system.

Assessment of evidence table summary

Table 1: Assessment of evidence for breast density

Outcomes	Number of	Quality of	of Overall results		
	studies	evidence			
Measuring breast density	12 studies	⊕⊕ Low	Data from 1 systematic review, 5 narrative reviews and 8 prospective studies found there is strong evidence as to how much the measurement of density has changed since its inception. There is evidence that there is inter- and intra- reader variability when using visual density assessment methods. There is evidence (largely based on prospective studies) suggesting that automated computer-based density measurements can provide consistent, reproducible, and objective results. There is no strong evidence as to the best way to classify breast density.		
The association between breast density and risk of breast cancer	22 studies	⊕⊕⊕ Moderate	Data from 4 systematic reviews, 3 narrative literature reviews and 15 prospective studies found that there is a very strong evidence that breast density is a risk factor for breast cancer. There is strong evidence that breast density changes with age; however, there is weak evidence as to how this is associated with cancer risk. There is moderate evidence that breast density differs due to genetic variation and ethnicity. There is some evidence that density is associated with different biological factors such as receptor subtypes.		
Breast density and masking	9 studies	⊕ Very low	No systematic reviews were found. Findings from 3 narrative literature reviews and 6 prospective studies propose an association between breast density, breast cancer and masking. There is some evidence that the sensitivity of mammography is reduced, and rate of interval cancers increased, for women with dense breasts. That said, most studies are of limited quality and the direct role of breast density in masking and interval cancer rates is unclear. There is no evidence for a method that best measures masking. There is also no strong evidence on how the relationship between breast density and masking affects the mortality reduction in a screening program.		
The role of supplementary screening	13 studies	⊕⊕ Low	7 systematic reviews (100 articles) and 6 narrative literature reviews found there is strong evidence that supplemental testing detects more cancers than FFDM alone but that this increases false positives and recall rates for women. Most of the literature in this area focuses on ultrasound and there is strong evidence for its use as a supplemental test, providing significantly improved rates of cancer detection that mammography alone (systematic review and prospective studies); however, there is no evidence that supplemental testing reduces mortality. There is some evidence that the use of MRI, DBT and MBI as supplementary screening methods provides better cancer detection rates however, more rigorous studies are needed. There is no strong evidence that any test other than bilateral, full-field digital mammography significantly reduces mortality from breast cancer, including for women with dense breasts.		

Outcomes	Number of studies	Quality of evidence	Overall results
Physical and mental health outcomes	11 studies	⊕ Very low	Overall, the literature in this area is scarce and is mainly focused in the United States. The literature that is available is mainly in the form of observational studies and is of low quality. It is currently unclear how breast density notifications affect physical and mental health outcomes, and whether they change screening behaviour.

1. INTRODUCTION

1.1. About breast density

Breasts are made up of fat and fibroglandular (non-fatty) tissue with the composition of breast tissue varying between women. Breast density can be affected by factors like changing hormone levels (eg, use of oestrogen, place in menstrual cycle, etc.), genetic factors, parity, use of tamoxifen, weight and inter/intra reader variability.

The look size or feel of a breast does not provide any information about breast density. Breast density is a radiological finding measured by mammography (either by a radiologist reviewing mammographic images or via computer aided assessment). There is no consensus about the most effective way to measure, classify, validate or manage breast density (see Chapter 3 of this report). While there are different ways to measure breast density, radiologists usually look at mammographic images to determine relative proportions of particular types of tissue, fat and other possibly other architectural features. On a mammogram, fatty tissue appears black while the remaining breast tissue appears white or radiographically 'dense', with the relative amount of fibroglandular tissue areas on a mammogram referred to as breast (or mammographic) density (i.e., heterogeneously or extremely dense breasts with little fat). Figure 1 (below) shows the differences in density using Breast Imaging Reporting and Data System (BIRADS) classification.

Figure 1: Breast density classification using BIRADS (reproduced from http://www.informd.org.au)



Breast density values are a continuous range. The amount of breast density ranges from negligible (BIRADS 1: mostly fatty) through to a majority of the breast area (BIRADS 4: extremely dense). Breast density declines with age, with international research indicating more than half of women under the age of 50 years have more dense breasts; for women over 50 years of age about one third have more dense breasts (Berg et al., 2008).

Bilateral full-field digital mammography (FFDM) is the current "gold standard" screening test for early detection of breast cancer in most national breast cancer screening programs including the

BreastScreen Australia (BSA) program. These programs are population-based and designed for average-risk, asymptomatic women. As discussed in Chapter 3 of this report, we know that women with more dense breasts have elevated cancer risk and that breast density can also have an impact on the sensitivity of screening with mammography. When FFDM is used, sensitivity for cancer detection can be lower for women with more dense breasts because, due to their similar X-ray attenuation properties, cancers may also appear as white areas on mammograms (*NB* fat has a lower X-ray attenuation and appears darker, making cancers in less dense breasts easier to see). Also, certain dense breast structures can be superimposed with mammographic compression which can mask cancers or make areas of normal tissue appear suspicious for cancer. Together, conspicuity is reduced making it more difficult for readers to clearly differentiate between normal tissue and malignancy. This makes some cancers more difficult to detect in some women with more dense breasts and can interfere with the accurate interpretation of mammograms. Classification of breast density relies on some subjective elements, such as qualitative visual assessment to give an estimate of breast density, which means that a woman may get different results depending on how her mammogram is analysed or who analyses it.

In screening programs, radiologists and breast physicians make assessments of breast density as part of the interpretation of mammograms; however, it is not clear if knowing breast density:

- impacts on clinical outcomes associated with breast cancer
- changes clinician behaviour (in terms of the advice provided to women about cancer screening participation or screening pathway advice and indications), or
- changes women's behaviour and choices when it comes to participating in breast cancer screening (either with mammography or other screening modalities).

Different screening programs assess, record and report on breast density in different ways, with some states in the United States providing comprehensive information to women and other jurisdictions providing less (or no) reporting. In Australia, only the Western Australia BSA program provides notification of breast density to women. In New Zealand, Breast Screen Aotearoa (the national breast cancer screening program) does not currently measure breast density, based on its 2016 review of the evidence on breast density (National Screening Unit, 2016). It states:

"For women with dense breasts who otherwise have an average risk of breast cancer, there is insufficient evidence to recommend additional imaging (such as ultrasound or MRI). The harms of extra imaging, such as causing anxiety, unnecessary needle biopsies, over-diagnosis and cost, are likely to outweigh the benefits. This is the reason breast density is not currently measured within the [Breast Screen Aotearoa] programme."

1.2. BreastScreen Australia's current position on breast density and screening

The BSA program has a current position statement on breast density and screening (BreastScreen Australia, 2016). Based on the current Standing Committee recommendations, the BSA program does not routinely record breast density or provide supplemental testing using other technologies for women with dense breasts. The position statement says:

"There is no randomised controlled trial data that shows supplemental screening (such as MRI, ultrasound or tomosynthesis) saves additional lives for asymptomatic women with dense breasts and no other risk factors."

The Standing Committee recommended mammography as the best screening test for the early detection of breast cancer in all asymptomatic women, including women with dense breasts. This

recommendation was made because, at 2016, there were evidence gaps relating to how breast density should be assessed and validated. There were also gaps about whether women with more dense breasts benefit more from different screening strategies compared to women with less dense breasts, or if their screening-related clinical outcomes differed. The position statement noted that breast density may have a role in determining the frequency and method of an individual's breast screening in the future, and that further research is required before any new approach to managing or reporting on breast density is considered.

1.3. Purpose and scope of this literature review

With media interest heightened about breast density and how it relates to mammographic screening, the Department of Health has received consumer interest from women who would like to hear whether they have more or less dense breasts when they have a mammogram.

The Department of Health has commissioned Allen + Clarke Policy and Regulatory Specialists Limited (*Allen + Clarke*) to:

- complete a literature review of the evidence base on the management and reporting of breast density in asymptomatic women aged over 40 years, and
- prepare any updates to BSA's position statement on breast density and screening if considered necessary by the Breast Screening Technical Reference Group and/or BSA program managers.

We want to know:

- the best (and validated) ways to measure breast density
- the established increase in risk of breast cancer for women with more dense breasts, the relative risk of breast cancer by age and by breast density and how (or if) the association between breast density and risk changes with adjustment for age
- the degree to which breast density masks breast cancer in modern digital mammography
- the role of supplemental testing in the early detection of breast cancer in asymptomatic women with dense breasts
- if there have been any changes in screening participation or health and psychosocial outcomes for women who have received information about their breast density, and
- notification and reporting of breast density to women and health practitioners.

Initially, the answers to these questions will support the Breast Screening Technical Reference Group's consideration of what updates (if any) are needed to BSA's position statement on breast density.

The literature review is not a systematic review. No original meta-analysis or other pooled analysis was completed.

1.4. Ongoing research

Our review of <u>www.clinicaltrials.gov</u> (completed on 2 July 2018) identified three large studies investigating screening modalities and screening frequency in women with dense breasts. These studies are recruiting women where increased breast density is their only risk factor:

- 1. Breast Cancer Screening With MRI in Women Aged 50-75 Years With Extremely Dense Breast Tissue: the DENSE Trial (estimated study completion date: December 2019).
- 2. Comparative Effectiveness of Breast Cancer Screening and Diagnostic Evaluation by Extent of Breast Density (estimated study completion date: September 2021).
- 3. Tailored Screening for Breast Cancer in Premenopausal Women. A Translational, Randomized Population-based Trial (estimated study completion date: January 2022).

Three further studies investigating the impact of breast density reporting were also identified, although these have small participant numbers:

- 1. Informed Implementation of Breast Density Reporting (estimated study completion date: May 2018).
- 2. ENGAGED 2 Study: Experiences With Mammography Screening and Breast Density 2 (estimated study completion date: August 2020).
- 3. DBTUST Dense Breast Tomosynthesis/Ultrasound Screening Trial (estimated study completion date: December 2022).

There are also other ongoing studies investigating the role of supplemental testing for women with more dense breasts. Results from all these studies will further contribute to our knowledge about the best ways to respond to the cancer risk posed by breast density and women's concerns about ensuring access to effective and safe screening modalities that have a positive effect on long-term health outcomes.

2. METHODOLOGY

Summary

- This literature review provides an overview of research about the management and reporting of breast density in asymptomatic women with more dense breasts. Information was drawn from systematic reviews, narrative literature reviews, RCTs and case-control or prospective studies only.
- This literature review is not a systematic review. We have provided statements about the quality of the evidence included in this review. No primary research or pooled analysis was undertaken.
- The following databases were searched on 15-19 January 2018: EMBASE, Ovid Medline, CINAHL, ProQuest and Scopus. The following websites were reviewed: clinicaltrials.gov, the Cochrane database, NICE. Additionally, a range of other websites reporting on breast density and screening were also reviewed.
- A follow-up search was conducted on the same databases and websites on 25 May to 5 June 2018 to identify case-control and prospective studies providing information on breast density measurement, risk, and masking.
- All returned citations and abstracts were assessed for relevance to the research questions and inclusion criteria. The same criteria were used to review the full-text and bibliographies of all articles proposed for inclusion. The methodologies of all included studies were critically appraised using the AMSTAR 2 tool or SIGN criteria.
- A total of 69 articles met the inclusion criteria.

2.1. Objectives

This literature review explores the effect that breast density has on the risk of breast cancer and the masking of breast cancer in asymptomatic women over 40 years alongside how to best measure both risk and density and respond in a way that improves long-term clinical outcomes for women with more dense breasts. It also explores the impact and acceptability of breast density reporting for women with dense breasts. In addition to this, we investigate the above areas for a subpopulation, women aged 40-50 years (inclusive) with no symptoms of breast cancer and screened by mammography. A systematic review with pooled analysis was not performed.

2.2. Research questions

2.2.1. Questions about classification, risk and masking

The three questions about breast density, breast cancer risk and masking are described overleaf.

- QUESTION 1: In asymptomatic women aged over 40 years, what is the reported increase in risk of breast cancer for women diagnosed by mammography to have higher breast density compared with women diagnosed to have lower breast density?
 - Is there a method that is the best for measuring breast density?
 - Is there a measure that is the best measure of risk?
- QUESTION 2: In asymptomatic women aged over 40 years, what is the level of reported masking of breast cancer in mammograms for women diagnosed with higher breast density compared with women with lower breast density?
 - Is there a measure that is the best measure of masking?
- QUESTION 3: In asymptomatic women aged over 40 years, what is the relative risk of breast cancer by age for women diagnosed by mammography to have higher density breasts compared with women with lower breast density?
 - Taking breast density into account, does age mitigate or exaggerate the risk of breast cancer?

The PICO(S) criteria underpinning these research questions are described in Table 2 (below).

 Table 2: PICO(S) criteria for questions relating to risk and masking

Criterion	Description
Population	Women aged over 40 years (inclusive) with no symptoms of breast cancer and screened by mammography
	Sub-population of interest: Women aged 40-50 years (inclusive) with no symptoms of breast cancer and screened by mammography
Intervention	2-view digital mammography (aka FFDM)
Comparators	Women with 'dense breasts' or higher breast density
	Women with 'non-dense breasts', fatty or lower breast density
Outcomes	Risk of breast cancer by breast density
	Risk of breast cancer by breast density and age
	Role of masking in detecting breast cancer in women with dense breasts
	Relative risk; odds ratios; risk difference
	Specificity (recall rates and over-diagnosis for specific types of breast lesions)
	Interval cancer rates
Study types	Systematic reviews and randomised controlled trials; case control; prospective

2.2.2. Questions about outcomes and notification of breast density

The question about outcomes and the provision of breast density information/reporting covered several areas.

- QUESTION 4: In asymptomatic women aged over 40 years (inclusive) who have received information about their validated breast density compared with women who have not received information on validated breast density:
 - What is the evidence on changes in clinical health outcomes with differential management?
 - What are the psychosocial outcomes for women in jurisdictions where breast density is reported?
 - Are there any lessons from jurisdictions where breast density information is reported to women, including acceptability of reporting (or not) and reporting protocols?
 - What advice and support do women want and need if density is reported?

The PICO(S) criteria underpinning this research question is described in Table 3 (below).

Table 3: PICO(S) criteria for questions relating to breast density reporting

Criterion	Description						
Population	Women aged over 40 years (inclusive) with no symptoms of breast cancer and screened by mammography and who have received information on validated breast density						
	Sub-population of interest: Women aged 40-50 years (inclusive) with no symptoms of breast cancer and screened by mammography						
Intervention	Validated breast density reported to screened woman						
Comparator	Women who have not received information on validated breast density						
Outcomes	Additional diagnostic tests undertaken and outcomes						
	Choice of adjunct screening (ultrasound, DBT, MRI)						
	Breast cancer diagnosis and stage at detection						
	Ongoing participation in breast screening						
	Frequency of breast screening						
	Mortality from breast cancer						
	Interval cancer rates						
	Seeking of support from primary care, counsellors, mental health services						
	Anxiety, depression						
	Additional costs incurred						
	Acceptability of reporting protocol by GP						
Study types	Systematic reviews, randomized controlled trials, cohort, longitudinal, observational, grey literature						

2.3. Literature search

The literature search was conducted in two phases: an initial search that included epidemiological studies including systematic reviews, narrative reviews and RCTs, and an additional search that extended the inclusion criteria to include prospective cohort or case-control studies.

In total, information from 69 articles was used to answer the research questions in this literature review.

2.3.1. Initial search

The following databases were searched on 15 and 19 January 2018:

- CINAHL
- Clinicaltrials.gov
- Cochrane Library database
- Embase
- National Institute for Health and Clinical Excellence
- OVID Medline
- ProQuest, and
- Scopus.

To complete a systematic search, we used combinations of subject/index terms where appropriate in combination with key words, or key words alone depending on the search functionality of each database or website (eg, main searches included 'breast density' PLUS 'breast cancer' in the title or abstract).

The following limits were applied on all searches:

- Currency (published between 1 January 2010 and 15 January 2018)
- English language
- Study type restrictions (where available and appropriate, we restricted returns from research databases to peer-reviewed systematic reviews, literature reviews, RCT, observational studies and clinical trials), and
- Human studies.

Duplicate citations and a small number of false hits/inaccurate returns were removed before all initial returned citations and abstracts were reviewed for relevance to the main research questions. Material was excluded if it:

- did not relate to breast density in a population screening setting for breast cancer (i.e., if it related to the impact of breast density in the treatment of breast cancer)
- focused on factors that alter breast density (for example, particular diets), or
- focused on a study population other than asymptomatic women.

From this first sweep, full texts for all proposed inclusions were retrieved and reviewed for relevance to the research questions, inclusion criteria and documented PICOT criteria. A critical appraisal of study design (to determine overall quality) was completed and the bibliography of each included article was reviewed to identify other relevant research that may be of interest.

We also searched a wide range of websites for relevant grey literature including: Australian Clinical Trials Registry, Breast Cancer Research Institute of Australia, Breast Cancer Network Australia, Clinical Trials Registry, Current Controlled Trials metaRegister, Health Technology Assessment International, International Network for Agencies for Health Technology Assessment, Medicines and Healthcare Products Regulatory Agency (UK), National Library of Medicine Locator Plus database, National Institute for Health Research UK HTA programme, New York Academy of Medicine Grey Literature Report, TRIP database, U.K. National Research Register, US Food and Drug Administration, Center for Devices and Radiological Health, and National Breast Cancer Foundation.

2.3.2. Literature review extension

A follow-up search was conducted from 25 May – 5 June 2018 using the same process, databases and websites, and search parameters, as those outlined above. The purpose of the search was to extend the literature search on the questions relating to the measurement of breast density, risk, and masking to include prospective cohort and case-control studies.

The search was limited to articles and reports published within the following timeframes, which were selected based on the most recent published systematic review in the subject area:

- Measurement of breast density: 2016 current.
- Breast density and risk: 2014 current.
- Breast density and masking: 2014 current.

From the initial studies returned by the search, articles already discussed in the systematic or narrative reviews included in the original search were removed, as were articles that fell outside the target time period for publication. The full text of the remaining studies was reviewed for relevance to the research questions and inclusion criteria. Common reasons for exclusion included: use of a symptomatic or non-human sample; use of a retrospective study design; not addressing the key research questions; focus on diagnosis rather than screening; and being unable to access the full-text article. This left 26 prospective cohort or case-control studies for inclusion in the literature review, in addition to the 42 articles originally identified in the first literature search.

Consumer survey

An online survey of consumer stakeholders was conducted by *Allen + Clarke* between 23 May and 27 June 2018 regarding BSA's position statement on breast density and screening. Respondents were asked to provide advice on any published scientific articles or major reports that influenced their views on breast density and breast cancer screening. Based on these responses to the survey, one additional narrative review was identified for final inclusion in the narrative review, in addition to the 68 studies identified through the literature searches outlined above.

The citation review process for both the original and extended literature search is displayed in Figure 2 (overleaf).

Figure 2: Citation review process



2.4. Limitations and interpretation

This review, together with the results from Colin and colleagues' (2013) review, highlights that there is no standard classification system used to measure breast density or for defining high breast density or the threshold in high density distribution. A range of models for classifying breast density exist and definitions of breast density vary by study. Different measures depend on when the study was completed, the jurisdiction and the availability of the technology at the time the study was active. There was also (often) a lack of reference values for non-dense breast comparator categories, particularly in studies which used percent density (i.e., varying from less than 25% density to less than 10% density). Until a consistent classification with clearly defined and consistent comparators is used across all studies that measure breast density, pooled analyses remain difficult, if not an impossibility. *Allen + Clarke*'s review recognises this issue and reports the system and thresholds used as defined by individual articles only.

The scope of this review for Questions 1-3 (classification of breast density, cancer risk, and the role of masking) was to gain evidence from systematic reviews and RCTs published between 2010-2017. Due to the limited number of systematic reviews or meta-analyses available, this review of the literature included some narrative and non-systematic reviews, which lack some essential components such as clear eligibility criteria, search strategies, study selection processes, outcomes, and assessment of bias in individual studies. Some more recent prospective cohort and case-control studies have also been used to provide up-to-date information on areas of particular importance to the literature review. Findings from these studies are subject to a number of biases, including Type

I and II error and sampling bias, and require validation through replication. Results from these studies should be interpreted with caution and should not be given the same weight as findings from systematic reviews or meta-analyses.

To support understanding, we also included some contextual material published prior to 2010. Inclusion of this additional literature may introduce reporting bias, but inclusion is warranted as this provides a bigger picture view and a wider look at the current evidence available related to breast density. Where needed, further analysis of individual studies included within the reviews has been undertaken to gain the necessary information to comment on findings or make conclusions where the systematic review itself may have been silent (eg, Huo et al.'s 2014 study reported results but did not include substantive discussion). This may mean that studies which could have met the scope of the question may not have been be included because it was not discussed by one of the included reviews.

Some studies included in *Allen + Clarke*'s review discussed factors that can potentially modify breast density including: BMI reduction, parity, hormone replacement therapy or tamoxifen use. Breast density modifiability was out of scope for this review: studies exploring this have not been included. The impact of breast density modifiability on cancer risk and appropriate population-based screening responses that consider modifiability is an interesting and developing area within the breast density literature. It could warrant further investigation and could be useful to inform the discussion around notification and information for women.

The Department of Health has commissioned two other literature reviews to investigate digital breast tomosynthesis' (DBT) role in breast cancer screening and in the assessment and diagnosis of breast cancer. DBT is one of the supplemental tests discussed in this report and further detailed information about its role in screening is provided in our other literature reviews. In addition, *Allen* + *Clarke* has also completed a horizon scan looking at developments relating to the role of magnetic resonance imaging (MRI), molecular breast imaging (MBI) and automated whole-breast ultrasound. Further information about these techniques and their potential role in screening asymptomatic women is provided there.

3. ASSESSMENT OF EVIDENCE AND PRESENTATION OF RESULTS: DENSITY CLASSIFICATION AND THE IMPACT OF BREAST DENSITY ON THE RISK AND MASKING OF BREAST CANCER

The sensitivity and specificity of FFDM alone can vary for different groups of women. FFDM can have significantly lower sensitivity in women who have more dense breasts compared to those with lower breast density (Mousa et al., 2014; this finding is further described in section 3.3 of this report). Because of reduced conspicuity on FFDM for women with more dense breasts (as discussed in section 1.1 of this report), understanding the impact of breast density on risk, masking and the best approach to early detection for women with more dense breasts is important for screening programmes, especially if there are adjunct screening modalities that could improve overall sensitivity and specificity for women with more dense breasts.

A large body of research exploring the relationship between breast density, breast cancer risk and breast cancer exists. This includes systematic reviews, narrative literature reviews and some randomised controlled trials. Chapter 3 of this report discusses systematic review, narrative literature reviews, RCTs, prospective cohort and case-control evidence on:

- the best (and validated) ways to measure breast density
- the established increase in risk of breast cancer for women with more dense breasts, the relative risk of breast cancer by age and by breast density, and how (or if) the association between breast density and risk changes with adjustment for age
- the degree to which breast density masks breast cancer in modern digital mammography, and
- the role of supplemental tests in the early detection of breast cancer in asymptomatic women with dense breasts.

The discussion for each area of interest includes a description of the number of systematic reviews, narrative literature reviews and prospective studies identified, a statement about the overall quality of the studies, and a summary of the results. Detailed study tables (including those drawn from the systematic reviews) provide additional material about study population, methodology, intervention, comparator and/or key results.

Definitions used in this review

Sensitivity: The percentage of women who are correctly identified as having breast cancer.

Specificity: The percentage of women who are correctly identified as not having breast cancer.

Recall rate (RR): The percentage of patients recalled from screening examinations who were assessed as needing additional imaging.

Positive predictive value 1 (PPV₁): The percentage of all positive screening examinations that result in a diagnosis of cancer within one year of screening.

Cancer detection rate (CDR) from screening: The number of cancers correctly detected per 1000 screening examinations (i.e., the number of true positive/number of screening examinations).

3.1. Classifying and validating breast density

High mammographic density is relatively common. Population-based data estimates that approximately 10% of women have almost entirely fatty breasts (BIRADS 1), 40% of women have scattered fibroglandular densities (BIRADS 2), another 40% have heterogeneously dense breasts (BIRADS 3), and 10% have extremely dense breasts (BIRADS 4). Dense breasts are defined as either heterogeneously dense (BIRADS 3) or extremely dense (BIRADS 4). Thus, using BIRADS, approximately 50% of the population undergoing mammography would be categorised as having dense breasts (Breast Cancer Surveillance Consortium, 2013). These proportions tend to change with age, with younger women being more likely to have more dense breasts.

As noted in its position statement, the BSA program:

"aims to provide women with accurate and useful information so that they can make informed decisions about their own breast health and their decision to participate in screening."

Having a validated and consistent measure of breast density is an important starting point when considering the role of breast density in screening. Breast density can currently only be determined by mammographic imaging. Breast density can be measured in two ways:

- 1. Through a qualitative visual assessment based on analysing a mammographic image of the breast to make an estimate of density, which is completed by a radiologist or screen-reading breast physician (or similarly qualified and experience health practitioner); or
- 2. By using commercially-available computer software to assess breast parenchymal patterns and provide a density score.

The BSA's 2016 position statement reported uncertainty about the best way to measure and validate breast density. A range of different models to determine breast density exist but overall specific limitations associated with the qualitative and subjective nature of visual assessment can lead to variability in inter- and intra-reader interpretation. While not mentioned in the position statement, natural variability based on hormone levels, genetic factors, parity, use of oestrogen, place in menstrual cycle, use of tamoxifen, and weight may also contribute to variability in breast density. Because of this variability, a woman may receive different breast density assessments depending on the reader or the point in time that a mammography is conducted (even if the different mammograms are read by the same person). As at 2016, computer algorithms also require additional development to consistently and accurately report breast density (BreastScreen Australia, 2016).

Our inclusion criteria for studies classifying and validating breast density was limited to systematic reviews, narrative reviews, randomised control trials (RCTs), and prospective cohort or casecontrol studies. We identified one systematic review (covering 24 studies), five narrative literature reviews (covering 515 studies) and eight prospective cohort or case-control studies that reported on ways to measure and validate breast density.

Systematic reviews

One review: Melnikow et al. (2016)

Narrative literature reviews

Five reviews: Mousa et al. (2015); Ng and Lau (2015); Freer (2015); Hooley (2015); Destounis et al. (2017a)

Prospective cohort or case-control studies

Eight studies: Astley et al. (2018); Busana et al. (2016); Duffy et al. (2018); Eng et al. (2014); Jeffers et al. (2017); Sartor et al. (2016); Winkel et al. (2015); Winkel et al. (2016)

There is strong evidence as to how much the measurement of density has changed since it was first reported. There is evidence that there is inter- and intra-reader variability when using visual density assessment methods. There is limited evidence suggesting that automated computer-based density measurements can provide consistent, reproducible, and objective results. There is no strong evidence or consensus as to the best way to classify breast density.

Key findings about the measurement and classification of breast density

Breast tissue comprises skin, blood vessels, ductal and stromal elements of the glands (which appear radio-opaque or white on mammography) and fat (which appears radiolucent or black on mammography). Mammographic breast density is defined as the relative amount of radio-opaque (white) elements to radiolucent (black) fat on the image. Increase in the proportion of radio-opaque elements leads to greater mammographic breast density.

High mammographic density is relatively common. One of the most common methods currently used to report breast density is the American College of Radiologists' BIRADS system. BIRADS estimates indicate that approximately 10% of women have almost entirely fatty breasts (BIRADS 1), 40% of women have scattered fibroglandular densities (BIRADS 2), another 40% have heterogeneously dense breasts (BIRADS 3), and 10% have extremely dense breasts (BIRADS 4). Dense breasts are defined as either heterogeneously dense (BIRADS 3) or extremely dense (BIRADS 4). Thus, approximately 50% of the population undergoing mammography could be categorised as having dense breasts. In addition, the same women can be classified as having dense or fatty breasts depending on how the results are read or interpreted. This can then affect clinical decision making around the information women receive on whether they should undergo supplementary screening.

There are six common systems used to classify breast density: BIRADS, Wolfe, Tabár, semiautomated visual estimation (eg, Cumulus), automated area-based methods, and volumetric estimation (eg, Volpara). The BSA position statement on breast density states that there is no consensus on the best measure of breast density. The evidence reported in this literature review still finds no consensus about which method is the most accurate. All classification systems have been shown to have high sensitivity in detecting density. All systems have been shown to have inter- and intra- report variability, particularly when categorising less dense breasts. This is because even though each system is underpinned by semi-objective measures, assessment still requires a reader's subjective assessment. Newer technologies such as fully-automated assessment methods (eg, Volpara) reduce this variability and have been found to have a strong association with breast cancer risk, but further work to develop consistent algorithms is still required.

Evaluating the impact of breast density on cancer risk and clinical outcome for screen-detected cancers requires thorough studies with consistent mammographic procedures, standardised methods of density measurement and breast density classification, as well as a standardised definition of high breast density; however, there is currently no consensus on any of these factors. This results in variations in estimates of the association between breast density and breast cancer risk, depending on the screening procedures and assessment methods used. These findings are consistent with the 2016 BSA position statement on the measurement and classification of breast density. The uncertainty described in the BSA's 2016 statement remains.

Breast density is measured as the absolute amount of dense or white areas in the breast (dense area) or a proportion of the mammogram that is composed of dense tissue (percent density). There are six main methods and scales used to classify breast density. These systems rely on the

subjective reporting of the breast composition, looking for mammographic parenchymal patterns. Conventional classification methods include the BIRADS, Wolfe and Tabár systems. BIRADS is the most widely used system for classifying breast density (and is the system used in most of the studies reported in this literature review, and reporting of other breast cancer research that investigates the impact of breast density) but there is no one preferred or best/most accurate measure of breast density. A summary of the different methods is provided in Box 1.

None of the systematic reviews identified for this literature review reported on whether certain breast density classification systems were more or less accurate for different population groups stratified by age.

	The breast parenchyma is given a score of 1–4 or A-D:
BIRADS	 1/A = Predominantly fat (<25% glandular) 2/B = Scattered fibroglandular densities (approximately 25–50% glandular) 3/C = Heterogeneously dense (approximately 51–75% glandular) 4/D = Extremely dense (>75% glandular)
BIRADS (5 th Ed)	 As of 2013, BIRADS was updated to remove the percentages: A. The breast is almost entirely fatty. Mammography is highly sensitive in this setting. B. There are scattered areas of fibroglandular density. The term density describes the degree of x-ray attenuation of breast tissue but not discrete mammographic findings. C. The breasts are heterogeneously dense, which may obscure small masses. Some areas in the breasts are sufficiently dense to obscure small masses. The breasts are extremely dense, which lowers the sensitivity of mammography.
Wolfe	The breast parenchyma is divided into four risk patterns: N1 = Predominantly fat P1 = Mainly fat with a few prominent ducts P2 = Prominent duct patterns involving at least one half of the parenchyma DY = Extremely dense
Tabár	The breast parenchyma is divided into five risk patterns based on four mammographic building blocks: Nodular, linear, homogeneous and radiolucent tissue, respectively: I = [25, 15, 35, 25%] II = [2, 14, 2, 82%] III = Similar to II in composition + periductal fibrosis IV = [49, 19, 15, 17%] V = [2, 2, 89, 7%]
Visual estimation (percent density)	Visually quantifies the proportion of the breast area occupied by the fibroglandular dense tissue and represents it as a percentage ranging from most fatty (0%) to most dense (>75%). The ranges are: 0%; <10%; 10–25%; 26 – 50%; 51 – 75%; and >75%.
Cumulus	Interactive thresholding software that relies on the user to select the whole breast and dense tissue areas on digitized mammographic images. It calculates the pixel sizes of selected areas based on a grey scale and converts the results to square centimetres: Percent dense area = dense area/whole breast area Non-dense area = whole breast area - dense area
Volumetric measure (eg, <i>AutoDensity</i>)	<i>AutoDensity</i> automatically identifies the breast area in the mammogram and classifies breast density in a similar way to <i>Cumulus</i> but is stand-alone.

Box 1: Breast density classification and measurement system (Huo et al., 2014; Mousa et al., 2014)

Visual density assessment

The first qualitative classification of mammographic density patterns was described by Wolfe in 1976. Wolfe measured the percentage of the breast containing radiographic densities on a continuous scale with the use of a polar planimeter. A modification of this method was proposed by Tabár based on relative proportion of specific mammographic building blocks.

The BIRADS classification (and later BIRADS 5th edition) was introduced as a more quantitative and standardised measure due to the lack reproducibility of the pattern-based methods. The BIRADS 5th edition redefines breast density determination and does not rely on quartile/percentage distribution; instead, it defines breast density according to the presence of a region of confluent fibroglandular tissue that may mask and obscure an underlying cancer (Hooley et al., 2017). Because of this, it is predicted that with the new BIRADS 5th edition breast density determination guidelines, it is possible that more women will be classified as having dense breast tissue (Winkler et al., 2015). It is now the most widely used method of measuring breast density in clinical radiology practice (Gram et al., 2005).

Another semi-quantitative approach to density measurement involves a visual estimation of the breast density using a Visual Analogue Scale (VAS). Readers mark along a continuous scale that represents 0–100% density, and these score sheets can then be scanned through software to obtain the percent breast density (Destounis et al., 2017a).

One consideration in the visual assessment of breast density includes the impact of inter- and intraobserver variability on classification and the impact of changing definitions which may result in different density findings for individual women, and which may affect the overall consistency of research findings between those studies using the BIRADS 4th edition definition and those using BIRADS 5th edition. Regardless of the classification system used, there is considerable inter- and intra-observer variability in the subjective classification of breast density (Freer, 2015; Ng and Lau, 2015). Melnikow et al. (2016) reviewed the consistency of categorical BIRADS breast density determinations in large, community practice-based studies in the United States. BIRADS density assessments at a population level were generally consistent across consecutive exams by the same or different readers. There was however variation for individual women. Approximately 80% of exams received a "2" or "3" BIRADS density assessment (that is, most women had scattered or consistently dense breasts, but not extremely dense or very fatty breasts). Categories 2 and 3 were also most likely to be reassessed differently, whether on a separate reading of the same exam or on a subsequent examination, and whether read by the same or a different reader. As a result, across three studies, 13–19% of women were reclassified from "non-dense" to "dense" or vice versa. In these instances, subsequent screenings could provide inconsistent information for the same woman in the span of 2 to 3 years (Melnikow et al., 2016; Lucas et al., 2010; the State of Connecticut, 2009).

Semi-automated visual density

Due to the limitations of visual density assessment, less subjective and more quantitative measures are being developed. One alternative to visual density systems is Cumulus, a semi-automated computerised measure of dense tissue area. Cumulus uses reader-based thresholds to define the breast edge and regions of density on a digital or digitised mammogram. It still requires the reader to select the area they consider dense. Other measures are also obtained, including the total breast area, the non-dense area and the dense area. The percent density is calculated by dividing the dense area by the total breast area. The use of Cumulus is likely to increase as more digital studies are reported (Destounis et al., 2017a).

A study by Winkel et al. (2015) compared the inter-rater reliability of breast density estimates from visual density assessment methods (BIRADS and Tabár) with a semi-automated area-based percent mammographic density method (PMD). In this study, two readers (one senior radiologist and one resident radiologist) assessed breast density with each assessment method, using digital mammographic images. The sample was obtained from a cohort of 14,736 women who attended biennial routine screening in Copenhagen, Denmark, in 2007, and who had a negative screening mammogram; women were followed up until 2010. In total, 122 women who developed cancer

during the study period and 262 matched controls were identified for the study. Good levels of absolute agreement were found when categorising breast density using BIRADS (77.3%) and Tabár (74.7%), with kappa values also suggesting substantial inter-rater agreement (0.68 and 0.65 for BIRADS and Tabár, respectively). A high level of agreement was also found using PMD (r = 0.94, ICC = 0.93), with at least 95% of the differences being within the range of one percent density quartile.

No significant difference in inter-rater agreement was found for controls versus cases. There were, however, differences in the trends in disagreements between readers depending on the method used. For BIRADS, disagreement was most pronounced for the borderline category 2 and 3 cases, with consistency the lowest in category 3 (62%); this finding aligns with results from Melnikow et al. (2016). For Tabár, discrepancies were most common for the borderline PI/PIV cases, and systematic disagreements were also found when classifying women as PI or PII. Disagreement levels were low using the PMD method but there were some differences in results caused by variations in what was considered to be dense area, particularly in the less dense breasts. Overall, the authors concluded that fully-automated assessment methods were needed to overcome the subjectivity of manual methods, as estimates of the association between breast density and risk of developing breast cancer are likely to vary across density assessment approaches.

Area methods

Many groups have developed automated area-based methods of breast density assessment, effectively taking out the 'reader' component of the Cumulus methods; however, these methods are predominantly used in research rather than clinical practice. One example is iReveal®, which uses commercially-available automated algorithms that compute area density and then classify density into BIRADS-analogous categories (iCAD, 2018).

Volumetric methods

More recent methods have harnessed the use of digital mammography to automatically record planar and volumetric measure. Examples of this include Volpara and Quantra. These methods are more efficient and reliable than the conventional methods listed above because they take less time to report and show improved classification outcomes (Huo et al., 2014).

A recent study by Sartor et al. (2016) utilised data from the Malmö Breast Tomosynthesis Screening Trial to assess the consistency of mammographic breast density ratings when made manually by radiologists (BIRADS 4th Edition, categories 1-4) compared with a fully-automated volumetric assessment method (Volpara). FFDM data from 8426 women (mean age = 58 years) was prospectively assessed by five radiologists using BIRADS and then retrospectively assessed using Volpara. Women with known breast implants were excluded from the study due to known difficulties in measuring volumetric breast density in these women. Results showed a good level of consistency between radiologists' BIRADS ratings (ratings agreed on 80.9% of cases; weighted kappa 0.77, 95% CI 0.76-0.79). There was a pattern of increasing mean percentage volumetric density by BIRADS categories (4.1%, 5.7%, 10.9% and 22.1%, for BIRADS categories 1,2,3 and 4, respectively); however, there was a spread of percentage densities across each BIRADS category, leading to moderate overall levels of agreement between the two assessment methods (57.1% observed agreement; kappa 0.55, 95%CI 0.53-0.56). Notably, levels of agreement were highest for the densest breasts (BIRADS 4; 85.1% observed agreement), with much lower but consistent levels of agreement for the remaining categories (60.9%, 50.2% and 57.3% for BIRADS categories 1, 2 and 3, respectively). This replicates the finding that less dense breasts are harder to consistently categorise, as reported in Winkel et al. (2015). The authors concluded that radiologists evaluate breast density differently to automated systems (with Volpara being more likely to categorise women in the densest breast category than radiologists); however further studies are needed to assess whether either method can more accurately predict breast cancer risk.

3.1.1. What does breast density mean for the detection of breast cancer?

Current evidence suggests that breast density is associated with increased risk of breast cancer (as discussed in section 3.2). That said, it is difficult to make conclusions about how the density classification system affects the association between density and breast cancer risk. Destounis and colleagues (2017a) described how some studies have applied multiple breast density measurement methods on the same cohort of women, allowing for direct comparisons to be made. Researchers involved in the Predicting Risk of Cancer at Screening (PROCAS) study found visual assessment methods to have a greater association with cancer risk, both for screen-detected as well as future cancers (Astley et al., 2016). That said, an update of this study (Astley et al., 2018) concluded that visual density assessment is impractical for population-based screening, and that fully-automated assessment methods (including Volpara and Densitas) provide a robust and practical alternative method of risk stratification. Similarly, researchers at the Mayo clinic (Brandt et al., 2016) investigated FFDM examinations from one of four sites within the San Francisco Mammography Registry. The study found moderate agreement when comparing visual assessment with automated methods (Volpara and Quantra) for BIRADS categorisation, but found differences of up to 14% in dense tissue classification. They also found BIRADS to produce a higher OR than volumetric methods. Destounis (2017a) noted that such an association may not be replicated with a different set of readers.

Further case-control studies were identified that supported the use of fully-automated density assessment methods for risk stratification. Winkel et al. (2016) compared the association between different breast density or breast texture assessment methods (BIRADS, Tabár, and a fullyautomated mammographic texture resemblance marker [MTR]) and breast cancer risk. The study used data from a cohort of 14,736 women with a negative mammogram from a population-based screening programme conducted in Copenhagen, Denmark in 2007. Women were followed up for 12 months following screening, and a sample of women who ended up being diagnosed with invasive breast cancer were identified (n = 121 cases). Two controls for each case were then identified, matched using age and incidence density sampling (n=259 controls). Digital mammograms were assessed using each of the three assessment methods. Table 4 (overleaf) shows the results of the study. All assessment methods showed the risk of women with denser breasts developing cancer was three to four times higher than the risk for women with less dense breasts, although many density categories (including the densest Tabár category) were not significantly different than the comparison group in terms of their associated risk. The different assessment methods did not differ significantly in terms of overall ability to predict breast cancer cases, as measured by AUC values. The authors concluded that breast cancer risk may be attributable to different mammographic features captured by the three assessment methods. This study underscores the importance of consistency in assessment methods when evaluating the relationship between breast density and risk, and provides support for the use of automated assessment methods as a replacement for manual assessment approaches.

Assessment method	Cases/controls (n)	OR (95%CI)	<i>p</i> -value	AUC (95%CI)
BIRADS				0.63 (0.57-0.69)
1	30/107	1 (reference)	-	
2	31/73	1.53 (0.85-2.75)	NS	
3	37/57	2.37 (1.32-4.25)	.004	
4	23/22	3.93 (1.88-8.20)	<.001	
Tabár				0.65 (0.59-0.71)
PI	38/96	1.81 (0.96-3.42)	NS	
PII	18/83	1 (reference)	-	
PIII	9/13	3.23 (1.20-8.75)	.021	
PIV	49/51	4.40 (2.31-8.38)	<.001	
PV	7/16	1.97 (0.70-5.57)	NS	
MTR				0.63 (0.57-0.69)
Quartile 1	19/65	1 (reference)	-	
Quartile 2	24/65	1.27 (0.63-2.54)	NS	
Quartile 3	21/65	1.11 (0.54-2.25)	NS	
Quartile 4	57/64	3.04 (1.63-5.67)	<.001	

Table 4. Association between mammographic density assessment methods and breast cancer (modified fromWinkel et al., 2016)

NS = not statistically significant

Providing further evidence for the validity of automated measurement approaches, Eng et al. (2014) compared the level of association with breast cancer risk for a number of area-based density measurement approaches (including BIRADS, Cumulus and fully-automated Image-J) and fullyautomated volumetric methods (including Volpara, Quantra and singe energy x-ray absorptiometry [SXA]). Using 3168 digital mammography images from 414 cases and 685 controls, they found Volpara showed the highest association with breast cancer risk (OR = 1.82, 95%CI 1.51-2.20, for each SD increase in percent density); this was statistically significantly higher than associations with all other measurement approaches except Cumulus (OR = 1.63, 95%CI 1.37-1.93). All six volumetric measurement approaches found positive associations between percent density and breast cancer risk, with women in the top percent density quintile (or BIRADS 4) having between 2.55 to 8.26 times the risk of women in the lowest quintile (or BIRADS 1), depending on the measure being used. The results of this study further highlight the importance of using consistent density measurement approaches when comparing findings across studies. This study is also important as it again shows that fully-automated approaches to measuring breast density (eg, Volpara) can provide valid alternatives to more labour-intensive approaches (eg, BIRADS and Cumulus).

This validation of fully-automated breast density assessment methods was supported by a further two studies. Jeffers et al. (2017) compared three breast density measurement approaches (BIRADS, Cumulus and Volpara) using FFDM images sourced from 125 cases and 274 matched controls who underwent screening during 2004-2013. Pre-diagnostic mammograms were used for the women diagnosed with breast cancer. This study found good levels of agreement between the percent density estimates produced by Cumulus and Volpara (r = .82) but only moderate level of agreement between density categorisation based on BIRADS and Volpara (kappa = 0.47). This matches the

findings of Sartor et al. (2016) discussed above. Jeffers et al. (2017) also found that compared to women in the second quartile for percent density, women in the highest quartile had a significant increase in odds of cancer based on Cumulus estimates (OR = 2.00, 95%CI 1.01-3.98, p = .047), but a non-significant increase in odds based on Volpara estimates (OR = 1.71, 95%CI 0.83-3.53, p = .147). Results were also mixed for BIRADS categorisations. When compared to women categorised as BIRADS 2, women categorised as BIRADS 3 had significantly increased odds of developing cancer (OR = 2.35, 95%CI 1.34-4.12, p = .017), but women categorised as BIRADS 4 did not have a significant increase in odds of cancer (OR = 2.06, 95%CI 0.85-4.97, p = .107). Overall, there was no significant difference in the ability of the different assessment methods to distinguish cases from controls (AUC = 0.68, 0.64 and 0.66 for BIRADS, Volpara percent density and Cumulus percent density, respectively). Although the small sample size means that findings need to be interpreted with caution, the mixed results from this study highlight the influence that choice of assessment method can have on estimates of the association between risk and breast density, as well as the impact that the choice of comparator group has on the size of the risk estimates. It also provides additional support for the viability of fully-automated methods as a replacement for more manually intensive approaches to breast density assessment.

A further study, Duffy et al. (2018), compared the visual assessment of breast density percentage with two fully-automated methods (Volpara and Quantra). They used a sample of 6020 routine screening cases (1158 of whom had breast cancer) and 1040 high-risk screening cases (two of whom had breast cancer) from the TOMMY trial (TOMosynthesis with digital MammographY in the UK Breast Screening Programme of the National Health Service); all cases had been recalled for further assessment. Consistent with the findings from Eng et al. (2014), Duffy et al. found that density assessment using Volpara showed the strongest association with breast cancer risk, equating to a 3% (95%CI 1-5%) increase in the odds of cancer per additional 10cm³ of dense tissue. Results for Quantra were similar, but slightly weaker (although not significantly different). This study provides further support for the use of fully-automated methods of assessing breast density and concluded that breast density could be a trigger for more intensive imaging techniques. It is important to note, however, that the use of a recalled sample in this study has the potential to inflate the measured association between breast density and risk, due to the sample being higher risk than the general screening population.

A study by Busana et al. (2016) also highlighted the importance of mammography image type (raw versus processed) when evaluating the link between breast density and breast cancer risk. Busana et al. compared the performance of Cumulus with a fully-automated density assessment method (Laboratory for Breast Radiodensity Assessment [LIBRA]) using both raw and processed mammographic images from 414 breast cancer cases and 684 controls. Findings showed that percent density measurements from the two assessment methods were more strongly correlated for the processed (r = .74, p < .001) compared with the raw (r = 0.65, p < .001) images. The association between percent density and breast cancer risk was also stronger for processed images than for the raw images. For each one SD increase in percent density, risk increased by 1.55 (Cumulus, 95%CI 1.29-1.85) or 1.32 (LIBRA, (95%CI 1.08-1.61) times based on processed images, compared with 1.35 (Cumulus, 95%CI 1.14-1.60) or 1.17 (LIBRA, 95%CI 0.99-1.37) times based on raw images. The authors concluded that the same digital image type and breast density assessment method should be used when comparing the impact of breast density across populations or across time in the same population.

In addition to evaluating the association between different breast density measurement approaches and breast cancer risk, it is also important to understand how different assessment methods influence the evaluation of breast density's impact on screening sensitivity. Table 5 (overleaf), modified from Mousa et al. (2014), summarises the impact of breast density on detecting

breast cancer using different density classification methods. BIRADS was the most common classification used. All classification (in all studies) reported a difference of similar magnitude between the sensitivity to detect breast cancer and breast density (i.e., the ability to detect cancer decreases as breast density increases with the 'most dense' categories having the lowest sensitivity). Further information about cancer detection is provided in section 3.3.

Not surprisingly, there is no consensus among clinicians or researchers as to what is the best measure of breast density or threshold for what constitutes high density. As a result, studies present density using all the different classification systems, making comparison difficult.

Study	Number of women	Density classification system	Aims	Sensitivity results			
Chiu et al. (2010)	15,658	Tabár	Baseline breast density effect on cancer incidence, stage, mortality and the natural course of it. No statistical comparison was completed.	Fatty: 82	Dense: 62.8	Chiu et al. (2010)	15,658
Cook et al. (2010)	638,947	BIRADS	Impact of women's breast cancer risk factors on radiologists' performance. No statistical comparison was completed.	Sensitivity OR BIRADS 1: 1.55	Sensitivity OR BIRADS 2: 1	Sensitivity OR BIRADS 3: 0.58	Sensitivity OR BIRADS 4: 0.29
Cawson et al. (2009)	1569	BIRADS	Comparison of current best practice with computer-aided-detection. No statistical comparison was completed.	BIRADS 1:90	BIRADS 2: 90	BIRADS 3: 93	BIRADS 4: 75
Osako et al. (2007)	165	Japanese 4 grading BIRADS	Comparison between ultrasound and mammography for palpable and nonpalpable breast cancer in women aged 30–39 years. No statistical comparison was completed.	BIRADS 1: 100	BIRADS 2: 100	BIRADS 3: 82	BIRADS 4: 86
Osoko et al. (2007)	165	Japanese 4 grading BIRADS	Comparison between ultrasound and mammography for detecting invasive and non- invasive breast cancer in women aged 30–39 years. No statistical comparison was completed.	BIRADS 1&2: 88	BIRADS 3&4: 62		
Kriege et al. (2006)	1779	Percent BIRADS	Factors affecting sensitivity and specificity of screening mammography and MRI in women with an increased risk of breast cancer.	BIRADS 1&2: 46.7	BIRADS 3&4: 37.9	ρ = 0.58	
Kavanagh et al. (2005)	First round: 1086 Subsequent round: 471	Cumulus	Effect of hormone replacement therapy and mammographic density on mammographic sensitivity. No statistical comparison was completed.	Percent density: <u>></u> 0- 10%: First round: 85.4 Subsequent round: 77.8	Percent density: 10- 25%: First round: 80.2 Subsequent round: 70.1	Percent density: 25- <50%: First round: 60.7 Subsequent round: 60.5	Percent density: <u>></u> 50%: First round: 54.8 Subsequent round: 35.3

Table 5. Summary of studies examining the impact of breast density on screening methods and the sensitivity of cancer detection (modified from Mousa et al., 2014)

Study	Number of women	Density classification system	Aims	Sensitivity results			
Berg et al. (2004)	111	BIRADS	Diagnostic accuracy of mammography, clinical examination, ultrasound and MRI in preoperative assessment of breast cancer. No statistical comparison was completed.	BIRADS 1: 100	BIRADS 2: 79	BIRADS 3: 70	BIRADS 4: 45
Ciatto (2004)	576	BIRADS	Factors decreasing the sensitivity of mammography in young women. No statistical comparison was completed.	BIRADS 1: 80	BIRADS 2: 80.4	BIRADS 3: 58.3	BIRADS 4: 29.2
Carney et al. (2003)	329,495	BIRADS	The relationships between breast density, age, and use of hormone replacement therapy on mammographic accuracy. No statistical comparison was completed.	BIRADS 1: 88.2	BIRADS 2: 82.1	BIRADS 3: 68.9	BIRADS 4: 62.2
Kolb et al. (2002)	11,130	BIRADS	Comparison between screening mammography, physical examination, and ultrasound and evaluation of the factors that affect this. No statistical comparison was completed.	BIRADS 1: 98	BIRADS 2: 82.9	BIRADS 3: 64.4	BIRADS 4: 47.8
Mandelson (2000)	537	BIRADS	The relationship between mammographic breast density and interval cancer risk. No statistical comparison was completed.	BIRADS 1&2: 80.3	BIRADS 3: 58.8	BIRADS 4: 30.4	
Rosenburg et al. (1998)	109,320	BIRADS	Factors affecting screening mammographic sensitivity and cancer stage at diagnosis. No statistical comparison was completed.	BIRADS 1&2 sensitivity: 85	BIRADS 3&4 sensitivity: 68		
Kerlikowske et al. (1996)	28,271	BIRADS	Effect of age, breast density and family history on the sensitivity of first screening mammography:	Women <50 years and BIRADS 1 & 2: 81.8 <i>p=.79</i>	Women <50 years and BIRADS 3 & 4: 85.4	Women >50 years and BIRADS 1 & 2: 98.4	Women >50 years and BIRADS 3 & 4: 83.7 <i>P</i> <.01
3.2. Risk of breast cancer: the association with breast density

The mechanisms by which breast density affects breast cancer risk are not fully understood. We know that density reflects the proportion of fibroglandular tissue in the breast as opposed to nondense fatty tissue. Furthermore, breast cancers originate in fibroglandular tissue (specifically in epithelial cells), so greater areas of fibroglandular tissue may reflect a greater number of cells that are at risk of carcinogenesis and/or an increased rate of epithelial proliferation (Boyd et al., 2005). It is also plausible that many of the established breast cancer risk factors influence risk through their effect on density. For example, as BMI increases, only the amount of fat (non-dense tissue) in the breast increases or the non-dense tissue increases at a greater rate than the dense tissue. Consequently, while the absolute area of dense tissue remains the same, the total breast area increases, and the percent density decreases (Vachon et al., 2000). These potential causal pathways between breast density and breast cancer raise the risk of developing breast cancer through cumulative exposure to breast density over the lifetime.

Boyd et al. (2007) noted that the decline of density with age parallels that of the rate of breast tissue aging in a model proposed by Pike et al. (1983) to explain the age-incidence curve of breast cancer. In this model, the age-specific rate of breast tissue aging is high between menarche and age at first birth, drops slightly after pregnancies and then considerably after the menopause. Breast cancer incidence rates are related to breast tissue age, which means age could potentially be used as a proxy measure for density.

Our inclusion criteria for the association between breast density and the risk of breast cancer was limited to systematic and narrative reviews, RCTs and prospective cohort or case-control studies. We identified four systematic reviews (covering 31 studies), three narrative literature reviews (covering 166 studies) and 15 prospective cohort or case-control studies that reported on ways to measure and validate breast density.

Systematic reviews

Four reviews: Bae and Kim (2016); Petterson et al. (2014); Bertrand et al. (2013); Yankaskas et al. (2010)

Narrative literature reviews

Three reviews: Hooley (2017); Huo et al. (2014); Colin et al. (2013)

Prospective cohort or case-control studies

Fifteen studies: Assi et al. (2015); Chowdhury et al. (2018); Habel et al. (2016); Kerlikowske et al. (2017); Krishnan et al. (2016); Krishnan et al. (2017); Masala et al. (2017); Maskarinec et al. (2017); Nguyen et al. (2015); Nguyen et al. (2017); Park et al. (2018); Rice et al. (2016); Trieu et al. (2017); Yaghjyan et al. (2015a); Yaghjyan et al. (2015b)

There is evidence that breast density is a risk factor for breast cancer (although much of this evidence predates the literature search undertaken in this review). There is strong evidence that breast density changes with ageing; however, there is weak evidence as to how this is associated with cancer risk. There is moderate evidence that breast density differs due to genetic variation and ethnicity. There is some evidence that density is associated with different biological factors such as receptor subtypes.

In this section, we discuss:

- McCormack and dos Santos Silva's 2008 review establishing the relationship between breast density and breast cancer risk
- Systematic reviews quantifying the relationship between breast density and cancer risk
- Age, breast density and breast cancer risk
- The role of ethnicity in the relationship between breast density and breast cancer risk
- Cancer characteristics, breast density and breast cancer risk
- Genetic links
- Mammographic density phenotypes, and
- Breast density as a modifiable risk factor.

Key findings about breast density and breast cancer risk

Breast density is an established risk factor for breast cancer through cumulative exposure over the lifetime, but the extent to which breast density affects risk for breast cancer is not absolutely established. Many (but not all) studies compare women with a percent density of more than 75% compared to women with a percent density of <5%, with the former group having four to six times higher risk for breast cancer. These studies inflate the breast cancer risk because this risk does not represent that posed to the average women (as these categories are at the extreme ends of the population continuum). When risk is compared between women with heterogeneously or extremely dense breast tissue and with women with average breast density, the relative risk decreases to approximately 1.2 to 2.1.

Despite the lack in standardisation of breast density thresholds, there is still an association between breast density and breast cancer regardless of how breast density is defined. When mammographic phenotypes are examined, percent density area (calculated by dividing the dense area by the total breast area) is generally found to have a stronger association to breast cancer than absolute dense area (i.e., the amount of fibroglandular tissue per mm² or cm²). That said, one large cohort study found that combining information on both absolute dense area and percent density significantly improved risk prediction compared to using the information independently.

The relative risk conferred by breast density in part depends on a woman's other risk factors for breast cancer. Many studies investigating breast density and breast cancer risk (and screening) comprise women with an elevated risk of breast cancer, independent of their breast density (eg, familial risk). Therefore, it is difficult to conclude what the risk and screening options for women with dense breasts and no other moderate or strong risk factors would be and much of the research is silent on this issue. That said, most studies that control for these potential confounding factors find that they do not have a significant impact on the association between breast density and breast cancer risk. This suggests that breast density is an independent predictor of breast cancer risk.

Kerlikowske et al. (2015) reported that breast density should not be the sole criterion for deciding whether supplemental imaging is justified because not all women with dense breasts have high interval cancer rates. Age and breast cancer risk influence screening performance, cancer incidence, and tumour stage at diagnosis. These factors should be considered along with breast density to optimise identification of women with high interval cancer rates or high rates of false-positive results who may benefit from supplemental imaging or alternative screening tests.

There is some evidence that breast density differs due to genetic variation and ethnicity, and that breast density is associated with different biological factors such as receptor subtypes. Increased breast density was found to be a risk factor for most breast cancers subtypes; however, the particular association for each subtype needs to be further explored, as current evidence is mixed regarding the association between breast density and specific subtypes of breast cancer. Similarly, high breast density was found to be associated with gene variation in a number of genes. It is likely that breast density will be affected by several genes that are largely unknown at the present time.

A number of studies were identified that reported women of Asian ethnicity have a lower risk of breast cancer related to breast density than that reported for European women. The reason for these findings are unknown. Further research is needed in women of different ethnicities.

There were limited studies focusing on the relationship between age and density. Findings from those studies suggest that the association between breast density and breast cancer risk (and screening performance) may be stronger for younger women. Even taking this into consideration, the risk of breast cancer remains low and the harms of screening (listed below in this review) are likely to outweigh the small benefits of screening for this population.

3.2.1. McCormack and dos Santos Silva's 2008 review on breast density and cancer risk

An extensive, and influential, review of the relationship between breast density and breast cancer risk was completed in 2008 (McCormack and dos Santos Silva, 2008). *Allen + Clarke*'s literature review was limited to research published between 2010 and 2018; however, to understand the post-2010 material (and the direction taken by the research community), it is important to understand McCormack and dos Santos Silva's findings.

McCormack and dos Santos Silva's (2008) review demonstrated that there is a relationship between breast density and breast cancer risk. They reviewed data on the association of breast density with risk of breast cancer in their systematic meta-analysis of data for more than 14,000 cases (women with more dense breasts) and 226,000 non-cases (women with less dense breasts) from 42 studies. The authors found that having more dense breasts was consistently associated with risk of breast cancer. Women with dense breasts were defined as having a percent density greater than or equal to 50%. The relative risk (RR) of cancer incidence ranged from 2.92 (95%CI 2.49-3.42) to 4.64 (95%CI 3.64-5.91) for women with 50-74% and \geq 75% density, respectively, compared to women with fatty breasts (<5% density). This means that the risk of developing cancer was 2.92 or 4.64 times higher for women with denser breasts compared to women with fatty breasts. The strength of the association between breast density and breast cancer risk was found to be greater than that for most other established breast cancer risk factors, except for age and some genetic factors.

Within McCormack and dos Santos Silva's review, there was no threshold level below which increased density was not associated with increased cancer risk. Based on their findings, if approximately 20% and 10% of premenopausal women have densities of 50% to 74% and \geq 75%, respectively, the population attributable fraction is 26.7% for densities over 75% and 42.8% for densities over 50%. This means that 26.7% of breast cancer cases involving women with densities greater than 75% and 42.8% of breast cancer cases involving women with densities greater than 50% are attributable to breast density. At postmenopausal ages, the corresponding fractions would be 9.8% and 23.2% (based on 10% and 3% of the population with densities of 50-74% and \geq 75%).

The increased cancer risk associated with breast density was found to be independent of other known risk factors for this disease but was confounded by age and body mass index (BMI) (the confounding relationship is explained in further detail below). Importantly, McCormack and dos Santos Silva's combined data suggested that breast density measured at both premenopausal and

postmenopausal ages is a marker of subsequent breast cancer risk. There was no clear evidence that the strength of this association differs between these ages. This means that breast density measured in either early adulthood (20-30 years) or later adulthood (after aged 60 years) is predictive of risk in later life. There was no evidence to suggest that this association does not hold in all studied ethnic groups (European, Asian, and African American women). Future studies based on or including women of other ethnicities would be informative.

3.2.2. Quantifying the relationship between breast density and breast cancer risk

Two more recent narrative reviews have continued to report that women with more dense breasts have increased breast cancer risk compared to women who have less dense breasts. These later studies have attempted to further quantify the magnitude of this risk; however, quantification is challenged by a body of literature that uses a range of different systems to assess, categorise and compare study participants.

A narrative review of 14 prospective and nested case–control studies was completed by Colin et al. (2013) to evaluate mammographic density as a breast cancer risk. Individual study results are provided in Table 6 (see pages 42-43). Details on study selection procedures and quality assurance were not provided, and a range of breast density classifications and thresholds were used in the primary research informing the review. This negatively influences the overall strength of Colin et al.'s findings.

Colin et al.'s overall finding was that the odds of developing breast cancer was higher for women in "the most dense" compared with "the least dense" breast tissue categories. Odds ratios (OR) ranged from 1.5 to 6 across studies, which means that the odds of developing breast cancer was 1.5 to 6 times higher for women with the most dense breasts compared to women with the least dense breasts. This is consistent with McCormack and dos Santos Silva's findings. Of the seven cohort studies included in Colin et al.'s review (Brisson, 1988, Ciatto, 1993, Olsen, 2009, de Stavola, 1990, Torres-Mejia, 2005, Vacek, 2004, Ziv, 2004 and van Gils, 1998), two showed that higher breast density (defined as BIRADS 3 and 4 or BIRADS 2-4) is associated with breast cancer, with ORs reaching a maximum of 2.1 (BIRADS 3 and 4) and 4.2 (BIRADS 2-4). That risk was independent of age, family history of cancer, BMI, use of hormone replacement therapy, menopausal status and race.

The remaining studies (n=7) discussed by Colin et al. (2013) had methodological biases that impacted on the strength of their findings, such as not adjusting risk for the use of hormone replacement therapy. Despite these methodological limitations, the direction of effect was similar to the studies with stronger methodologies. For example, a large cohort study (Brisson et al., 1998) of 48,052 women followed for 11 years found an increased odds of breast cancer in women with high breast density (OR 2.45, 95%CI 2.14–2.81) compared to women with non-dense breasts. However, this result must be taken with some caution. First, the breast density was evaluated by arbitrarily categorising women as having dense or non-dense breasts (derived from BIRADS classification), and secondly, the mammography screening was different according to the first breast density evaluation. In the case of women with fatty breasts, a single mammogram view (mediolateral-oblique or craniocaudal) was always taken at each round of the follow-up whereas two views were taken when the radiologist assessed density as high.

Colin et al.'s review presented a number of studies with high participant numbers that describe a link between breast tissue mammographic patterns and risk for breast cancers. That said, all studies have considerable flaws, including variations in definitions of high breast density and methods of measuring breast density, non-specified modalities of breast cancer diagnosis, and uncontrolled confounding factors.

Huo et al. (2014) undertook a narrative review to investigate more current (2007-2013) literature for breast density to provide an update of breast density and cancer risk. This review covers similar material to the McCormack and dos Santos Silva study (breast density as a risk factor for breast cancer) but follows on by analysing specific factors associated with breast density such as biological and genetic factors. Study selection criteria was not defined by Huo et al. and the analyses and commentary on the studies were not provided, which limits the usefulness of this study overall.

Huo et al. included 119 studies. Studies included research involving women of all ages; however, data were not presented for the risk associated with breast density by different age groups. A variety of breast density classification systems were used including Tabár, Cumulus, BIRADS and computer assisted methods. Table 7 (page 44) describes the 18 studies included as part of the analysis of mammographic density and its association with breast cancer risk. Studies included in Huo et al. mainly had large sample sizes with the smallest study having 358 cases of breast cancer compared to 859 controls (Lokate et al., 2011).

All studies discussed in Huo et al. (2014) found a positive association between increased breast density (as defined by each study) and breast cancer risk, with OR ranging from 1.37 -3.47. This means that the odds of developing breast cancer was 1.37 to 3.47 times higher for women with higher breast density compared to women with lower breast density. Unfortunately, the studies used different density thresholds in their analysis. For example, Boyd et al. (2007) defined women with more dense breasts as density \geq 75%; the odds of these women developing breast cancer was 4.7 times higher than the odds for women with density <10%. On the other hand, Tamimi et al. (2007) and Shepard et al. (2011) compared women with breast density in the highest quartile compared with the lowest quartile. They found that the odds or risk of women in the highest for women in the lowest quartile. The classification of density was more inclusive in this latter study, which potentially led to the lower odds and risk ratios than was found in Boyd et al. (2007). This makes it extremely difficult to pool analyses and provide a more conclusive estimate of the association between risk and breast density.

Research continues to be conducted that adds to the body of evidence regarding the association between breast density and breast cancer risk. For example, Habel et al. (2016) provided estimates of this association in a case-control study nested within the Research Program in Genes, Environment and Health of Kaiser Permanente Northern California. The sample comprised 297 cases and 1149 age-matched controls, all of whom were non-Hispanic White females between the ages of 40 and 74 years; women with breast implants were excluded from the study. Cumulus was used to assess breast density from screening images produced by FFDM. As with the other studies discussed above, they found that percent density was significantly associated with breast cancer risk, with the odds of developing breast cancer increasing 1.70 times (95%CI 1.41-2.04) for every one standard deviation increase in percent density. This association held after controlling for BMI, parity, family history of breast cancer and hormone use. Absolute dense area was also significantly positively associated with breast cancer risk, although this association was weaker than the association for percent density (OR = 1.54, 95%CI 1.34-1.77).

One recent nested case-control study conducted in a Mediterranean population was also identified (Masala et al., 2017). This study sourced their sample from the 10,083 women enrolled in the EPIC Florence cohort, using 136 cases and 635 age-matched controls. Breast density was visually assessed using BIRADS. Compared to women categorised as BIRADS 1, the odds of developing cancer were 1.83 (95%CI 1.12-3.00), 2.29 (1.35-3.89) or 2.68 (95%CI 1.14-6.30) times higher for women categorised as BIRADS 2, 3 or 4, respectively. These associations remained similar after controlling for education, BMI, parity, breast feeding, family history of breast cancer, previous biopsy, and hormone therapy use. The odds ratios found in this study were relatively smaller than

other studies comparing the same breast density categories, however results were likely to be affected by the small sample size (this is suggested by the large confidence intervals associated with each OR).

Table 6. Characteristics of population studies, mammographic assessments, breast density definitions and classifications, in relation to breast cancer incidence (modified from Colin et al., 2013)

Study	Study design	Study participants	No. breast cancers (screening or interval cancers)	Age (mean ± SD) or range (years)	Follow-up screening (years)	Mammographic feature: classification	Definition of high breast density	OR: breast cancer dense versus non-dense (CI)
Olsen et al. (2009)	Cohort study	48,052	1009	50–69	11	BIRADS	>50%	2.5 (2.1–2.8)
Pisano et al. (2008)	Comparative prospective study	42,117	335	47–69	1.25	BIRADS	>50%	Not indicated
Van Gils et al. (2008)	Nested case– control study	922 control group	352	>35	6	Wolfe, PD	>25%	3.3 (1.5-7.1)
Boyd et al. (2007)	Nested case– control study	1112 control group	1112	56.7 ± 9.1	18	Wolfe, PD	>75%	4.7 (3.0–7.4)
Boyd et al. (2005)	Nested case– control study	354 control group	354	40–59	5.25	Wolfe, PD	"The least extensive, The most extensive"	6.0 (2.8-12.3)
Bryne et al. (2005)	Nested case– control study	2152 control group	1880	35–74	16	Wolfe, PD	>75%	5 (3.6-7.1)
Maskarinec et al. (2005)	Nested case– control study	667 control group	607	45–75	4	Wolfe, PD	≥50%	3.6 (2.3–5.6)
Torres-Mejia et al. (2005)	Cohort study	3211	111	≥35	18	Wolfe, PD	DY	3.9 (1.8–8.6)
Vacek & Geller (2004)	Cohort study	61,844	1191	54 ± 12	3.1	BIRADS	>25%	BIRADS 3: 3.0 (2.2-4.0) BIRADS 4: 4.0 (2.8-5.7)

Study	Study design	Study participants	No. breast cancers (screening or interval cancers)	Age (mean ± SD) or range (years)	Follow-up screening (years)	Mammographic feature: classification	Definition of high breast density	OR: breast cancer dense versus non-dense (CI)
Ziv et al. (2004)	Cohort study	44,811	701	54 ± 12	7.5	BIRADS	>75%	2.0 (1.6-2.6)
Ciatto & Zappa (1993)	Cohort study	17,911	40	40–70	5	Wolfe	P2 + DY	2.0 (1.4-13.3)
De Stavola (1990)	Cohort study	4954	69	35–75	7	Wolfe	P2 + DY	1.5 (0.9-2.7)
Brisson et al. (1988)	Cohort study	55,053	3392	35–74	9	BIRADS	Glandular + homogeneously dense	Not indicated
Van Gils et al. (1998)	Cohort study	19,152	403	50–69	19	Wolfe, PD	>25%	Not indicated

Abbreviations: PD = percent density; P2 = prominence involving more than a quarter of the breast and often with a nodular component; DY = increased density of the parenchyma with or without areas of nodularity (Wolfe's classification)

Table 7. Studies included in the Huo et al.'s (2014) review

Study	Study design	Study population	Matching variables	Variables adjusted for in analysis	No. cases: non- cases	Age (years)	Mammogra phic feature	Key finding
Tice et al. (2013)	Cohort	Breast Cancer Surveillance Consortium (BCSC), USA, 1994-2009	N/A	Age, race, HRT, BMI	1,359: 41,459	30+	BIRADS	Combination of atypical hyperplasia, and HD was associated with high risk of BC (HR 5.34, 95%CI 3.52–8.09, <i>p</i> < 0.001)
Linton et al. (2013)	Case-control	Sisters from Breast Cancer Family Registry, USA; Weekend to End Breast Cancer, Canada; Canadian twin study	Age at menopause	Age, BMI, menopausal status, parity, HRT	687: NK	Mean 50	Cumulus	PD was associated with an increased risk of BC when comparing cases to sister controls (interquartile OR = 2.19) and to unrelated controls
Yaghjyan et al. (2013)	Nested case- control	Nurses' Health Study, USA	Age at time of blood collection, menopausal status, HRT, follow-up time	Age (at diagnosis, menopause, at first birth), BMI, parity, HRT, menopausal status, smoking, alcohol, family history	1,045: 567	30–55	Cumulus	The magnitude of the association between PD and BC remains similar for up to 10 years after the first mammogram
Pollán et al. (2013)	Case-control	Navarre Breast Cancer Screening Program, Spain, 1990-2004	Screening round, year of birth, place of residence	Age (current, at first birth, at menopause), menopausal status, family history, previous biopsies	1,172: 1,831	45–65	Boyd semi- quantitative scale	OR for PD >75% compared to PD <10% was 3.47 for ductal carcinoma in situ, and 2.95 for invasive tumours
Cecchini et al. (2012)	Cohort	National Surgical Adjuvant Breast and Bowel Project, USA, 1999-2004		Age, BMI, smoking, diabetes, treatment group	13,409: 6,338	NK	BIRADS	High BIRADS density was associated with increased BC risk
Razzaghi et al. (2012)	Case-control	Carolina Breast Cancer Study, USA, 1993-2001	Age, BMI, HRT, parity	Age (current, at menarche), race, BMI,	1,019: 1,292	20–74	BIRADS	HD is associated with increased BC risk, and the effect measure

				menopausal status, family history, HRT				modification by race was not significant
Lokate et al. (2011)	Cohort	Dutch contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC), 2001- 2006	N/A	Age (at menopause, at first birth), parity, HRT, oral contraceptive, family history, BMI	358: 859	49–70	Cumulus	HD tissue and fat tissue were independently associated with higher BC risk (OR 2.8 and 2.4 respectively)
Pettersson et al. (2011)	Nested case- control	Nurses' Health Study (1976-1990) and Nurses' Health Study II (1989- 1999), USA	N/A	Age (at menarche, at first birth, at menopause), BMI, family history, parity, HRT	1,424: 2,660	Mean 47	Cumulus	HD tissue was associated with a greater risk of BC (OR = 2.01 for premenopausal and OR = 2.19 for postmenopausal women) whereas non-dense area was associated with decreased risk of BC
Shepherd et al. (2011)	Case-control	Screening programme at the California Pacific Medical Center, USA, 2004- 2006	Age, race	Age at first birth, family history, BMI, previous biopsies	275: 825	18+	CAM	Fibroglandular volume and PD were associated with BC risk (highest vs. lowest quintile: OR 2.5 and 2.9 respectively)
Stone et al. (2010)	Case-control	Cambridge and Norwich Breast Screening Programs, UK, 1995-2003	Age	N/A	634: 1,880	50–75	CAM	Dense area was a better predictor on BC risk than PD
Chiu (2010)	Cohort	Koppaberg Randomised Control Trial, Sweden	N/A	Age, BMI, tumour size, grade, nodal status	15,658: 1,045	45–59	Tabár	Dense tissue was associated with BC incidence (RR = 1.58) and BC mortality (RR = 1.91)
Martin (2010)	Nested case- control	National Breast-Screening Study (1984-1990), British Columbia Screening Mammography Program (1988-1999), Ontario Breast-Screening Program (1992-1998)	Year and age at entry to screening programme, study site	Age (current, at first birth, at menopause, at menarche), family history	1,164: 1,158	Mean 56	CAM	Density was associated with increased BC risk. (OR 1.37 for having one affected relative, 2.45 for having ≥2 affected relatives)

Stone (2009)	Cross- sectional	International Breast Cancer Intervention Study I trial, 1992-2001	N/A	Age, BMI, menopausal status, study site	799:11:00	35–70	Cumulus	PD was negatively associated with age, BMI, menopausal status, predicted BC risk and study site; however, dense area was negatively associated with only age and BMI
Olsen (2009)	Cohort	Mammography Screening Program, Denmark, 1991- 2001	N/A	Age	989: 133,651	50–69	BIRADS	The OR of an interval cancer for women with dense breasts was 1.62, and age-adjusted RR was 2.45 for BC incidence
Kavanagh (2008)	Case-control	Mammography Screening Program, Australia, 1994- 1996	N/A	Age, HRT, family history	1,706: 5637	50–69	САМ	The risk of large screen-detected cancers was almost 3-fold for the second quintile, and about fourfold for the third and fourth quintiles compared with low quintiles of density
Tamimi (2007)	Nested case- control	Nurses' Health Study, USA, 1989-1990	Age, fasting status at time of blood collection	Age (at first birth, at menopause, at menarche), BMI, parity, HRT	253: 520	30–55	Cumulus	The relative risk of BC associated with density (RR for highest quartile compared with lowest quartile = 3.8
Boyd (2007)	Nested case- control	National Breast-Screening Study (1984-1990), British Columbia Screening Mammography Program (1988-1999), Ontario Breast-Screening Program (1992-1998)	Age (current, at entry to programme), study site	Age (current, at menarche, at menopause), BMI, parity, menopausal status, HRT, family history	1,112:97	40–80	САМ	Women with density ≥75% had an increased risk of BC (OR 4.7) than women with density <10%. The increased risk persisted for ≥8 years after study entry and was greater in younger than in older women
Vachon (2007)	Case-control	Mammography Screening Program, Mayo Clinic, USA, 1997-2001	Age, final screening exam date, menopausal status, time between baseline and final mammogram, number of prior mammograms	Age at first birth, BMI, menopausal status, family history, parity, HRT	372: 713	50+	Cumulus	Density represented a general marker of BC risk that is not specific to breast side or location of the eventual cancer

Abbreviations: BC = breast cancer; HD = high density; HRT = hormonal replacement therapy; PD = percent density;

3.2.3. Breast density as an independent risk factor for breast cancer

High breast density has been shown to be an independent risk factor for breast cancer, but the degree of risk remains controversial due to limited research plus the historic lack of standardised breast density classification criteria. Huo et al. (2014) and Colin et al.'s (2013) studies show that compared to women with predominately fatty breast tissue, women with extremely dense breasts have up to 4 to 6 times increased risk for breast cancer. However, as stated earlier, only approximately 10% of women have predominately fatty or extremely dense breasts. Most women have scattered fibroglandular tissue or heterogeneously dense breasts, each accounting for approximately 40% of the population. Relative risk among the general population is therefore likely to be lower than the estimates derived using women with fatty breasts as the comparator. Comparing women with heterogeneously or extremely dense breast tissue with women with average breast density, the relative risk decreases to approximately 1.2 and 2.1, respectively (Hooley et al., 2017). Taking methodological limitations into account, compared with other known risk factors, having extremely dense breast tissue appears to place a woman at intermediate risk of breast cancer.

This need to differentiate risk at the extremes of density was highlighted by a recent study conducted on a small sample of Australian women, 354 with breast cancer and 944 age-matched controls (Nguyen et al., 2017). In this study, breast density was measured with Cumulus using three different thresholds for dense area detection: the standard Cumulus threshold, and then two increasingly higher thresholds (i.e., identifying areas that were more dense than standard thresholds). The researchers found that risk of breast cancer was more strongly associated with dense area identified using the two higher thresholds (OR = 1.74 and 1.73, per one SD increase in density) than with dense area identified using the standard threshold (OR = 1.62; p <.001). Furthermore, after controlling for dense area identified using the higher thresholds, dense area identified using the standard threshold was no longer significantly predictive of cancer risk (p > .06). These results suggest that the association between absolute dense breast area and breast cancer risk relates to denser areas of tissue than are currently considered "dense" by standard measurement thresholds; the strength of this association was close to 30% stronger for areas of higher mammographic density compared to conventional measures of density.

It is important to note that this relationship was not found for percent breast density, and that the study is relatively small and retrospective in design. That said, these results do replicate the similar findings from a previous case-control study conducted by Nguyen and colleagues (2015) using a small sample of Korean women (although in this study results were also significant for percent density). Nonetheless, this finding needs to be replicated in large prospective studies to ensure an accurate understanding of how breast density increases the risk of women across the density spectrum.

It is also not yet known to what extent the risk of breast cancer associated with risk factors such as weight, parity, and menopause are mediated through their associations with breast density. One nested case-control study was identified that assessed whether breast density mediates the relationship between other known risk factors and breast cancer risk (Rice et al., 2016). The study used 1290 cases and 3422 controls sourced from the Nurses' Health Studies cohort in the United States, with breast density measured using Cumulus. Results showed that for premenopausal women, percent breast density significantly mediated the relationship between breast cancer risk and a number of risk factors, including: BMI at age 18 (82% mediated); adolescent body type (73% mediated); birth index (sum of total years from each birth to woman's age at mammogram; 38% mediated); and history of confirmed benign breast disease (17% mediated). Percent breast density was also a significant mediator for several risk factors for postmenopausal women,

including: history of confirmed benign breast disease (33% mediated); child and adolescent body type (26% mediated); hormone therapy use (22% mediated); and age at first birth (13% mediated). There were also several notable risk factors that were not significantly mediated by percent breast density for either group, including current BMI, family history of breast cancer, and age at menopause.

Rice et al. (2016) concluded that breast density may be an important mediating factor in several biological pathways for breast cancer development. For example, in Huo et al's review, all studies adjusted for BMI except Kavanagh et al. (2008), Olsen et al. (2009), and Stone et al. (2010). The adjustment for age and BMI is necessary because breast density decreases with age and having more dense breasts is more strongly associated with lower BMI. Breast cancer risk, however, increases with age and, for women of population screening age, with increasing BMI postmenopause (Nguyen et al., 2013). Therefore, the case-control studies have adjusted for this 'negative confounding'. Huo et al. (2014) suggested taking care with the conclusions drawn from the studies that adjust for BMI because although high BMI is associated with increased non-dense area in the breast (which is a fat storage site), it also has been found to negatively correlate with absolute dense area in many, but not all studies. The reason for this possible inverse relationship is unclear. It is hypothesised that androgens derived from increased adiposity may play a role in reducing fibroglandular components or high BMI stimulates the differentiation of stromal preadipocytes into fat rather than collagen.

When studies adjust for confounders as shown above, women with more dense breasts remain at higher risk of breast cancer than those with less dense breasts, suggesting breast density is an independent risk factor (Habel et al., 2016; Huo et al., 2014; Masala et al., 2017; Yaghjyan et al., 2015a). There are no studies that have investigated breast cancer risk where breast density is the only factor. For example, Ho et al. (2014) noted that the participants in the ACRIN6666 study (explained in more detail in section 3.4.2) comprised women with an elevated risk of breast cancer, independent of their breast tissue. Therefore, it is difficult to conclude what the risk and screening options for women with dense breasts and no other moderate or strong risk factors would be. Recruiting women with breast density as their only risk factor is likely to be very difficult to achieve given the interlinking and associations between breast cancer risk factors such as age, BMI and breast density. More evidence from large prospective studies is required to fully understand how and to what extent breast density mediates the relationship between known risk factors and breast cancer risk.

A more recent study by Kerlikowske et al. (2015) aimed to determine which combinations of breast cancer risk and BIRADS breast density categories are associated with higher interval cancer rates. They analysed 365,426 women aged 40 to 74 years who had 831,455 digital screening mammography examinations from the Breast Cancer Surveillance Consortium (BCSC) study, recording BIRADS breast density, BCSC 5-year breast cancer risk, and interval cancer rate (invasive cancer ≤ 12 months after a normal mammography result) per 1000 mammography examinations. They found that high interval cancer rates (≥ 1 case per 1000 examinations) were observed for women with:

- A five-year breast cancer risk of 1.67% or greater, and extremely dense breasts
- A five-year breast cancer risk of 2.50% or greater, and heterogeneously dense breasts (24% of all women with dense breasts)

Five-year risk was low to average (0% to 1.66%) for 51.0% of women with heterogeneously dense breasts and 52.5% with extremely dense breasts. These women had an interval cancer rate of less than 1 case per 1,000 mammography examinations.

They concluded that breast density should not be the sole criterion for deciding whether supplemental imaging is justified because not all women with dense breasts have high interval cancer rates. Age and breast cancer risk influence cancer incidence and tumour stage at diagnosis (and therefore screening performance). These factors should be considered along with breast density to optimise identification of women with high interval cancer rates or high rates of false-positive results who may benefit from supplemental testing or alternative screening strategies.

3.2.4. Age, breast density and breast cancer risk

Understanding the strength of association of breast density variation by age is important for utilising breast density in risk models. No reviews were found that solely focus on breast density, cancer risk and age. We identified one meta-analysis (Bertrand et al., 2013) that linked breast density, tumour status and age.

Bertrand et al. (2013) used a sample of 3,414 women with breast cancer and 7,199 without breast cancer who underwent screening mammography; the data was pooled (Table 8 overleaf). Percent density was measured using a computer-assisted threshold method. Polytomous logistic regression found that percent density was significantly associated with risk of breast cancer across all ages, with risk doubling for high (>51%) versus average density (11-25%). This association between breast density and risk was stronger for younger women. Compared to women with more dense breasts aged 55–64 or 65 years or older, those aged below 55 years had an increased risk of ductal carcinoma in situ (p=.02) and a stronger association of breast density with ER-negative breast cancer than ER-positive tumours (p=.04). The relationship between density and tumour type is also discussed in section 3.2.5. Breast density was also positively associated with both HER2-negative and HER2-positive tumours across all age groups. Overall, Bertrand et al. found that breast density is strongly associated with all breast cancer subtypes across all ages, and with ER-negative tumours for women aged younger than 55 years. They concluded that high breast density may play an important role in tumour aggressiveness, especially in younger women.

One additional nested case-control study was identified that evaluated whether a range of demographic characteristics (including age at menopause and age at first child birth) moderated the association between mammographic breast density and breast cancer risk (Yaghjyan et al., 2015a). This study used a sample of 1,044 postmenopausal cases and 1,794 matched controls sourced from the Nurses' Health Study cohort in the United States. They found that increased percent density was related to an increase in the odds of developing cancer for women across all ages at menopause (less than 50, 50 to less than 55, and 55 or over), with women with greater than 50% breast density having 2.76-4.33 times the odds of cancer compared to women with less than 10% density. Furthermore, no significant differences were identified in the odds ratios between these three groups, indicating that age at menopause did not significantly moderate the relationship between breast density and cancer risk. Other possible confounding factors also did not significantly moderate the relationship between density and cancer risk, including BMI, age at menarche, parity, family history of breast cancer, and history of benign breast disease. This provides some support to the idea of breast density as an independent risk factor for breast cancer, as discussed section 3.2.3. Notably, the association with cancer risk did differ depending on the use of postmenopausal hormone use, with percent density being more strongly related to breast cancer risk for current postmenopausal hormone users (OR = 5.34, 95%CI 3.36-8.49) compared to women with past (OR = 2.69, 95%CI 1.32-5.49) or no hormone history (OR 2.57, 95%CI 1.18-5.60; *p*-interaction = .03). These results are consistent with Bertrand et al.'s (2013) finding that breast density is associated with breast cancer risk across all ages.

Table 8 Studies included in Bertrand et al.'s (2013) meta-analysis

Study name (abbreviation)	Reference	Study design	Number of cases/controls	Enrolment year(s)	Mammogram film view	Median interval (years) between mammogram and diagnosis (index date)	Source of cases	Source of pathology	Source of covariate data
Mayo Mammography Health Study (MMHS)	Heine et al., 2012 + Olsen et al., 2012	Nested case– control	404/1,207	2003 to 2006	CC average	3.6	Linkage to clinic and state cancer registries	Clinic and three state cancer registries; medical records	Questionnaire and medical record review (BMI)
Mayo Clinic Breast Cancer Study (MCBCS)	Kelemen et al., 2008 + Wang et al, 2008	Case– control	261/179	2001 to 2008	CC contralateral	1.3	Clinic	Clinic cancer registry; medical records	Questionnaire and medical record review (BMI)
Nurses' Health Study (NHS)	Tamimi et al., 2005 + Colditz and Hankinson, 2005	Nested case– control	1,108/2,163	1989 to 1990	CC average	5.2	Self-report	Pathology reports and tumour tissue microarray	Questionnaire
Nurses' Health Study II (NHSII)	Tworoger et al., 2006	Nested case– control	365/992	1996 to 1999	CC average	4.2	Self-report	Pathology reports and tumour tissue microarray	Questionnaire
Mayo Clinic Mammography Study (MCMAM)	Vachon et al., 2007	Case– control	372/679	1997 to 2001	CC average	7.1	Clinic	Clinic cancer registries; medical records	Medical record review
Bay Area Breast Cancer SPORE and San Francisco Mammography Registry (SFMR)	Kerlikowske et al., 2000 + Kerlikowske et al., 2005 + Ziv et al., 2004	Nested case– control study	904/1,979	1996 to 2007	CC contralateral	3.1	Linkage to state-wide SEER program	SEER	Questionnaire

Younger age (<50 years) and breast cancer risk

A subpopulation of interest for this review was women aged 40-50 years with no symptoms of breast cancer and screened by mammography. Some jurisdictions recommend regular breast screening from a younger age (30-40 years) for women deemed to be at high risk of breast cancer (eg, family history).

There is no strong evidence relating to age, breast density and screening (Wellings et al., 2016). Our search identified one narrative review investigating this population of women. Kerlikowske (2011) reviewed and described the benefits and harms of performing screening mammography, accuracy of digital mammography, and new evidence on the effectiveness of risk-based screening in women of this age group. This review was mainly focused around two studies: Yankaskas et al. (2010) and Hubbard et al. (2011).

Yankaskas et al. (2010) pooled data from six mammography registries across the United States from the Breast Cancer Surveillance Consortium. The final sample included 117,738 women who were aged 18-39 years when they had their first screening or diagnostic mammogram during 1995-2005. The women were followed for one year to determine accuracy of mammography assessment. Performance was measured using recall rate, sensitivity, specificity, positive predictive value (PPV), and cancer detection rate (CDR) for all screening mammograms. No cancers were detected using screening mammograms for women aged 18-24 years (Table 9, below).

Age	Sensitivity (95%Cl)	Specificity (95%Cl)	PPV (95%Cl)	Recall rate (95%Cl)	CDR (95%Cl)
18-24 years n = 637 screenings	7.6% (14.8 - 20.6)	0.0 (no cancers, reference)	0	17.6% (14.8 - 20.6)	0
35-39 years n = 73, 335 screenings	76.1% (69.2 - 82.6)	87.5% (87.2 - 87.7)	1.3% (1.1 -1.5),	12.7% (12.4 - 12.9)	1.6 cancers per 1000 mammograms (1.3 to 1.9)
All women	76.5% (70.1 - 82.5)	87.1 (86.9 to 87.4)	1.3 (1.1 to 1.5)	13.0% (12.8 - 13.2)	1.7 cancers per 1000 mammograms (1.4 to 1.9)

Table 9. Performance of screening mammogram in younger women (Yankaskas et al., 2010)

Although this study focused on women younger than those who might participate in the BSA program, it is included here for comparison to women aged 40-49 years. Women aged 18-39 years had low breast cancer rates but after mammography experienced high recall rates, high rates of additional imaging, and low CDR. Screening mammography also performed poorly for the large group of women aged 35-39 years. In a theoretical population of 10,000 women aged 35-39 years, 1,266 women who are screened will receive further workup, with 16 cancers detected and 1,250 women receiving a false-positive result. While no information was provided regarding breast density, population demographics tell us that a high percentage of these women would likely be categorised as having dense breasts. Even taking this into consideration, the risk of breast cancer remains low and the harms of screening are likely to outweigh the small benefits screening provides for younger women.

In Hubbard et al.'s study, the authors constructed a separate cohort for analyses of cancer stage. The full sample included women aged 40–59 years diagnosed with an incident invasive breast cancer between 1996 and 2006, at or following a screening mammogram and who had at least one additional prior mammogram. Based on 169,456 women, they found a woman's adjusted cumulative probability of experiencing a false positive recall after 10 years of screening increased across risk profiles (i.e., BIRADS 1 compared to BIRADS 4), radiologists' recall rates, and annual

compared to biennial screening. However, there was little difference in these recall rates between low risk women who began screening at 40 years (29.4%) and women who began at 50 years (32.4%). After 10 years of annual screening, more than half of women will receive at least one false-positive recall, and 7–9% will receive a false-positive biopsy recommendation. The probability of this is lower if screening commences at age 40 (compared to 50) and is biennial (compared to annual) but this may be associated with a small absolute increase in the probability of being diagnosed with late stage cancer.

Kerlikowske (2011) also cited the Digital Mammography Imaging Screening Trial (DMIST) study which included more than 42,760 women and performed film-screen and digital mammography in asymptomatic American women at the same screening encounter (Pisano et al., 2005). DMIST found that overall accuracy of film-screen and digital mammography for breast cancer detection was similar, but that digital mammography was more accurate in premenopausal or perimenopausal women younger than 50 years with mammography in this subgroup (57 versus 27%, *p*=.0013). The Breast Cancer Surveillance Consortium recently published a study based on mammography performed in community practice and found similar results to DMIST; women aged 40–49 years, premenopausal or perimenopausal women, and those with dense breasts had a higher sensitivity of mammography. However, the study also reported a lower specificity for digital than film-screening mammography for women aged 40–49 years (Kerlikowske, 2011).

A nested case-control study was also identified that compared the strength of the association between breast density and breast cancer risk across a number of age groups, including women aged 40-49 (Park et al., 2018). They used a sample of 1,561 cases and 6,002 matched controls who were randomly selected from the National Cancer Screening Program in Korea. Breast density was visually assessed using BIRADS. Table 10 (overleaf) shows the ORs found by breast density and age group. There was a significant trend of increasing risk with increasing breast density across all age groups (p<.001). Results also showed that the increase in risk with increasing breast density was more pronounced for women aged 40-49 years compared with women in older age groups; the odds of women aged 40-49 years developing breast cancer was 4.4, 7.0, or 9.4 times higher for women categorised as BIRADS 2, 3 or 4 (respectively), compared to women with mostly fatty breasts. For women aged 60-69, the odds were only 2.0, 2.7 or 5.1 times higher for these same density groups. This study suggests that while breast density is a predictor of breast cancer risk across all ages, it may be a stronger predictor for women aged 40-49 years compared to older women. Although the study used a large sample of women in total, the number of women within each subgroup used in the study was relatively small (eg, less than 100 women aged 40-49 years with fatty breasts, and no women aged 70+ years with extremely dense breasts). Therefore, these findings need to be replicated in other large prospective cohorts before conclusions can be drawn about the effect of breast density on breast cancer risk amongst younger women.

Density	40-49 years OR (95%Cl)	50-59 years OR (95%Cl)	60-69 years OR (95%Cl)	70+ years OR (95%Cl)	All sample OR (95%Cl)
BIRADS 1	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
BIRADS 2	4.4 (1.5-13.2)	2.8 (1.7-4.6)	2.0 (1.3-2.9)	2.2 (1.1-4.2)	2.4 (1.8-3.1)
BIRADS 3	7.0 (2.4-20.3)	4.8 (2.9-7.7)	2.7 (1.7-4.4)	2.5 (1.1-6.0)	3.8 (2.9-4.9)
BIRADS 4	9.4 (3.2-27.4)	6.0 (3.5-10.1)	5.1 (2.1-12.2)	-	5.0 (3.7-6.7)

Table 10. Breast density as a risk factor of breast cancer, by age group (Park et al., 2018)

One further nested case-control study assessed the strength of the association between breast density and breast cancer risk in women aged 40-49 years, although the sample comprised women of intermediate familial risk of breast cancer (Assi et al., 2015). The sample was sourced from 6,710 women participating in the FH01 cohort study in the United Kingdom, with a total of 103 cases of breast cancer and 195 age-matched controls. Mammographic density was assessed using Cumulus on images from the last mammogram prior to diagnosis for cases, and for controls, the mammogram closest to that of the cases'. Women had a mean age of 44.3 years at the time of their selected mammography. After controlling for absolute non-dense area (a proxy for BMI), the study found that absolute dense area was significantly predictive of breast cancer (OR = 1.07 per 10cm2, 95%CI 1.00-1.15, p=.04), but percent density was not. Categorising percent density based on cut-off points did lead to significant differences in breast cancer risk based on breast density; women with breast density 10% or greater had 3.08 to 4.43 times the odds of developing cancer compared to women with less than 10% density (p=.05). Overall, the study found a relatively weak association between breast density and breast cancer risk for women aged 40-49 years. This is inconsistent with the findings from Park et al. (2018), but it is important to note the limitations associated with this study. These include the use of a relatively small sample with intermediate familial risk, which could have created an under-estimate of the true strength of the association between density and cancer risk.

Research on the use of primary and supplemental breast imaging in young women is scarce, with gaps in understanding of who has screening, how accurate this is, and how the outcomes in women younger than 40 years compare with those of women aged 40 years or older (for whom regular screening is recommended). Further prospective and large-scale studies are needed in this area, especially for women at high risk of developing cancer, such as those with extremely dense breasts.

3.2.5. Ethnicity, breast density and breast cancer risk

Although some studies in the United States (such as Mousa et al., 2014) have not found any detectable differences between different racial groups (particularly Latin American and African American compared to European), few studies have clearly investigated the risk relationship between breast density and breast cancer for different racial groups.

Although not a specific investigation of the relationship between ethnicity, breast density and risk, Bae and Kim (2016) provided the first systematic review to evaluate breast density and breast cancer risk in Asian women (but they did not use other ethnic groups as comparators). Following standard systematic review search methods, six articles (one cohort and five case-controlled studies) were included in the meta-analysis (Kim et al., 2015; Lee et al., 2015; Park et al., 2014; Kotsuma et al., 2008; Nagata et al., 2005; Nagao et al., 2003). Details of the studies are presented in Table 11 (overleaf). Summary effect sizes (sESs) and 95%CI were calculated by conducting a meta-analysis applying a random effect model. Heterogeneity was assessed by I-squared values (%).

The results of Bae and Kim's study show that the percent density index was significantly associated with elevated breast cancer risk for pre-menopausal (sES, 3.23; 95%CI 2.23 to 4.66; $I^2=0.0\%$) and post-menopausal (sES, 1.62; 95%CI 1.13 to 2.32; $I^2=0.0\%$) women. Total breast area index did not show a statistically significant association with increased breast cancer risk for either group. This confirms the findings presented below (section 3.2.7) that percent density is more predictive of breast cancer risk than total breast area.

The risk calculated for pre-menopausal and post-menopausal women with a higher percent density was estimated to be 2.21 times that of baseline (95%CI 1.52 to 3.21). This is lower than the risk elevation of four to six times that has been found in studies of European women with BIRADS 2 to 4 compared to BIRADS 1. Bae and Kim suggested four factors that may account for this discrepancy:

- 1. Breast density itself is not a risk factor for breast cancer but is a phenomenon determined by other risk factors (which is a finding different from McCormack and dos Santos Silva); breast density can be affected by obesity, family history, genotype as well as parity.
- 2. Cancer occurrence is underestimated in Asian women due to the lower sensitivity of mammography with denser breasts and resultant decreased PPV in breast cancer diagnosis.
- 3. The estimation of risk elevation differed across different methods of classifying and measuring breast density, highlighting the influence of measurement indices on findings and suggesting that different measurement indices may be appropriate depending on race.
- 4. The paper included a relatively small number of studies (six), meaning that the conclusions should be treated with caution.

One additional case-control study found a lower level of risk for Asian women with denser breasts (Trieu et al., 2017). This study evaluated the predictive strength of risk factors, including having dense breasts (defined as BIRADS 4), using a sample of 269 cases and 519 age-matched controls sourced from hospitals in Vietnam. The odds of women with dense breasts developing cancer were 1.7 (95%CI 1.3-2.4) times higher than women with non-dense breasts (BIRADS 1-3). This association was stronger for postmenopausal women (OR = 2.0, 95%CI 1.2-3.6) than for premenopausal women (OR = 1.6, 95%CI 1.1-2.3). Consistent with the findings from Bae and Kim (2016), these odds ratios are lower than those found in studies involving European women. That said, the choice of a less-extreme comparison group could be influencing the size of the association found in this study. As discussed in section 3.2.3, studies that compare women with denser breasts to women with average density (rather than mostly fatty breasts) typically find weaker associations between breast density and breast cancer risk. In support of this possibility, the nested case-control study conducted by Park et al. (2018) using a sample of Korean women (and discussed in the preceding section) found ORs closer to those found in studies of European women. Notably, Park et al. used women with mostly fatty breasts as their comparison group.

Study	Region	Source of subjects	Menopausal status	Ratio of cases to controls	Breast density index	Intervals	OR	95%CI
		Giboku				P1	1.03	0.69, 1.55
Nagao et al. (2003)	Japan	General	N/A	237:742	Wolfe	P2	0.68	0.36, 1.31
		Hospital				DY	2.2	1.02, 4.77
						1-24	2.27	0.64, 8.08
						25-49	4.01	1.16, 13.9
					PD	50-75	4.37	1.24, 15.4
						75+	1.36	0.31, 6.60
						0.1-12.0	1.58	0.41, 6.23
			PreM	71:370	DA	12.1-26.3	4.03	1.14, 14.2
					DA	26.4-44.4	5.14	1.45, 18.3
						44.5+	2.78	0.77, 10.1
						52.3-66.0	0.66	0.28, 1.56
Nagata et	lanan	Gifu			ТВА	66.1-83.8	0.85	0.36, 2.04
al. (2005)	заран	Hospital				83.9+	1.53	0.64, 3.65
			PostM	75:289		1-24	1.17	0.55, 2.49
					PD	25-49	3	1.20, 7.48
						50+	4.19	1.33, 13.2
						0.1-9.5	0.83	0.33, 2.12
					DA	9.6-21.3	1.07	0.41, 2.80
					ТВА	21.4+	4.02	1.80, 8.94
						57.7-73.7	1.89	0.61, 5.91
						73.8-97.0	4.15	1.39, 12.4
						97.1+	4.65	1.50, 14.4
						3.4-8.8	0.98	0.51, 1.91
Kotsuma et al	lanan	Osaka University	PostM	205.223	חפ	8.9-16.5	0.94	0.48, 1.84
(2008)	заран	1999-2003	rostivi	205.225	ΓŬ	16.6-28.7	1.36	0.70, 2.65
						28.8-	3.02	1.58, 5.77
			PostM	302.774		8.0-15.0	2.64	1.85, 3.78
Park et	Korea	National	rostivi	502.774	VDG	15.1+	3.07	1.89, 4.99
al. (2014)	Korea	Center	ProM	271.125	VDG	8.0-15.0	1.87	0.91, 3.86
			FICIVI	374.435		15.1+	2.05	0.99, 4.23
						5-9	2.46	0.52, 11.52
Kim et al.	Korea	Samsung	PreM	134:395	5 PD	10-24	3.04	0.71, 12.96
(2015)	NUIEd	Medical Center				25-49	4.08	0.93, 17.82
, - <i>,</i>						50+	5.73	0.93, 35.40

Table 11: Studies included in Bae and Kim (2016) review

Study	Region	Source of subjects	Menopausal status	Ratio of cases to controls	Breast density index	Intervals	OR	95%CI
						Q2	0.7	0.43, 1.14
					TBA	Q3	1.07	0.67, 1.73
						Q4	0.97	0.57, 1.67
						Q2	1.5	0.72, 3.12
					ADA	Q3	1.56	0.77, 3.17
						Q4	1.99	1.00, 3.97
						5-9	1.11	0.58, 2.10
					חפ	10-24	1.05	0.54, 2.06
					FD	25-49	1.4	0.48, 4.08
			PostM			50+	3.96	1.38, 40.87
				70.225		Q2	1.2	0.53, 2.70
				75.255	ТВА	Q3	1.26	0.57, 2.79
						Q4	1.52	0.64, 3.57
						Q2	0.88	0.47, 1.62
					ADA	Q3	0.78	0.36, 1.67
						Q4	1.55	0.78, 3.06
		Singapore Breast Cancer				11-20	1.6	1.22, 2.10
Lee et al.	Cinenana		(17 y follow-	680:23		21-30	2.2	1.65, 2.92
(2015)	Singapore	Screening	up)	481	MDA	31-40	2.33	1.71, 3.20
		Programme				41-50	2.12	1.43, 3.14
						51-60	3.27	2.24, 4.76

Abbreviations: aOR, adjusted odds ratio; PreM, premenopausal; PostM, postmenopausal; Wolfe, Wolfe classification; PD, percent density (%); DA, density area (cm2); MDA, mean dense area (cm2); TBA, total breast area (cm2); VDG, volumetric density grade (%); ADA, absolute dense area (cm2). Statistically significant results have been bolded.

Further studies evaluating breast density using several different measurement indices, and the risk of breast cancer in non-European women are needed. Additional research about breast cancer and breast density in other population groups would also be useful to determine the association of ethnicity to density and cancer risk.

3.2.6. Cancer characteristics, breast density and breast cancer risk

The biological basis for the association between breast density and breast risk is not well understood. It has not been clearly established whether this association holds for all breast carcinomas or whether the increased risk is restricted to certain subtypes, defined by receptor status or molecular profiles. Determinants of breast density show greater consistency with risk factors for oestrogen receptor positive (ER+) breast cancer than they do for ER- breast cancer. Because ER+ tumours are the majority subtype and represent an increasing proportion of cancers as women age (i.e., 75% postmenopausal tumours are ER+), it is possible that the density/breast cancer association is driven by its positive association with this subtype, and that the association may be weaker, or null, for ER- tumours.

A meta-analysis was undertaken by Antoni et al. (2013) using standardised search methods that included seven cohort/case-control and 12 case-only studies, comprising a total of 24,000 breast cancer cases. Antoni et al. investigated the potential association between receptor type, breast density and risk of breast cancer. Random effects meta-analysis models were used to combine RR for breast density with subtype-specific breast cancer for case-control studies, and in case-only studies to combine relative risk ratios (RRR) of receptor positive versus negative breast tumours. The RRs were adjusted for age (eligibility criteria) and for breast cancer risk factors, in particular BMI, in all but the two European studies (Ding et al., 2010; Olsen et al., 2009). Density was classified depending on the original studies (eg, BIRADS 4 compared to BIRADS 1-2 or fatty vs dense in visual estimation).

In case–control/cohort studies, relative to women in the lowest density category, women in the highest density category had 3.1-fold (95%CI 2.2 - 4.2) and 3.2-fold (95%CI 1.7 - 5.9) increased risk of ER+ and ER- breast cancer, respectively. In case-only analyses, RRRs of breast tumours being ER+ versus ER- were 1.13 (95%CI 0.89, 1.42) for medium versus minimal breast density.

Breast density remained associated with screen-detected ER+ tumours, despite the expectation that this association would be attenuated due to masking bias and over-diagnoses of ER+ tumours. In eight contributing studies, the association of breast density did not differ by HER2 status.

This combined evidence strengthens the importance of breast density as a strong marker of overall and of subtype-specific risk, however the magnitude of the association between breast density and breast cancer of differing subtypes was similar.

Huo et al. (2014), in a narrative review of 12 studies, investigated the association of mammographic density with breast cancer subtypes and tumour characteristics. Table 12 (overleaf) outlines the studies included in this review.

The studies presented by Huo et al. found differing associations between receptor subtypes and breast density. As there was no systematic analysis of these studies by Huo et al., it is difficult to reconcile these differences and key findings into a coherent conclusion. Our observations of these studies suggest that many of the studies including younger women found no association (Gierach et al., 2010; Passaperuma et al., 2010) between receptor subtype and breast density. The method used to classify breast density does not appear to be associated with the outcomes, as all methods had positive and negative findings for receptor subtype. All receptor subtypes (eg, ER-, ER+, PR+ and PR-) had at least one study report a positive association with higher breast density.

Table 12. Studies included in Huo et al., 2014 (cancer subtype and breast density)

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammographic feature	Key finding
Bertrand et al. (2013)	Case-control	Mayo Mammography Health Study; Mayo Clinic Breast Cancer Study; Nurses' Health Study (NHS); NHS II; Mayo Clinic Mammography Study; San Francisco Bay Area Breast Cancer; San Francisco Mammography Registry; 1989- 2008	Age, BMI, parity, family history, HRT, study	3,414: 7,199	Mean: 57	Cumulus	Density is positively associated with BC of all subtypes, particularly with BC of large size and positive lymph nodes in all age groups, and ER-negative status in women <55 years of age
Eriksson et al. (2012)	Cohort	Cancer Hormone Replacement Epidemiology in Sweden study, 1993-1995	Age (current, at menarche, at menopause), BMI, HRT, oral contraceptive, parity, family history, breastfeeding ever, mode of detection	2,720: 625	50–74	Cumulus	No association found between density and tumour phenotype, except for tumour size which was partially confounded by mode of detection
Heusinger et al. (2012)	Cohort	Breast Cancer Database, Franconia, 1995-2009	Age at diagnosis, BMI, parity, grade, HRT	2,410: 2,700	<45–70	CAM	PD appears to be inversely associated with ER expression and positively associated with PR expression
Phipps et al. (2012)	Cohort	Breast Cancer Surveillance Consortium, USA, 1999-2008	Age at entry to programme, race, family history, previous biopsies	13,797: 1,040,669	40–84	BIRADS	Density was positively and similarly associated with BC of all subtypes
Yaghjyan et al. (2011)	Case-control	Nurses' Health Study, USA, 1988- 2004	Age (at diagnosis, at menarche, at first birth, at menopause), BMI, parity, HRT, alcohol, smoking, family history	1,042: 1,794	Mean: 60.2	Cumulus	≥50% density showed a 3.39-fold increased risk of BC compared to <10% density. The associations were stronger for in situ (vs. invasive) tumours, high- grade, larger (>2 cm) tumours and ER- negative (vs. positive) tumours

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammographic feature	Key finding
Conroy et al. (2011)	Nested case- control	Multi-Ethnic Cohort, USA, 1993- 1996	Age (at diagnosis, at first birth, at menarche), race, parity, menopausal status, HRT Matched on: Age, race	667: 607	Mean 62	Cumulus	Mean PD was significantly greater for ER- positive and PR-positive tumours
Arora et al. (2010)	Cohort	Memorial Sloan-Kettering Cancer Centre, USA, 2005-2007	Age	1,323: NK	27–91	BIRADS	BIRADS-4 dense breasts occurred more commonly in younger women, more often mammographically occult
Passaperuma et al. (2010)	Case-control	High-Risk Screening Program, Canada, 1997-2008	Age, mutation type	46: 376	25–65	Cumulus	High density was not associated with increased BC risk in women with BRCA mutations
Ding et al. (2010)	Case-control	National Health Service Breast Cancer Screening Program, UK, 1998-2004	Age Matched on: Age	370: 1,904	50–75	Cumulus	≥50% density was associated with 2.63- fold risk of developing BC compared to density <10%. High density was also associated with ER- positive tumours
Gierach (2010)	Cohort	National Cancer Institute's Clinical Genetics Branch Breast Imaging Study, USA	Age (current, at menarche, at first birth), BMI, parity, menopausal status, HRT, previous biopsies	143: 119	25–56	САМ	No difference found in density between unaffected BRCA mutation carriers and women at low-to-average risk of BC
Ma (2009)	Case-control	Women's Contraceptive and Reproductive Experiences Study, USA, 1994-1998	Age (at menarche, at first birth), race, menopausal status, parity, HRT Matched on: age	479: 376	35–64	САМ	PD was positively associated with luminal- A and triple-negative BCs

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammographic feature	Key finding
Ghosh (2008)	Cross- sectional	Postmenopausal Breast Cancer Study, USA, 1997-2001	Age (current, at first birth), BMI, HRT, family history, parity	286: 799	40+	САМ	Density was not associated with tumour size, histological type, ER/PR receptor status, mitotic activity or nuclear pleomorphism

Abbreviations: BC = breast cancer; HRT = hormonal replacement therapy; PD = percent density.

Two further nested case-control studies evaluated the relationship between breast density and tumour characteristics. Maskarinec et al. (2017) used 820 cases and 820 matched controls sourced from the French E3N cohort study and found no evidence for significant differences in tumour size, lymph node status, grade, or hormone receptor status by absolute dense breast area or percent density. They did find that the association between percent density and breast cancer risk was significantly stronger for women with familial history of breast cancer (OR = 2.25, per 1 SD increase in density, 95%CI 1.67-3.04) than women without (OR = 1.41, per 1 SD increase in density, 95%CI 1.24-1.60), suggesting a shared genetic component to both breast density and breast cancer risk (discussed in the following section).

Consistent with the results of Maskarinec et al. (2017), the other nested case-control study identified also did not find a significant link between breast density and specific tumour characteristics (Yaghjyan et al., 2015b). The sample used in this study comprised 1,010 postmenopausal cases with 2,077 matched controls sourced from two prospective cohorts in the United States: the Nurses' Health Study and the Nurses' Health Study II. Breast density was assessed using Cumulus software. Results showed that the association between percent density and breast cancer risk was stronger for ER+ (OR = 4.61, 95%CI 2.36-9.03) compared with ER- (4.61, 95%CI 2.36-9.03) tumours, however this difference was not statistically significant. Additionally, no significant differences in the association between percent density and breast cancer risk were found by progesterone receptor or human epidermal growth factor receptor 2 status. Both of these studies add to the mixed findings regarding the relationship between breast density and breast cancer subtype, highlighting the need for further good-quality research in this area.

One additional case-control study assessed the relationship between mammographic breast density and contralateral breast cancer (i.e., developing cancer in the opposite breast subsequent to a primary diagnosis of breast cancer; Chowdhury et al., 2018). This study sourced 847 cases and 2,541 age-matched controls from the Breast Cancer Surveillance Consortium. Breast density was visually assessed using BIRADS. Results showed that the risk of developing contralateral breast cancer increased across BIRADS categories. The odds of developing contralateral breast cancer were 1.64 (95%CI 1.03-2.60), 2.08 (95%CI 1.32-3.30) or 2.27 (95%CI 1.37-3.77) times higher for women categorised as BIRADS 2, 3 or 4 (respectively), compared to the odds for women categorised as BIRADS 1 (p <.001). The authors concluded that breast density is an independent and significant predictor of contralateral breast cancer, and its contribution to clinical decision making should be further explored.

Combined evidence from all studies to date suggests that percent of mammographic density is a risk factor for most breast cancer subtypes; however, the association for each subtype needs to be further defined. As the research in this area moves forward, breast density may be able to help stratify women into different breast screening strategies (including intervals or modalities) based on breast cancer subtypes, as part of a more personalised breast screening approach. These studies show there is potential for breast density to be used in overall breast cancer risk assessment and monitoring for both research and clinical purposes.

3.2.7. Genetic links

Demographic or lifestyle factors including age, parity, BMI and exogenous hormone levels explain only 20-30% of the between-women variation in percent mammographic density (Vahcon et al., 2000). It has been estimated that 63-67% of the residual variation could be attributable to genetic factors but linkage and candidate gene association studies have been largely unsuccessful in reproducibly identifying loci related to mammographic density (Boyd, 2002). Breast cancer also has a genetic component, with first degree familial relatives of individuals diagnosed with breast cancer having approximately twice the risk of developing breast cancer compared with non-relatives (Collaborative Group on Hormonal Risk Factors in Breast Cancer, 2001). It is therefore plausible that these two phenomena (breast density and breast cancer) share a common genetic basis.

Lindstrom et al. (2011) conducted a meta-analysis of five genome-wide association studies (GWAS) of percent mammographic density adjusted for age and BMI. The studies included were within the Marker Of DEnsity (MODE) consortium: the Nurses' Health Study (NHS; n=1,590), the Singapore and Swedish Breast Cancer Study (SASBAC; n=1,258), the European Prospective Investigation Into Cancer and Nutrition - (EPIC-Norfolk; n=1,142), the Minnesota Breast Cancer Family study (MBCFS; n=571) and the Toronto/Melbourne study (n=316). The final sample consisted of 4,877 European women, the majority (89%) of whom were post-menopausal. All studies used the Cumulus software to measure breast density. Because studies did not use the same breast density measurement units (eg, some used extreme sampling whereas others measured density as a continuous trait), a meta-analysis of estimated effect sizes was not possible. Instead, a combined test for each single nucleotide polymorphisms (SNP; a small change in a person's DNA, the most common type of genetic variation) was derived from combined p-values, direction of associations, sample sizes and study-specific weightings.

This study found that the 'A' allele of rs10995190 in *ZNF365* was associated with both decreased breast cancer risk ($p = 5.1 \times 10^{-15}$) and lower breast density ($p = 9.6 \times 10^{-10}$). To assess whether its relationship with lower breast cancer risk is mediated through its association with lower breast density, the relationships between rs10995190 and breast cancer risk were calculated before and after controlling for breast density. These analyses used case-control data from three of the included studies (NHS, SASBAC and MCBCS), totalling 2,107 breast cancer cases and 2,433 controls. Before controlling for breast density, they found a small but significant association between rs10995190 and breast cancer risk (OR = 0.85, 95%CI 0.76-0.96, p=.008). After controlling for breast density, the association increased slightly (OR = 0.90, 95%CI 0.80-1.01, p=.09).

The results indicate that genetic variation in *ZNF365* could reduce breast cancer risk through its negative association with the level of dense tissue in the breast. That said, the study did not control for the possibility of a confounding factor influencing the genetic variation, breast cancer risk and breast density independently. This was the only meta-analysis found within our date range looking specifically at the association between genes and breast density; further investigation is needed for a more conclusive link.

Huo et al. (2014; as described above) included 28 studies investigating the link between breast density and factors such as gene variants, hereditability, gene polymorphisms, variation in cellular pathway signalling. The results of this are described in Table 13 (overleaf).

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammogra phic feature	Key finding
Sun et al. (2013)	Cohort	Population-based Polish Women's Breast Cancer Study, 2000-2003	Age, BMI	121: NK	20–74	Cumulus	Inactive subtype of extratumoral gene expression was associated with increased density
Ozhand et al. (2013)	Cohort	Norwegian Breast Cancer Screening Program, 1996- 2005	Age, BMI	2,755: 4,419	50–69	CAM	9 tagging SNPs in the <i>IL6</i> gene had an effect of 3– 5% on density per variant allele
Lee et al. (2013)	Cohort	Singapore Breast-Screening Project	Age at menopause, BMI	2,164: 1,538	NK	NK	161 SNPs in 15 hormone metabolism pathway gene regions were not associated with density
Lee et al. (2013)	Cross- sectional	Singapore Breast-Screening Project, 1993-1998	Age, BMI, dialect group	3,695: 82	45–74	САМ	$TGF\beta1$ genetic variations were found to be associated with PD
De Aguiar et al. (2012)	Cohort	Screening Centre, Brazil, 2005-2006	N/A	890: NK	45–69	BIRADS	Density in postmenopausal women was significantly associated with the combined GSTM1 and GSTT1 null genotypes
Stone et al. (2012)	Case-control	Australian Twin Registry, 1995-1999	Age, BMI	327: 272	40–70	Cumulus	Genetic components of density variation are established before mid-life, and density measures are highly correlated over time
Stevens et al. (2012)	Cross- sectional	The Mayo Clinic, USA	Age, BMI	1,241: 5,777	NK	Cumulus	RS1265507 on 12q24 was associated with PD

Table 13. Literature on the genetic variations of mammographic density presented in Huo et al. (2014).

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammogra phic feature	Key finding
Vachon et al. (2007)	Cross- sectional	DENSNP consortium, USA	Age, BMI, menopausal status	5,110:11,78 5	NK	Cumulus	The C-allele of rs3817198 in LSP1 was positively associated with BC and density
Varghese (2012)	Cohort	Genome-Wide Association Studies, UK	Age, BMI, population stratification	3,628:5,190	NK	Cumulus	PD and BC have a shared genetic basis that is mediated through a large number of common variants
Greenwood et al. (2011)	Cohort	Australian Twin Registry	Age, parity, menopausal status, HRT, BMI	3,253: 699	Mean 52.8	PD	Maximum logarithm of odds from the genome- wide scan was on chromosome 7q32.3-q34 (LOD32) and 12.11.22-q13.11 (LOD 3.3)
Maskarinec et al. (2011)	Cohort	Mother and daughter pairs, USA	Age, BMI, race	101:203	38.7–64.3 (mothers); 10.2–16.9 (daughters)	BIRADS	No association was found between percent and absolute fibroglandular volume of mothers and daughters
Giacomazzi (2011)	Cohort	Mammography Screening Program, Brazil	Age (at screening, at menopause, at menarche, at first birth), parity, race, BMI	750: NK	40–69	BIRADS	HD was associated with BC more frequently in premenopausal women with the risk genotypes <i>STK15 F31I AA</i> and <i>AT</i> .
Sung et al. (2010)	Cohort	Healthy Twin Study, Korea, 2005-2007	Age (current, at first birth, at menarche), BMI, smoking, alcohol, parity,	730: 667	30+	Cumulus	PD demonstrated high heritability in Korean women

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammogra phic feature	Key finding
			breastfeeding ever, HRT, menopausal status				
Odefrey (2010)	Cross- sectional	Australian Twin and Sisters Mammographic Density Study, 2004-2009	Age, BMI	2,288: NK	40–70	Cumulus	rs3817198 (LSP1) and rs13281615 (8q) were associated with dense area and PD
Yang et al. (2010)	Pre-clinical	Frozen Tissue Bank, USA	N/A	66: NK	29–88	BIRADS	High density was associated with reduced TGFβ signalling and increased COX2 expression in high-risk women
de Moura Ramos et al. (2009)	Cross- sectional	Patients from Climacterium Sector and Diagnostic Section of the Department of Gynaecology, Federal de São Paulo, Escola Paulista de Medicina, 2008	Age (current, at menopause), BMI, menopausal status, parity	120: NK	NK	BIRADS	Polymorphism Xbal may be strongly related to density ($p = 0.02$)
Crandall et al. (2009)	Cohort	Study of Women's Health Across the Nation, USA	Age, race, parity, BMI, smoking	451:643	42–52	PD	The CYP1B1 rs162555 CC genotype was associated with a 9.4% higher density than the TC/TT genotype ($p = 0.04$). The CYP19A1 rs936306 TT genotype was associated with 6.2% lower density than the TC/CC genotype ($p = 0.02$)

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammogra phic feature	Key finding
Kataoka et al. (2009)	Case-control	Mammography Screening Program, UK, 2002-2007	Age (at screening, at menopause, at menarche, at first birth), BMI, smoking, alcohol, menopausal status, parity, breastfeeding ever, history of benign disease	746: NK	37–79	Cumulus	Sister–sister pairs and monozygotic twin pairs showed that density had a strong heritable basis
Chambo et al. (2009)	Cross- sectional	Patients from Climacterium Sector and Diagnostic Section of the Department of Gynaecology, Federal de São Paulo, Escola Paulista de Medicina, 2006	Age, parity, BMI	123: NK	NK	BIRADS	Wild-type PROGINS and mutated CYP17 taken together were associated with a 4.87 times higher chance of having dense breasts ($p = 0.030$)
Woolcott et al. (2009)	Nested case- control	Multi-Ethnic Cohort, USA, 1993-1996	Age, race, BMI Matched on: race, age group	361:464	45–75	Cumulus	The polymorphism rs12443621 in TOX3 was associated with PD
Douglas et al. (2008)	Cohort	Sister-pairs Study, USA, 2005-2007	Age (current, at menarche, at menopause), menopausal status, BMI	550: 474	40–88	САМ	Genetic effects accounted for >33% of the total variance of density
Tamimi et al. (2008)	Cross- sectional	Nurses' Health Study, USA, 1989-1990	Age, BMI	1,121: NK	33–55	Cumulus	No association between the 11 BC susceptibility loci and density was seen

Study	Study design	Study population	Variables adjusted for in analysis	No. cases: non-cases	Age (years)	Mammogra phic feature	Key finding
Diorio et al. (2008)	Cross- sectional	Mammography Screening Program, Canada, 2001	Age at screening, BMI, parity, smoking, previous biopsies	741:46	Mean 46.8	Cumulus	Women carrying increasing number of copies of the rare allele of IGF-I rs1520220 and rs6220 SNPs had increased PD
Verheus e al. (2008)	Cohort	European Prospective Investigation into Cancer and Nutrition Study, 1993-1997	Age (current, at first birth), BMI, parity, HRT, smoking, oral contraceptive	656: 1,272	50+	PD	Common genetic variations in the IGF-1 gene were not associated with density
Vachon et al. (2007)	Cross- sectional	Multigenerational families ascertained though a breast cancer proband, USA, 1990- 1996	Age	583:306	46–70	Cumulus	The maximum logarithm of odds for linkage score from the genome wide scan was on chromosome 5p (likely to account for up to 22% of variation in density)
Stone et al. (2007)	Cross- sectional	Australian Twin and Sisters Mammographic Density Study	Age, BMI, parity, HRT, smoking, menopausal status	457: 499	40–70	САМ	Each additional copy of the HSD3B1 Asn(367)Thr variant allele was associated with lower PD
Olson et al. (2007)	Cross- sectional	The Mayo Clinic, USA	Age, geographic location, BMI, menopausal status, parity	550: 182	NK	Cumulus	CYP19 variants were not associated with density
Tamimi et al. (2007)	Cross- sectional	Nurses' Health Study, USA, 1998	Age, BMI, alcohol, parity, family history, history of benign disease, menopausal status, HRT	1,121:21	42–78	Cumulus	Two haplotype-tagging SNPs in IGF1, rs1520220 and rs2946834 showed a strong association with density

Abbreviations: BC = breast cancer; HD = high density; HRT = hormonal replacement therapy; PD = percent density; SNP = single nucleotide polymorphism.

Results from included studies are varied; however, some key findings were:

- genetic components of breast density variation are established before mid-life, and genetic effects accounted for >33% of the total variance of breast density
- breast density and breast cancer have a shared genetic basis that is mediated through a large number of common variants, and
- breast density also appears to be highly heritable (Sung et al., 2010 and Kataoka et al., 2009).

While studies of common variants (polymorphisms) in candidate genes based on biological arguments identified some associations, these are small in number and therefore cannot be considered conclusive. Huo et al. (2014) concluded that around 10% of common SNPs associated with breast cancer risk are also associated with the breast density measures that predict breast cancer risk, but to date these explain only a few percent of the variance.

Genomics is a rapidly evolving field. It is likely that more gene studies will help to provide stronger understanding about any links between breast density and breast cancer risk. We know that breast density is likely to be affected by a number of genes that are largely unknown at the present time. Both inherited and somatic genomic variation for breast density will provide useful information for customising screening and treatment regimens for breast cancer (Ellsworth et al, 2010).

3.2.8. Mammographic density phenotype

The breast density classification systems (described in section 3.1) are subjective and vary. For example, Wolfe's pattern used four categories, BIRADS (5th edition) also uses four and percent density provides a value between 0-100%. Computer-assisted methods have also been developed, such as *Cumulus*. These programs assess breast density as the proportion of the area with dense breast tissue in relation to the whole breast area on a mammogram. These methods have served to date as the gold standard for assessing the percent density. The percent density is calculated by dividing the dense area by the total breast area (known as phenotypes; Rauh et al., 2012). Computerised systems now also provide other measures: the total breast area, the non-dense area and the dense area. It has been hypothesised that the absolute dense area is an indicator of breast cancer risk because a higher amount of dense breast tissue could directly correlate to a higher probability of one of the cells within the dense area progressing to a malignant cell.

Pettersson et al. (2014) conducted a meta-analysis of 13 case–control studies that examined the associations between mammographic density phenotypes and risk of breast cancer, providing results from logistic regressions for associations between one standard deviation (SD) increments in mammographic density phenotypes and breast cancer risk. They used random-effects models to calculate pooled OR and 95%CI. Table 14 (below) shows the summary OR when pooling estimates were adjusted for age, BMI, and parity.

	Absolute dense area	Absolute non-dense area	Percentage dense area
Premenopausal women (n =			
1,776 case patients; <i>n</i> =	1.37 (95%Cl = 1.29 to 1.47)	0.78 (95%Cl, 0.71 to 0.86)	1.52 (95%Cl, 1.39 to 1.66)
2,834 control subjects)			
Postmenopausal women (n =			
6,643 case patients; n =	1.38 (95%Cl = 1.31 to 1.44)	0.79 (95%Cl, 0.73 to 0.85)	1.53 (95%Cl, 1.44 to 1.64)
11,187 control subjects)			

Table 14. Summary of odds ratios for pre- and post-menopausal women, by density phenotypes

The results suggest that percent dense area is a stronger breast cancer risk factor than absolute dense area. Absolute non-dense area was inversely associated with breast cancer risk, but it is unclear whether the association is independent of absolute dense area.

A pair of nested case-control studies by Krishnan and colleagues (Krishnan et al., 2016, 2017) also addressed the association between different mammographic density phenotypes and breast cancer risk. Using samples sourced from the Melbourne Collaborative Cohort Study, they found that both percent breast density and absolute dense area were significantly associated with breast cancer risk, to a similar degree (with odds of cancer increasing by approximately 1.2 times for each standard deviation increase in breast density). Percent density and absolute density were also found to have similar levels of associations with risk of large tumours (OR \sim 1.6 per 1 SD increase in density) and positive lymph node involvement (OR \sim 1.8 per 1 SD increase in density). Non-dense area was not found to be significantly related to breast cancer risk, risk of large tumours, or risk of node-positive tumours. These results differ to those found in the study by Pettersson et al. (2014), in that they suggest that both percent density and absolute dense area are significant predictors of risk. Results from meta-analyses are often more reliable than results generated from single case-control studies, so further evidence is required to validate Krishnan and colleagues' findings. Further information on the findings from Krishnan et al. (2016) are discussed in section 3.3 on masking.

One potential way of reconciling the mixed findings regarding the best choice of density phenotype or measurement approach is to combine multiple approaches when estimating risk. One recent nested case-control study was identified that assessed this possibility by exploring the independent contribution of BIRADS density classifications and absolute dense volume (measured using Volpara) to the prediction of breast cancer (Kerlikowske et al., 2017). In total, 1,720 women with invasive cancer and 3,686 age-matched controls were sourced from two prospective breast imaging cohorts (the San Francisco Mammography Registry and the Vermont Breast Cancer Surveillance System). Results found that using both BIRADS classifications and absolute dense volume in risk models significantly increased their predictive accuracy (p < .001).

Table 15 (overleaf) shows the odds ratios for different combinations of BIRADS and dense breast volume, after controlling for a number of confounders. Women categorised as BIRADS 2 and with second-quartile dense breast volume were used as the reference group; odds ratios that differ significantly from the reference group have been bolded. The odds of women with heterogeneously or extremely dense breasts and third- or fourth-quartile dense breast volume developing cancer was 1.43 to 2.56 times higher than the reference group, but women with heterogeneously or extremely dense breasts and first- or second-quartile dense breast volume did not have significantly different risk to the comparison group. This indicates a moderating effect of dense breast volume on the risk associated with the different BIRADS categories. The authors concluded that combining information about dense breast volume with BIRADS categorisation may provide more accurate risk stratification for clinical decision-making.

Dense breast volume	BIRADS 1 OR (95%CI)*	BIRADS 2 OR (95%CI)*	BIRADS 3 OR (95%CI)*	BIRADS 4 OR (95%CI)*
Quartile 1	0.63 (0.45-0.89)	0.94 (0.72-1.21)	1.03 (0.71-1.49)	1.53 (0.75-3.09)
Quartile 2	0.60 (0.43-0.84)	1.00 (reference)	1.25 (0.92-1.69)	1.50 (0.82-2.73)
Quartile 3	0.70 (0.49-0.99)	0.98 (0.76-1.27)	1.43 (1.09-1.89)	2.87 (1.84-4.47)
Quartile 4	0.87 (0.54-1.41)	1.15 (0.87-1.53)	1.67 (1.31-2.12)	2.56 (1.87-3.52)

Table 15. Odds ratios by BIRADS classification and absolute dense volume (Kerlikowske et al., 2017)

*Odds ratios calculated after controlling for age, BMI, family history of breast cancer, history of breast biopsy, and race/ethnicity

3.2.9. Summary

There is now extensive evidence that increased breast density is a strong risk factor for breast cancer and is associated with large relative and attributable risks for the disease. Taking methodological limitations into account, compared with other known risk factors, having extremely dense breast tissue appears to place a women at intermediate risk of breast cancer. Further research is needed to improve measurement of breast density, understanding of the genetics and biological basis of the association of breast density with breast cancer risk, and the clinical significance of change in breast density. Prospects for the application of breast density include improvements in mammographic screening, risk prediction in individuals, breast cancer prevention research, and clinical decision making.

3.3. Masking

Breast density reflects the ratio of fibroglandular (dense) to adipose (fatty) tissue in the breast. The sensitivity of mammography is reduced for women with more dense breasts because cancers can be hidden by the radiopaque fibroglandular tissue. Masking occurs when surrounding breast tissue obscures a cancer. The cancer is thus difficult to discern mammographically, limiting the sensitivity of mammography as a screening or diagnostic test in women with more dense breasts (Wang, et al., 2014).

Whereas the overall level of breast cancer risk associated with breast density relates to the effect of cumulative exposure to breast density over the lifetime, masking relates to the impact of breast density on the day of the mammogram. Although breast density relates to masking, the relationship between the risk of masking and density on cancer detection is likely to be more complex than a simple dependence on the amount of fibroglandular tissue (Hooland et al., 2017). The distribution of dense tissue may also play a role. Distribution of radiopaque tissue within the breast is spatially autocorrelated, with high-density areas clustering in the central regions of the breast regardless of the average level of density across the whole breast. In general, the clusters of high density and low density tend to be located roughly in the same regions in the left and right breast for the same woman and among different women (Pereira et al., 2009). The importance of distribution is reflected in the new BIRADS definition, which no longer considers the total amount of fibroglandular tissue within the breast, but rather the densest area (He et al., 2015).

Our inclusion criteria for considering the degree to which breast density masks breast cancer in modern digital mammography was systematic reviews, narrative reviews, RCTS, and prospective cohort or case-control studies. No RCTs or systematic reviews specifically focusing on the

relationship between breast density and masking (or masking more broadly) were found. In addition, no studies provided quantification or measurement of masking due to breast density. How the risk of masking should be quantified is an open question. No studies were identified which investigated the relationship between masking and age.

The identification of mammographic density as a risk factor mainly took place in the predigital era, and most of the studies demonstrating the effect of density on breast cancer risk and masking pertain to measures from film/screen mammography, predate this review. There is a current need to demonstrate and validate measures of breast composition from digital mammography which are equally strongly associated with breast cancer risk and masking (Duffy, 2018).

What the search undertaken in this review did find were studies discussing masking and CDR, and studies evaluating supplemental testing as a method of reducing the masking effect of breast density. The results of these studies are presented in section 3.4.

We identified no systematic reviews or RCTs; however, we did identify three narrative literature reviews (covering 149 articles) and six prospective cohort or case-control studies which reported on the masking effect of breast density.

Narrative literature reviews

Three reviews: Patterson and Roubidox (2014); Destounis et al. (2017a); Lourenco and Mainiero (2016)

Prospective cohort or case-control studies

Six studies: Buchberger et al. (2018); Duffy (2018); Krishnan et al. (2016); Krishnan et al. (2017); van der Waal et al. (2017); Weigel et al. (2017)

There are a number of studies that propose an association between breast density, breast cancer and masking however, these are of limited quality and provide weak evidence for this association.

Key findings about breast density and masking

The proportion of women aged over 40 years who have dense breasts is estimated to be between 30-60%. This is inversely proportional with age: a higher proportion of women in their 40s have more dense breasts compared to those in their 70s.

It is well accepted that mammography is the primary screening tool for breast cancer and has been shown in multiple RCTs to reduce the death rate from breast cancer. However, even in the best circumstances, mammography may miss up to 20 percent of breast cancers. The sensitivity of mammography reduces further with increasing breast density, resulting in the potential for masking of cancer and non-detection; current evidence suggests that the sensitivity of mammography reduces from around 85-90% for women with average density to around 60-65% for women with dense breasts,

The increased risk of interval cancer attributed to masking cannot easily be separated from the potentially rapid growth of tumours in dense tissue, although there is preliminary evidence that higher density is related to increased risk of interval cancers after controlling for fast-growing tumours. One study found lower rates of mortality reduction from screening for women with dense breasts compared to those with fatty breasts, although this difference was not significant.

The number of studies specifically assessing the masking effect of breast density (eg, reduced sensitivity and higher interval cancer rates) is relatively small, and further evidence is needed to gain a clear understanding of this relationship. That said, the growing recognition of the likely
negative impact of breast density on the performance of mammography screening has resulted in an increasing focus on the potential of supplemental testing as a method that could reduce the masking effect of breast density.

3.3.1. Sensitivity, cancer detection and masking

Breast screening, particularly with FFDM has demonstrated effectiveness at reducing cancer mortality by detecting breast cancers when they are smaller, node negative and of a lower stage and grade (all of which are associated with improved patient outcomes; Wang et al., 2014). However, the ability of mammography to detect early cancers is reduced when women have more dense breasts. The CDR for screening mammography (with FFDM) averages 4.3 per 1000 screening examinations. The sensitivity in women with fatty breasts (using BIRADS 1) is approximately 98% compared with a much lower sensitivity in women with more dense breasts which ranges from 30 to 69% (Lourenco and Mainiero, 2016; Patterson, 2014). These studies did not report specificity; however, other studies have shown that this decreases from around 95% for fatty breasts (BIRADS 1) to a range of 50-70% for extremely dense breasts (BIRADS 4; Wanders, 2017; Devolli-Disha, 2009).

Figure 3 (below) has been modified from a 2017 study (Destounis et al., 2017a). It demonstrates the loss of breast cancer detection sensitivity as breast density increases. This study included a large cohort of women (~250,0000) undergoing screening mammography. Breast density was measured using both visual BIRADS and an automated volumetric analysis algorithm that graded density using categories analogous to the BIRADS categories. Figure 3 shows the results found for automated density grades, and clearly depicts that as breast density increases there is a decrease in the sensitivity of mammograms to detect cancers. The decrease in sensitivity was more pronounced for automated density grades 1 to 4 (95%, 89%, 83%, 65%) than for the visual BIRADS grades 1 to 4 (82%, 90%, 84%, 66%).



Figure 3: Relationship between breast density and mammographic sensitivity (Destounis et al., 2017a)

Further prospective or case-control studies were identified that evaluated the decrease in the performance of mammographic screening as a result of breast density. Buchberger et al. (2018) assessed the masking effect of breast density using a sample of 66,680 women who underwent both mammography and ultrasound screening between June 2008 and May 2010 in Helsinki,

Finland. They found that sensitivity of FFDM (?) was significantly lower for women categorised as BIRADS 3 or 4 (n = 31,918; 61.5%, 95%CI 51.0-71.2%) compared with women categorised as BIRADS 1 or 2 (n = 34,762; 86.6%, 95%CI 81.2-91.0%), although PPV₁ (11.3% and 13.3%), PPV₂ (33.5% and 32.6%), and PPV₃ (56.5% and 52.7%) rates were not significantly different between women with less or more dense breasts, respectively. Similar results were found for mammography plus ultrasound, although sensitivity rates were significantly higher for mammography plus ultrasound compared with mammography alone; further discussion on the utility of supplemental imaging for women with denser breasts can be found in the following section. Overall, this study provides further evidence for the negative impact of breast density on successfully detecting cancers using a large retrospective sample. Contrary to previous studies, breast density did not have a significant impact on any PPV rate in this study, although this could be because of the use of a less extreme comparison group (i.e., combining categories 1/2 and 3/4, rather than comparing categories 1 and 4).

A prospective study of 25,576 women who underwent routine biennial mammographic screening in Germany also provided evidence for the negative impact of breast density on screening performance (Weigel et al., 2017). Breast density was classified according to the American College of Radiology (4th edition; ACR), which categorises density into four groups using quartile ranges of percent dense tissue, ranging from entirely fatty to extremely dense. The study found that the sensitivity of mammography screening decreased as breast density increased (100%, 83.9%, 72.9% and 50% for ACR 1-4, respectively), with the difference between ACR 4 and all other categories being statistically significant (p <.001). The study also found that interval cancer rates per 1,000 women screened increased as breast density increased (0, 1.56, 2.54 and 3.15 for ACR 1-4, respectively), although only the difference between ACR 1 and 4 was statistically significant (p <.001).

One recent nested case-control study specifically explored the masking effect of breast density by evaluating rates of interval cancer by density levels (Krishnan et al., 2016). The premise of this study was that the risk of interval cancer reflects the risk of masking, as it relates to the risk of the tumour not being detected at initial screening (i.e., a missed cancer/false negative). The sample for the study was sourced from the Melbourne Collaborative Cohort Study, a prospective cohort study of 41,514 people, including 20,444 women who had attended BreastScreen Victoria at least once. The final sample included 244 screen-detected cases matched to 700 controls, and 148 interval cancer cases matched to 446 controls. Results showed that the risk of breast cancer was best predicted by BMI in combination with absolute dense area or percent density, but that the risk of masking (i.e., the risk of interval cancers) was best predicted by the percent density alone, with higher density predicting greater risk of masking. Analyses were replicated by tumour size to control for the possibility of fast-growing tumours causing the higher interval cancer rates; results were not significantly different by tumour size. An update to this study (Krishnan et al., 2017) confirmed that the association between percent density and risk of masking did not significantly differ by tumour characteristics (including tumour size and nodal status), although results did indicate that the risk of tumours with poorer prognosis (eg, larger or node-positive tumours) increased with increasing breast density. Together, these studies provide further support to the link between breast density and interval cancers (and therefore masking). They also suggest that the prediction of breast cancer risk (including specific types of breast cancer) and of masking risk may be associated with different risk factors (eg, BMI), and therefore require different responses.

The potential danger of the masking effect of breast density was highlighted in a study that evaluated the impact of breast density on mortality reduction from a Dutch national screening programme (van der Waal et al., 2017). This study matched 333 women who died from breast

cancer between 1975 and 2008 with 1,665 cancer-free controls (five controls for each case). Importantly, controls were not matched on age or any other characteristic; given that the sample was obtained from a routine screening population, it is likely that some women in both the case and control groups had additional risk factors other than breast density, however this was not explicitly reported. Mammographic density was visually assessed using a dichotomised Wolfe scale (fatty versus dense breasts), from screen-film mammograms. Mammogram data was only available for a subgroup of controls who had been recalled for additional testing or who had been diagnosed with breast cancer, so breast density was estimated for most of the controls using log-binomial modelling.

Results from van der Waal et al. showed that women with dense breasts accounted for a greater proportion of interval cancer cases and false-positive recalls than women with fatty breasts. Sensitivity was also found to be lower for women with dense breasts (57.8%) compared with fatty breasts (75.7%). Perhaps most importantly, the mortality reduction from mammography screening attendance was found to be lower for women with dense breasts (OR = 0.87, 95%CI 0.52-1.45) than for women with fatty breasts (OR = 0.59, 95%CI 0.44-0.79), although this difference was not statistically significant (p>.05). The authors concluded that high breast density results in poorer mammography screening performance and could be associated with a smaller mortality reduction from screening. That said, the lack of matched controls and the fact that breast density was estimated for a large proportion of the control group means that the results from this study should be interpreted with caution. More research is needed to further explore the link between breast density and screening harms, including the necessity of risk-stratified screening or supplemental testing (discussed further below).

Although further research is needed to precisely identify the impact of breast density on screening performance, the overall findings from the studies outlined above indicate that high breast density is associated with lower cancer detection with mammography and an increase in diagnosed interval cancers. The underlying causes of the link between high breast density and breast cancer risk are thought to be numerous, however one primary explanation for an increase in breast cancer incidence with increased breast density is because of a 'masking bias' that makes mammographic screening less sensitive to cancer detection (McCormack, 2006; Krishnan et al., 2016). For example, in one nested case-control study, Van Gils et al. (1998) studied 359 cases and 922 abnormalities referred for further assessment, identified in a breast cancer screening. Women with dense breasts had 1.4 times the odds of developing breast cancer compared to those with less dense breasts (95%CI 0.7 to 6.2). After a 3-4-year period the odds ratio increased to 3.3 (95%CI 1.5 to 7.1), before decreasing back down to 1.2 times the odds (95%CI 0.6 to 2.7) after 5 or more years. Overall, interval cancers were only more frequent in patients with more dense breasts in the first eight years of the screening programme. This rise and decline in risk aligns with the masking hypothesis. That is, tumours in dense breasts may be concealed at the first examination but manifest themselves in later years, artificially suggesting an increase in breast cancer incidence among women with more dense breasts.

More recent studies, however, have shown that there is increased risk for at least 7–10 years following a screening examination, indicating that 'masking bias' is only one of the mechanisms linking breast density to an increased cancer risk (Boyd et al., 2007; Vachon et al., 2007). In addition, the increased radiation dose needed to acquire acceptable mammographic images in dense breasts and cumulative lifetime exposure from screening indicates that there may be a less favourable benefit to harm ratio associated with mammographic screening of women with dense breasts, particularly in younger women (Duffy, 2018) compared to older women with less dense breasts.

As discussed in section 3.2, women with mammographic density of 75% or more of the breast have been shown to have an increased risk of breast cancer (independent of other risk factors), either detected by screening or less than 12 months after a negative screening mammogram (interval cancer). This risk persists even after accounting for masking of cancers with certain screening modalities (Patterson and Roubidoux, 2014). But, we do not know to what extent the increased risk of interval cancer is due to masking of cancer from dense tissue or to rapid growth of tumours in dense tissue.

There are various reasons why interval cancers are not detected by screening, and masking is only one of them. For example, some fast-growing cancers may be not detected by screening because they develop during the screening interval or they are occult on FFMD. Despite the current mixed findings relating to the association between breast density and interval cancers, the evidence does suggest that mammographic sensitivity is diminished in women with more dense breasts (Destounis et al., 2017a; Weigel et al., 2017). This is a major contributor to the drive for supplemental testing to be used in conjunction with mammography.

3.4. The role of supplemental testing

Taken together, the higher risk of cancer and lower rates of sensitivity for FFDM for women with dense breasts indicate that supplemental testing may be beneficial for this population. The most widely offered supplemental test is whole-breast ultrasound but other screening modalities exist and are used (including MRI, DBT, optical mammography and MBI). There is strong evidence that supplemental testing detects more cancers than FFDM alone but that, depending on the test used, false positives and recall rates are increased. Currently there is no consensus on which screening modality should be recommended as either a primary screening test or an adjunct screen to FFDM for women whose only risk factor is high breast density. No guidelines have been established in Australia or other jurisdictions as to which screening modality women should undergo. This is because supplemental testing is a relatively new strategy that was introduced after the recent introduction of breast density notification. As such, there is limited research that specifically reports on improved long-term cancer-related health outcomes for women with more dense breasts and who undergo supplemental imaging (if those women have no other moderate or strong risk factors for breast cancer). Controversy remains as to the optimal supplemental testing modality to complement FFDM as each imaging modality has variable benefits and limitations. These benefits and limitations are described in Table 16 (page 78).

Our inclusion criteria for the role of supplemental imaging was systematic reviews, narrative reviews and RCTs. We identified seven systematic reviews (100 articles) and seven narrative literature reviews (covering 410 articles).

Systematic reviews

Seven reviews: Houssami & Turner (2016); Coop et al. (2016); Sari et al. (2013); Melnikow et al. (2016); Gartlehner et al. (2013); Scheel et al. (2015); Nelson et al. (2016)

Narrative literature reviews

Seven reviews: Holbrook & Newel (2015); Jalalian et al. (2013); Hruska (2017); Lourenco and Mainiero (2016); Ravet et al. (2010); O'Flynn et al. (2015); Burkett and Hanemann (2016); Berg and Mendelson (2014)

Randomised Controlled trials

One study: Ohuchi et al. (2016)

Prospective Studies

One study: Berg et al. (2012)

NB Additional articles reporting on the ASTOUND and J-START trials are also discussed in the systematic and literature reviews.

Most of the literature in this area focuses on ultrasound and there is strong evidence for its use as a supplemental testing tool, providing significantly improved rates of cancer detection than mammography alone (systematic review and prospective studies), however there is no evidence that supplemental imaging reduces mortality. There is some evidence that the use of MRI, DBT and MBI as supplementary testing methods provides better cancer detection rates however, more rigorous studies are needed to describe the impact of these testing methods on reduction in cancer mortality.

Key findings about the role of supplemental testing

Approximately one-half of women undergoing screening mammography have dense breasts. As discussed in previous sections, there is evidence to suggest that increased breast density is associated with higher breast cancer risk and a decrease in mammography performance. This suggests that supplemental imaging could be beneficial for women with dense breasts; however, there is no direct, robust evidence that supplemental imaging reduces mortality from breast cancer.

Furthermore, there are a number of potential harms associated with supplemental testing following a negative mammography, including increased false-positive screening results, recall rates and unnecessary breast biopsies, and potential increases in screening-related anxiety. These potential harms become more pertinent when one considers the variability of breast density classification. The classification of breast density for individual women has been found to vary between readers, and across time due to several factors, including age and weight changes. It is therefore possible to receive incorrect or outdated information about breast density, which could unduly influence clinical or personal decision-making regarding screening.

Evidence and expert consensus remains unclear as to the risk-benefit balance of supplemental testing using DBT, ultrasound, MRI, and MBI for women whose <u>only</u> risk factor is high mammographic density and who have an average lifetime risk of developing breast cancer. Each of these adjunct modalities has advantages and disadvantages related to factors such as accuracy, cost, radiation dose, acceptability, and availability. Not surprisingly, there is therefore no one measure that is best at overcoming the masking issues seen with mammography for women with more dense breasts. For this reason, there are also no guidelines or consensus established in Australia or other jurisdictions as to which screening modality women should undergo if they have the denser breasts (as the only risk factor.

The Connecticut Experiment suggested that supplementary screening with ultrasound benefits all women through improved CDR (even those with fatty breasts). There are still gaps regarding

if women with more dense breasts benefit more from different screening strategies compared to women with less dense breasts, or if their screening-related clinical outcomes differ.

Some cancers are mammographically occult and can be detected only by other (nonmammography based) breast imaging. Whether performing supplemental testing to identify mammographically occult cancers provides more benefit in terms of reduced cancer mortality than harm is not established.

3.4.1. Supplemental imaging modalities

Brief descriptions of the following supplemental imaging modalities are provided before evidence of sensitivity and specificity relating to breast density is provided:

- DBT (tomosynthesis)
- MRI
- MBI
- Optical mammography, and
- Ultrasonography.

DBT is a mammographic imaging technology that can be used to detect, assess and diagnose breast cancer. DBT records between 11 and 25 low-dose images of a compressed breast (depending on the imaging unit used). These images are reconstructed in 1mm (or more) parallel slices to form a three-dimensional image of the breast. Radiologists then analyse the images to determine the presence of suspected abnormalities or to further investigate an area identified as suspicious on a digital mammogram. The thin cross-sectional images created by DBT minimise the masking effects of breast tissue overlap, which can improve margin visibility for soft tissue tumours and increase lesion conspicuity. This potentially increases screening sensitivity (especially for women with dense breasts) as abnormalities are easier to see.

MRI is a non-invasive medical test that uses magnetic fields to produce detailed cross-sectional images of tissue structures. MRI creates images of the breast by measuring changes in the movement of protons in fat and water with the application of changing magnetic fields and by utilizing the differences in tissue relaxation characteristics. The contrast between different types of breast tissues (fat, glandular tissue, lesions, etc.) depends on the mobility and the magnetic environment of the hydrogen atoms in water and fat, which contribute to the signal intensity (brightness) of the breast image. In the breast, this results in images showing predominantly parenchyma and fat, and lesions (if they are present). In high-risk populations, screening with both MRI and mammography annually improves the sensitivity of screening but decreases specificity relative to screening with mammography alone.

Research in high-risk woman has indicated that MRI is limited in its ability to identify non-invasive breast cancer (eg, DCIS; Health Quality Ontario, 2016). and could therefore be used as an adjunct to, rather than a replacement for, mammography. The benefits and harms of adjunct screening with MRI among women at less than high risk for breast cancer (including those whose only risk factor is more dense breasts), however, are unclear.

MBI is a nuclear imaging technique which is also known as breast-specific gamma imaging (BSGI), or breast scintigraphy. MBI can detect cancer because of metabolic differences between the lesions and normal breast tissue in their uptake of an injection of a single-photon emitting radiopharmaceutical, ^{99m}Tc-sestamibi, which emits 140-keV gamma rays. These rays can be detected using a gamma ray camera. Because MBI relies on metabolic rather than physical differences between lesions and breast tissue, it could be of benefit to women with dense breasts and a high chance of masking (Lourenco and Mainiero, 2016; Holbrook & Newel, 2015).

Ultrasonography is used in the assessment and diagnosis of breast cancer and has traditionally been performed by a health practitioner moving a hand-held device (called a transducer) over the breast. Ultrasonography uses high-frequency soundwaves that 'echo' as they pass through various types of tissue. These echoes are used to create an image called a sonogram, which depicts the internal structures inside the body. Ultrasonography is a popular imaging technique because it is

comfortable for women, widely available at a relatively low cost, and does not involve the use of ionising radiation or contrasting agents (Geisel et al., 2018). Ultrasonography can distinguish benign from malignant lesions because it can differentiate between cysts and solid tumours and thus lowers the number of unknown mammographic findings. Accuracy of ultrasound is highly dependent on operator experience and expertise.

Of the supplemental testing modalities, MRI is reported to have the highest sensitivity for detecting breast cancer in women across all risk categories (Freer, 2015); however, as an adjunct screening modality in women of average risk or women whose only risk factor is mammographic density, it is limited by cost, access, and exclusion criteria such as claustrophobia, renal compromise, and pacemakers, in addition to concerns about increasing false positives. In comparison, ultrasound is available at the time of mammography, does not use ionising radiation, is generally better tolerated by a wide range of women. Both MRI and ultrasound have been found to have decreased specificity compared to mammography (MRI 71%-77% and ultrasound 81%-95%) and a resultant increase in false positive examinations, potentially requiring these women to undergo further and ultimately unnecessary imaging/diagnostic work-up (Lourenco and Mainiero, 2016). Table 16 (below) summarises advantages and disadvantages of the different supplemental testing modalities. Trade-offs occur in relation to cost, radiation dose, availability and screening performance.

Imaging modality	Advantages	Disadvantages
DBT	 Improved cancer detection compared to FFDM alone Reduced false-positives and recalls compared to FFDM alone Can be obtained in a single compression at the same time as FFDM Is becoming widely available Could be adopted as a primary screening modality 	 Additional ionizing radiation when added to FFDM (approximately double the dose, although newer synthesised DM techniques result in a decreased dose) Additional out-of-pocket costs if funders do not cover it
MRI	 Highest sensitivity for detecting additional cancers No ionizing radiation 	 Not widely available Requires intravenous gadolinium injection (although less allergenic than other iodine- based contrasting agents) Increased false-positives Increased benign biopsies Additional out-of-pocket costs if funders do not cover it Limited ability to identify non-invasive cancer Relatively cost and time intensive Requires experienced radiologists to conduct screening Can be issues with claustrophobia
мві	 Improved cancer detection compared to FFDM Potentially improved specificity Improved ability to detect sub-centimetre lesions 	 Not widely available Requires intravenous radioactive tracer injection Additional ionizing radiation Relatively time-intensive
Ultrasonography	Widely available	Highly operator-dependentIncreased false-positives

Table 16. Advantages and disadvantages of the most commonly-used supplemental imaging modalities

Imaging modality	Advantages	Disadvantages				
	 Improved cancer detection when used as an adjunct screening test with FFDM No ionizing radiation 	 Increased benign biopsies Additional out-of-pocket costs if funders do not cover it 				

3.4.2. Screening with supplemental imaging modalities for women with more dense breasts

The section below outlines the current literature around supplemental testing in addition to mammography in women with dense breasts. Unless otherwise noted, all discussion refers to screening that is adjunct to FFDM.

DBT

DBT has been approved by the US Food and Drug Administration and the EU for routine clinical use as an adjunct to standard mammography. No reviews demonstrating mortality reduction in women who received supplemental testing with DBT exist. That said, DBT shows promise in increasing cancer detection, and reducing false-positive and recall rates, for women with dense breasts. There are no current universal guidelines on patient selection or frequency of use.

Coop et al. (2016) cited evidence that the addition of DBT to FFDM reduces the effects of tissue overlap and can lead to overall increases in CDR and invasive CDR for women with heterogeneously or extremely dense breasts (BIRADS 3 or 4). They noted that the greatest difference in CDR was experienced by younger women with heterogeneously or extremely dense breasts (BIRADS 3 or 4), although no further discussion of the evidence underpinning this statement is provided.

In July 2016, Houssami & Turner (2016) completed a rapid evidence review investigating incremental CDR for DBT when used as an adjunct screen to mammography for women with more dense breasts. While not a systematic review, this rapid review provided pooled analysis of 10,188 women across eight studies. The authors considered data from large prospective, fully-paired trials embedded in population-based screening programs and retrospective studies separately. Houssami & Turner reported differences in the magnitude of effect for incremental CDR between the results reported from larger prospective studies compared to retrospective studies. Most of the results (including from the Italian trial, Screening with Tomosynthesis or Regular Mammography, and all the retrospective studies) reported on FFDM + DBT compared to FFDM alone. Prospective trials reported incremental cancer detection results of an increase of between 2.5 and 4.0 cancers per 1000 screening examinations (pooled analysis = 3.9 per 1000 screening examinations) for FFDM + DBT compared to FFDM alone. In another prospective, fully paired trial using a sequential approach to screening with FFDM followed by DBT, Lång et al. (2016) reported that DBT alone detected more cancers in both more dense and more fatty breasts compared to FFDM alone. Lång et al. reported that this may mean that increases in CDR are not only due to improved conspicuity seen with DBT compared to FFDM alone.

It is important to note that other prospective trials (STORM and OTS) also reported increased CDR for all women regardless of BIRADS classification (eg, Skaane et al. [2013] reported comparable CDR for BIRADS 1-2 compared to BIRADS 3-4; Ciatto et al. [1993] reported CDR of 2.8 cancers per 1000 screening examinations for women with BIRADS 1-2 compared to 2.5 per 1000 screening examinations for BIRADS 3-4).

Results for CDR stratified by breast density may present results that are surprising, given that DBT improves conspicuity and should, in theory, provide improved images for women with more dense breasts which could lead to increased CDR for this population. However, the use of BIRADS to assess breast density can result in unreliable allocation to BIRADS category 2 and 3 (as discussed in section 3.1 of this report). This is because density classification can be affected by a wide range of factors and inter/intra reader variability. It is possible for women to be classified as having non-dense breasts (BIRADS 2) in one mammogram but be reclassified to having more dense breasts in the next mammogram (BIRADS 3) and vice versa. This creates a level of unreliability that could account for the smaller-than-expected incremental increase in CDR between women with more dense or less dense breasts. It may be that density classifications which report CDR, recall and false positives by 25th percentile (very dense) and 75th percentile (very fatty) could result in clearer (and possibly more accurate) incremental differences in CDR by density.

The DBT studies included in Melnikow et al.'s 2016 review are shown in Table 17 (below). Due to the limited availability of good quality DBT studies included within this review, it is difficult to draw further conclusions on the use of DBT as a supplemental testing tool for women with more dense breasts, other than it may be associated with increased cancer detection and lower recall rates, but studies informing Melnikow et al's systematic review are few and mostly retrospective (except for Ciatto et al. [1993], who reported on the STORM trial discussed above).

Table 17. Summary of studies on DBT as a screening modality for women with more dense breasts (Melnikowet al., 2016)

Study	Sensitivity	Specificity	PPV	Additional CDR	Recall rate
DBT Three studies, comprising of 10,937 exams Ciatto et al., 2013; McCarthy et al., 2014; Rose et al., 2013	N/A	N/A	N/A	1.4–2.5 per 1000	7-11%

Burkett and Hanemann (2016) as part of their narrative review discussed the ASTOUND trial. The ASTOUND trial is the largest prospective study of supplemental DBT and ultrasound testing to date, undertaken in Italy with 3,231 mammography-negative screening participants (median age, 51 years; interquartile range, 44 to 78 years) with dense breasts. This trial has released interim findings and found an increased cancer detection with supplemental ultrasound compared to DBT (ultrasound: 7.1 per 1000 women; DBT: 4.0 per 1000; p = .006), with a similar false-positive recall rate (ultrasound: 2.0%; DBT: 1.7%).

There are limited studies investigating the use of DBT in women with dense breasts. Overall, while tomosynthesis shows promise, particularly among those with dense breasts, there are no prospective large studies with survival outcomes to justify its routine use at this time.

MRI

MRI is recommended by some organisations for screening high-risk women. For example, the American Cancer Society (2018) recommends annual screening with MRI in women who are BRCA positive, who have had radiation to the chest between the ages of 10-30 years, or whose lifetime risk of breast cancer is greater or equal to 20%. The role MRI plays in screening is still unclear for women with dense breasts, as most of the studies focus on women with a range of risk factors for breast cancer (not just those with dense breasts).

No systematic reviews solely focused on the use of MRI as a supplemental testing tool for women with dense breasts were identified. We identified one narrative literature review (Lourenco and Mainiero, 2016). This review reported that MRI detected an additional 11 to 18 cancers per 1000 screening examinations compared to FFDM alone. MRI used in combination with ultrasound has a sensitivity of 90% for cancer detection in women with more dense breasts (Lourenco and Mainiero, 2016).

A systematic review was undertaken in 2016 to investigate supplemental testing (Melnikow et al., 2016). This review tested performance characteristics (eg, sensitivity, PPV) and clinical outcomes (eg, CDR, recall rates) of supplemental testing with breast ultrasound, MRI, and tomosynthesis in women with dense breasts and negative mammography. Limited methodological information was available; however, the flowcharts indicate that a systematic approach was undertaken. Metaanalysis was not performed due to few good-quality studies. In total, 18 studies were extracted; however, only four ultrasound/MRI good-quality studies and three fair DBT (as defined by the review process) were included for further analysis. MRI results of the three studies are included in Table 18 (below). These data suggest supplemental testing using MRI is beneficial for women with more dense breasts, with high sensitivity rates found. Although these investigations were also associated with increased recall rates for diagnostic investigation, additionally detected cancers were small. Kuhl et al.'s study found four DCIS and seven invasive carcinomas (Kuhl et al., 2014). Further examination of the ACRIN 6666 study found MRI significantly increased detection of early breast cancer beyond that seen with mammography or mammography combined with ultrasound. The 56% absolute increase in cancer detection seen in the MRI sub-study (as below) was greater than the 34% absolute increase in invasive cancer detection (explained in more detail below in the section on ultrasound) seen by adding annual ultrasound to mammography in the main ACRIN 6666 study.

Evidence on whether diagnosis of additional breast cancers identified by supplemental testing leads to improved clinical outcomes or what proportion of the cancers diagnosed represent overdiagnosis was not evaluated in this review.

Table 18. Summary of studies on MRI as a screening modality for women with more dense breast	s (Melnikow
et al., 2016)	

Study	Sensitivity	Specificity	PPV	Additional CDR	Recall rate
MRI Three studies, results from 2,057 exams (Berg, 2012; Kriege, 2006) + 105 women (Kuhl, 2014)	75-100%	78-94%	3-33%	3.5 - 28.6 per 1000 (34-86% invasive)	12-24%

O'Flynn et al. (2015) provided a narrative review on the use of MRI as a supplemental testing tool in women with dense breasts. No information on study selection was provided; however, two of the three studies reported were also included in Melnikow's review (Kuhl, 2014; Kriege, 2006). These were discussed along with the ACRIN 6666 study, which we have examined more closely (Berg et al., 2012). In the ACRIN 6666 study, 703 women with heterogeneously dense or extremely dense breasts (57.9%), with a mean age of 54.8 years, were enrolled in the MRI sub-study. Of the MRI participants, 16 women (2.6%) had breast cancer diagnosed.

• CDR for screening with MRI was 14.7 cancers per 1000 screening examinations (95%CI 3.5-25.9; *p*=.004).

- Sensitivity for MRI and mammography plus ultrasound was 1.00 (95%CI 0.79-1.00), specificity 0.65 (95%CI 0.61-0.69) and PPV₃ 0.19 (95%CI 0.11-0.29).
- The number of screens needed to detect one cancer was 127 (95%CI, 99-167) for mammography; 234 (95%CI 173-345) for supplemental ultrasound; and 68 (95%CI 39-286) for MRI after negative mammography and ultrasound results.

The addition of screening ultrasound or MRI to mammography in women at increased risk of breast cancer resulted in not only a higher CDR but also an increase in false-positive findings. There was, however, a large refusal rate which need to be considered if including MRI in a screening programme. In total, 512 women refused to participate in the MRI screening (42% of women invited). Some of the main reasons for refusal were: claustrophobia (25.4%); time constraints (18.2%); financial concerns (12.1%); physician did not provide referral and/or did not believe MRI was indicated (9.2%); not interested (7.8%); medical intolerance to MRI (7.6%); did not want intravenous injection (5.7%); and because of additional biopsy or other procedures that might be required after the MRI (5.3%; Berg et al., 2010). Notably, women with a higher lifetime risk of developing breast cancer (25% or greater) were more likely to participate.

The potential of MRI for screening women with dense breasts who have no other moderate or strong risk factors remains controversial because of the paucity of clinical evidence, the possibility of overdiagnosis, and the cost-effectiveness of the technique in this population. At present, no large randomised clinical trial has completed investigating the effects of supplemental MRI imaging in women with dense breasts, but the ongoing DENSE trial is expected to address this (see section 1.4 for further information on the DENSE trial). There are currently no long-term outcome studies that evaluate the effect of MRI screening on breast cancer mortality. With up to 50% of the population exhibiting dense breasts at mammography, replacing mammography with MRI screening in this cohort would impose a very substantial MRI burden. The health economic implications of such a change in practice would need to be fully and clearly justified. However, MRI preferentially detects the smaller node-negative cancers missed on mammography in dense breasts, and those which may be more aggressive. There is also evidence showing a survival benefit in women with a familial risk of breast cancer screened by MRI (Evans et al., 2014; Saadatmand et al., 2013). MRI screening has potential to improve outcomes for women with dense breasts. Nonetheless, the use of MRI for screening such a large section of the population would be subject to intense debate until evidence from large scale clinical trials emerges.

Optical mammography

Optical mammography is a new diagnostic method that uses near-infrared light for detection of functional abnormalities and shows tissue activities by measuring absorption and scattering of near-infrared light. It is unclear whether it has a screening application yet (and as such has not been discussed in detail before in this section). One systematic review of 12 studies (including 10 diagnostic studies, a systematic review and a multicentre clinical trial) aimed to evaluate the safety and effectiveness of this technology (Sari et al., 2013). Mammographic density was an outcome included in this study, so we have included this modality for completeness.

Different performance measures were used by the included studies, limiting the analysis. The included RCT, a 4-year clinical trial, was conducted at five institutions using infrared imaging of women for whom breast biopsy had been recommended for further review (Parisky et al., 2003). This study found that among 875 biopsied lesions, suspicion index led to 97% sensitivity, 14% specificity, 95% negative predictive value and 24% PPV. No measures were provided specifically for dense breasts. Sari and colleagues' (2013) review, which provided few details of other studies and limited information regarding breast density, concluded that optical mammography is a safe,

non-invasive, non-ionized diagnostic technology that can be used as a diagnostic supplement alongside conventional mammography for differentiating benign and malignant tumours. The review also recommended that younger women with higher breast density should be screened more often by optical mammography than those who have a lower breast density (although provided no supporting evidence for this claim). Optical mammography may serve as a viable, cost effective and non-ionized alternative for screening women with dense breasts and who have restrictions in using mammography, but further studies involving larger sample sizes are needed before optical imaging can be used as a reliable tool for breast cancer screening, particularly in women with dense breasts.

MBI

No reviews demonstrating mortality reduction in women who received supplemental testing with MBI exist. While there is a lot of information on MBI, clinical data on supplemental testing with MBI in non-high-risk women with dense breasts and negative mammography is also limited as the research is yet to progress to large prospective studies.

Holbrook and Newell (2015) undertook a review (non-systematic) to investigate the use of a newer MBI imaging modality. Holbrook and Newell's review did not outline the search strategy but included 26 different studies, most of which have small sample sizes, are retrospective, or both. This review concluded that some studies confirm MBI has high sensitivity (91–96%) in finding cancers in more dense breasts (and up to 100% in less dense breasts) and suggest improved specificity (60–77%) compared with other technologies such as MRI.

One of the most prominent studies within Holbrook and Newel's review was Rhodes (2011). Two prospective single-centre trials (Rhodes, 2011 followed by Rhodes, 2015) examined MBI as a supplement to mammography in women with dense breasts (as defined by visual scale of >51% percent density). In both trials, asymptomatic women presenting for screening mammography were offered supplemental MBI if they were known to have dense breasts based on a prior mammography study. Supplemental MBI increased cancer detection by 7.5 - 8.8 cancers per 1000 screening examinations. The sensitivity of MBI + mammography of both studies was significantly higher than that of mammography alone (98% + 91%, respectively vs 27% (mammography)). Adding supplemental MBI to screening mammography resulted in a similar rate of additional recalls (5.9% and 6.6%, respectively) and similar rate of malignancy per biopsy for MBI findings (PPV₃ = 24% and 28%, respectively).

A more recent (non-systematic) review completed by Hruska (2017) aimed to provide an update on MBI as a supplemental testing tool (including the Rhodes studies). Hruska provided a 'summary of studies' evaluating the performance of screening MBI, however it was not described how these studies were selected or screened. Table 19 (below) provides a summary of these studies.

Study	Participant Inclusion Criteria	Administered Activity of 99mTc Sestamibi	Invasive Cancer and DCIS detection rate	Invasive Cancer Only detection rate	Size of Cancers Detected Only by MBI or BSGI (Median, Range - cm)	Additional Recall Rate ^a	PPV ₃ of MBI Findings
Brem et al. (2016)	Recent negative mammogram; at least one breast cancer risk factor N=849	590–1190 MBq (16–32 mCi) or 260–500 MBq (7–13.5 mCi)	16.5	7.1	2.5, 0.3 – 4.0	25%	14.4%
Shermis et al. (2016)	Recent negative mammogram; dense breasts; primarily < 20% lifetime risk N=1696	300 MBq (8 mCi)	7.7	6.5	1.0, 0.6 – 2.4	8.4%	19%
Rhodes et al. (2015)	Dense breasts N= 1585	300 MBq (8 mCi)	8.8	6.9	0.9, 0.5 – 4.1	6.6%	33%
Rhodes et al. (2011)	Dense breasts; at least one additional breast cancer risk factor N= 936	740 MBq (20 mCi)	7.5	5.3	1.1, 0.4 – 5.1	5.9%	28%

Table 10	Cummers	fI itomotumo	Even in in a MI	DI and DCCI	a a Cummlann amtal	Ima aima '	Fachulauaa
Table 19.	Summary C	of Literature	Examining ME	si and BSGI	as supplemental	Imaging	rechniques

ICDR = incremental cancer detection rate of MBI relative to screening mammography in number of women diagnosed with cancer per 1000 women screened, DCIS, PPV3 = proportion of positive findings on MBI or BSGI that resulted in a diagnosis of malignancy, ^a Refers to proportion of patients recalled due to screening MBI findings beyond the proportion or patients already recalled for screening mammography findings,

One of the studies included in Hruska's (2017) review was a retrospective study based in a large community practice (Shermis, 2016). MBI was performed on 1,696 women who had negative findings on mammography, had dense breast tissue, and were not otherwise considered high risk. Positive MBI findings occurred in 143 of the 1,696 women, predominantly among women with more dense breasts:

- 14 women were BIRADS category 0
- 73 women were BIRADS category 3
- 55 women were BIRADS category 4, and
- one women was BIRADS category 5.

The recall rate was 8.4% (143/1,696). PPV₁ was 9.1% (13/143). An additional 8.4% of women were recalled due to MBI findings, and MBI detected 7.7 cancers per 1000 screening examinations. The lack of one-year follow-up information on a number of image sets (966 of 1,696) precluded this study from determining the total number of interval cancers and the absolute sensitivity and specificity of MBI.

Another retrospective review reported the performance of MBI in women with dense (BIRADS3-4) breasts, recent negative mammography findings and who were considered at increased risk due to one or more risk factors, primarily including personal or family history of breast cancer (Brem et al., 2016). MBI screening in these women resulted in an incremental CDR of 16.5 cancers per 1,000 screening examinations relative to mammography; this is within the range of other reported findings for MRI supplemental testing (Berg, 2012; Kriege 2006; Kuhl, 2014). MBI supplemental testing led to additional recalls in 25% of women, considerably higher than the recall rate reported for the other MBI studies listed above (5.9–8.4%). This difference may be partially explained by a known greater likelihood of radiologists to recall women with multiple risk factors.

One important measure of supplemental testing effectiveness is the relative detection of clinically important cancers versus non-invasive cancers that may contribute to overdiagnosis. In this review, of the reported 41 malignancies detected only by supplemental MBI imaging, 31 (76%) were invasive and 10 (24%) had invasive lobular histology. The studies also revealed a wide range of tumour sizes that were occult on mammography in dense breasts.

Despite the promising results such as increased sensitivity and CDR of MBI compared to FFDM alone, for women with dense breasts considerable barriers still exist to the widespread adoption of MBI. MBI has not yet been validated as an effective screening tool in large prospective studies (Holbrook & Newel, 2015). In addition, whole-body radiation dose remains a significant concern, with a radiation dose estimated to be 10–20 times that of mammography for patients in studies such as Rhodes et al. (2011) and Brem et al. (2016), who used doses of 590–1190 MBq (16–32 mCi) of 99mTc-sestamibi (Hendrick, 2010). That said, more recent studies have been finding promising results using a lower dose of 8 to 30 mCi, corresponding to a smaller radiation (2.4 mSv) dose, which is closer to that of mammography and tomosynthesis (0.5 and 1.2mSv, respectively; Hruska, 2017). This slight increase in radiation may be more acceptable for women with dense breasts, given the much higher sensitivity for MBI vs FFDM. Further clinical studies are needed, alongside social studies which educate the medical and lay communities about the risk of radiation at low medical imaging doses (Hruska, 2017).

Ultrasonography

No reviews demonstrating mortality reduction in women who received supplemental testing with ultrasound exist. Data on supplemental testing with ultrasound in non-high-risk women with dense breasts and negative mammography is also limited. However, we identified four systematic reviews and three narrative reviews exploring the role of ultrasound for supplemental imaging of women (although some included more information about women with more dense breasts than others).

Systematic reviews

In 2013, a Cochrane review (Gartlehner et al., 2013) was undertaken to assess the comparative effectiveness and safety of mammography in combination with breast ultrasonography compared to mammography for breast cancer screening for women aged 40-75 years at average risk of breast cancer (this was defined as a lifetime risk of less than 15% or who have dense breasts without any additional risk factors for breast cancer). The main inclusion criteria were RCTs with either individual or cluster randomisation and prospective, controlled non-randomised studies with a low risk of bias and a sample size of at least 500 participants. Studies needed to have a follow-up period of at least one year and had to include at least one relevant outcome. This Cochrane review did not find any controlled studies assessing the incremental benefits and harms of adjunct screening ultrasonography in women at average risk for breast cancer. Based on extrapolations from women at elevated risk of breast cancer, they found that false-positive recall rates would exceed 98% for women at average risk screened using ultrasonography. Overall, the authors concluded that there is no methodologically sound evidence available to justify the

routine use of ultrasonography for supplemental testing in women at average risk of breast cancer, or for women with dense or very dense breasts.

In 2015, Scheel and colleagues undertook a systematic review examining studies published from January 2000 through April 2013 that used either automated breast ultrasound (ABUS) or handheld ultrasound (HHUS) as an adjunct to screening mammography for women with heterogeneously or extremely dense breasts (see Table 20, overleaf). Included studies were both retrospective and prospective in design. Participants included in the studies were of varying ages, with mean ages ranging from 45 to 65 years (HHUS) and 53 to 57 years (ABUS). Melnikow et al. (2016) also reviewed ten out of the 12 studies included in Scheel and colleagues' work. Comparisons between these two reviews are difficult, as limited analysis and study details are provided by the Melnikow et al. review.

Scheel et al. (2015) reported a median CDR for all adjunct breast ultrasound of 4.2 cancers per 1000 screening examinations. Melnikow et al. (2016) reported a slightly higher CDR, at 4.4 cancers detected per 1000 screening examinations. The authors noted that three of the studies included in the analysis were conducted in Connecticut after it passed legislation requiring breast density notification to women. In these three studies, the additional biopsy rate and additional CDR ranged from 32.8 to 71 biopsies per 1000 examinations and 1.8 to 4.6 cancers per 1000 screening examinations. This is much lower than the mean values reported for the whole sample by the Melnikow and Scheel studies, and is likely to reflect the routine clinical use of adjunct ultrasound and the populations receiving adjunct breast ultrasound in this state.

Most of the breast cancers identified by adjunctive ultrasound were small in size and node negative in stage. Scheel et al. suggested that these are the cancers that are potentially curable by early detection and amenable to less aggressive treatment. Women with screen-detected breast cancers are more likely to be eligible for lumpectomy rather than mastectomy and may not require systemic chemotherapy compared with women whose breast cancers present clinically between screens. Thus, earlier detection with screening ultrasound may improve both quality and quantity of life. Conversely, some of these early-stage cancers may not have progressed significantly before the next routine screening examination with mammography. Thus, they may ultimately have been detected and cured following mammographic screening alone.

An additional concern related to detecting additional breast cancers with adjunctive ultrasound is the high number of breast biopsies performed during the diagnostic process. The biopsy rate for HHUS after negative mammography ranged from 12 to 107 per 1,000 women screened, with a median of 56. This is more than five times greater than the approximately 10 biopsies performed per 1,000 women screened with mammography reported previously (Rosenburg et al., 2006). Given that the chance of biopsy recommendation with adjunct ultrasound screening is far higher than with screening mammography and the CDR is lower, it will be important to consider an individual woman's preferences when deciding whether to pursue adjunctive ultrasound screening.

Table 20. Studies included in Scheel et al. (2015)

20A: HHUS

Study	Years of study	Study design	Location	Number of women	Mean age, Y	Mammographic breast density	Biopsy rate (per 1000 examinations)	CDR (per 1000 examinations)	Invasive cancers, n, %	Mean invasive cancer size, mm	Node negative, n, %
Crystal et al. (2003)	2000-2002	NR	Israel	1517	52.1	Scattered, heterogeneously and extremely dense	25	4.6	7 (100)	9.6	6 (86)
De Felice et al. (2007)	2000-2006	Prospective	Italy	1754	65	Heterogeneously and extremely dense	106.6	6.8	10 (83)	10	NR
Brancato, et al. (2007)	2003-2006	NR	Italy	5227	51.9	Heterogeneously and extremely dense	11.9	0.3	2 (100)	NR	NR
Corsetti, et al. (2008)	2000-2007	Retrospective	Italy	9157	52	Heterogeneously and extremely dense	56.1	4	36 (97)	NR	29 (86)
Berg (2008)	2004-2006	Prospective	United States	2501	55	Heterogeneously and extremely dense	68	4.4	10 (91)	10	8 (89)
Leong et al. (2012)	2002-2004	Prospective	Singapore	141	45.1	Heterogeneously and extremely dense	99.3	14	1 (50)	13	1 (100)
Hooley et al. (2012)	2009-2010	Retrospective	United States (Connecticut)	648	52	Heterogeneously and extremely dense	71	4.6	2 (67)	6.5	2 (100)

Study	Years of study	Study design	Location	Number of women	Mean age, y	Mammographic breast density	Biopsy rate (per 1000 examinations)	CDR (per 1000 examinations)	Invasive cancers, n, %	Mean invasive cancer size, mm	Node negative, n, %
Weigert & Steenbergen (2012)	2009-2010	Retrospective	United States (Connecticut)	8647	NR	Heterogeneously and extremely dense	48.3	3.2	24 (85)	19	NR
Parris et al. (2013)	2009-2010	Retrospective	United States (Connecticut)	5519	52	Heterogeneously and extremely dense	32.8	1.8	9 (90)	9.7	7 (78)
Girardi et al. (2013)	2009-2010	Retrospective	Italy	9960	51	Heterogeneously and extremely dense	NR	2.2	NR	8	NR

20B: ABUS

Study	Years of study	Study design	Location	Number of women	Mean age, Y	Mammographic breast density	Biopsy rate (per 1000 examinations)	CDR (per 1000 examinations)	Invasive cancers, n, %	Mean invasive cancer size, mm	Node negative, n, %
Kelly et al. (2010)	2003-2007	Prospective	United States	4419	53	Heterogeneously and extremely dense	11.7	3.6	22 (96)	NR	NR
Guiliano & Giuliano (2013)	2010-2011	Prospective	United States	3418	57	Heterogeneously and extremely dense	NR	12.3	42 (100)	14.3	41 (98)

Melnikow et al. (2016) also reported on ultrasound. The values reported below represent the sensitivity and specificity for detection of additional cancers in women with negative mammography. Similarly, the defined CDR, recall rates and biopsy rates include only those additional cancers, recalls, and biopsies related to supplemental testing after negative mammography. No details were provided about the sampling population for these studies, no pooled analysis was completed, and no p values were calculated. The results of these are summarised below in Table 21:

	Sensitivity	Specificity	PPV	Additional CDR	Recall rate
Ultrasound (2 studies, results comprising of 10,638 exams) Berg, 2012 ([ACRIN 6666) +Corsetti, 2011	80-83%	86 -94%	3-8%	4.4 per 1000 (89- 93% invasive)	14%

Table 21. Summary of studies presented in Melnikow et al. (2016)

Narrative reviews

Lourenco and Mainiero (2016), in their narrative review, provided a commentary of 75 studies of varying design and quality and evaluated established and newer alternative breast imaging technologies as well as recent data regarding their role in optimising patient care. One of the main studies was the ACRIN 6666 study. In the American College of Radiology Imaging Network (ACRIN) 6666 prospective trial of 2,712 women, supplemental testing ultrasound resulted in added detection (after mammography) of 3-4 cancers per 1,000 screening examinations in incidence studies compared to FFDM alone. Most of the additional cancers were node-negative invasive cancers (Berg et al, 2008). The incidence rounds of the trial also reported that supplemental ultrasound resulted in biopsy in 5% of women compared with 2% of women referred for biopsy based on mammography alone, and a low PPV_1 of 6.8%.

For comparison, Lourenco and Mainiero (2016) reported that MRI detects an additional 11-18 cancers per 1000 screening examinations for women with dense breasts, depending upon a woman's risk factors. In addition to being less sensitive than MRI, ultrasound has poorer specificity, even when women have had prior ultrasound screening (i.e., incidence screening). Berg and Mendelson (2014) also completed a narrative review of 85 studies looking at the use of ultrasound in breast screening, with a particular focus on the current evidence regarding the use of HHUS. The studies included were of varying design and quality. Based on findings from four studies including 1,037 women, Berg and Mendelson concluded that there is no added benefit to screening using ultrasound where MRI is already being performed. This is because ultrasound has not been found to be effective at identifying cancers occult to MRI, whereas MRI is able to detect cancers that are not detectable by ultrasound. This aligns with conclusions drawn from other reviews previously discussed.

An integrative review of studies with a non-randomized prospective design sought to appraise breast cancer screening studies utilising mammography, ultrasound, or breast MRI (Ravet et al., 2010). As a subset of this review, four studies compared mammography to that of ultrasound in women with dense breasts (with density being defined as a BIRADS density category of 2–4 [approximately 75% of women]) according to the mammogram. All four studies found an increase in the diagnosis of breast cancer by ultrasound in women with dense breast tissue however

different metrics were used so it is difficult to compare across studies. One study (Kolb et al., 2002) found the sensitivity of mammography decreased with an increase in density, whereas the sensitivity of ultrasound increased with an increase in density; the sensitivity for mammography for BIRADS 4 was 47.8% and for ultrasound 76.1%. It was recommended that women with a BIRADS density category of 2–4 should receive a yearly ultrasound along with mammography, however data was not presented to support this claim and the studies were small with large variability in findings (Ravet et al., 2010).

Burkett and Hanneman reviewed the literature (52 studies were included) to determine if supplemental testing ultrasound may be beneficial for women with dense breast tissue and intermediate or average risk for breast cancer, including women in specific ethnic populations or of younger ages.

In this narrative review, the results from the Connecticut experiment were discussed to investigate the role of supplemental imaging for women with intermediate or average risk and increased breast density. Following implementation of breast density reporting laws, a multicentre retrospective study was conducted in Connecticut (Weigert and Steenbergen, 2012) investigating the performance of supplemental testing ultrasound in women with dense but mammographically normal breasts:

- 86% (7,451/8,647) of the ultrasounds were BIRADS 1 or 2
- 9% (767/8,647) were BIRADS 3
- 5% (429/8,647) were BIRADS 4 or 5

No specific risk factors were required in the inclusion criteria aside from at least 50% breast density on mammography. The use of supplemental ultrasound imaging in women of average risk had high sensitivity and specificity and resulted in an additional 3.25 malignant lesions detected per 1,000 examinations when compared to mammography alone, a result consistent with the ACRIN 6666 study. Table 22 (below) compares the findings from the two studies.

Author	Study	Sensitivity (%)	Specificity (%)	PPV (%)	Additional cancer detection rate per 1000 examinations
Weigert & Steenbergen (2012)	Connecticut experiment	96.60	94.90	6.70	3.25
Berg et al. (2012)	ACRIN 6666	76	84	16	3.70

Table 22. Connecticut Experiment compared to the prospective ACRIN 6666 Study

Following on, Burkett and Hanemann (2016) also reviewed the results of the J-START trial; these results are discussed below under RCTs. Lastly, the Burkett and Hanemann review examined the difference in supplementary screening by ethnicity. All studies (Shen et al., 2015; Chae et al., 2013; Leong et al., 2012) described in Table 23 (overleaf) investigated the additional cancers detected by ultrasound and mammography compared to mammography alone in women with increased breast density. Burkett and Hanemann noted that in similar studies the additional CDR for

European women ranges from 3 to 5 per 1,000. Sensitivity of supplemental testing by ultrasound was significantly higher than that of mammography alone in the two studies that investigated this.

Study	Population Geography	Number of Patients Enrolled	Sensitivity (Ultrasound) (%)	Sensitivity (Mammography) (%)	<i>P</i> Value for Sensitivity	Additional Cancer Detection per 1000 Examinations
Shen et al. (2015)	China	13,339	100	57.1	0.04	1.3
Leong et al. (2012)	Singapore	141	100	N/A	N/A	14
Chae et al. (2013)	Korea	20,864	100	54.5	0.002	2.5

Randomised Controlled Trials

One RCT was identified for this literature review (Ohuchi et al., 2016). As discussed in section 3.2, younger women (<50 years) have higher breast density but lower cancer risk than that of older women. Some studies have found that the sensitivity of screening mammography for women aged 40 to 49 years in the general population is unacceptably low. Women in this age group may benefit from supplemental testing by ultrasound.

Between July 2007 and March 2011, the J-START trial enrolled asymptomatic women aged 40–49 years at 42 study sites in 23 prefectures. Eligible women had no history of any cancer in the previous five years and were expected to live for more than five years. Participants were randomly assigned in 1:1 ratio to undergo mammography and ultrasonography (intervention group) or mammography alone (control group) twice in two years. The primary outcome was sensitivity, specificity, cancer detection rate, and stage distribution at the first round of screening. Analysis was by intention to treat.

Table 24 (below) shows that this study found sensitivity was significantly higher (p=.0004) in the intervention group than in the control group, whereas specificity was significantly lower (p=.0001)

	Sensitivity (95%CI)	Specificity (95% Cl)	Number of cancers detected	Number of cancers at stage 0 or I	Interval cancers
Intervention (n=36,859)	91.1% (87.2-95.0)	87.7% (97.3-88.0)	184 (0·50%)	144 (71·3%)	18 (0·05%)
Control (n=36,139)	77.0% (70.3-83.7)	91.4% (91.1-91.7)	117 (0·32%)	79 (52·0%)	35 (0·10%)

Table 24. Results from Ohuchi et al. (2016) RCT

More cancers were detected in the intervention group than in the control group (p=.0003) meaning the use of adjunctive ultrasonography was associated with a 0.17% overall increase in the screening detection rate (similar to the studies presented above by Scheel et al. [2015] and Burkett and Hanemann [2016]). Smaller and, node-negative cancers (stage 0 and I) cancers were found more frequently in the intervention compared to the control group (p=.0194). The frequency of breast cancers of clinical stage II or worse did not differ significantly between groups. Fewer interval cancers were detected in the intervention group compared with the control group (p=.034) providing a reduction in interval cancers by 0.05%.

An important limitation of this study is that sensitivity and specificity were calculated with the data from the first round of screening. Since characteristics of breast cancer, such as distribution of tumour size or sojourn time (i.e. the amount of time that a person is asymptomatic but the cancer is detectable through screening), would differ between the first and later rounds of screening, findings cannot be extended beyond the first round. In this study, 57.7% of the women were classified as having dense breasts (scores of 3 or 4 BIRADS); results relating to this population will be reported in more detail in the future. In conclusion, this study found adjunctive ultrasonography increases sensitivity and detection rate of early cancers in women aged 40–49 years, but reduces specificity, relative to mammography alone.

Summary

Ultrasound is widely available, easy to conduct, and does not expose women to radiation. It also costs less than some other supplemental imaging modalities discussed in this section. It can detect more cancers and may be beneficial in a variety of population subtypes; however, it will also increase false positives and recall rates compared to FFDM alone. Ultrasound can detect cancers that are small in size and node negative in stage, which improves patient outcomes and can avoid more invasive treatments such as mastectomy. Therefore, ultrasonography could offer a low-cost way to increase sensitivity and detection rates of early cancers in women with dense breasts. Long-term follow-up is needed to assess whether the combined approach could reduce the frequency of advanced breast cancers at detection and breast cancer mortality.

3.4.3. The role of computer-aided detection

Recently, computer-aided detection (CADe) systems have been developed to reduce the expense and to improve the capability of radiologists in the interpretation of medical images and differentiation between benign and malignant tissues. CADe can be used in conjunction with any imaging modality as the outputs are derived using various techniques in computer vision to present some of the significant parameters such as the location of suspicious lesions and the likelihood of malignancy of detected lesions. In mammography, CADe highlights microcalcification clusters and hyperdense structures in the soft tissue. This assists the radiologist in drawing conclusions about the condition of the pathology and improves efficiencies. CADx (diagnosis) helps determine the grading of malignant tissues.

A 2013 review (non-systematic) on computer-aided detection in screening mammography concluded that computer-aided detection systems have high sensitivity (>90%) in cancer detection with both mammography and ultrasound. However, the benefits of using computer-aided detection in dense breast tissue remains uncertain. If breast density is masking malignant tissues, the computer-aided detection system cannot read this area well (Jalalian et al., 2013). It is unlikely that in its current state CAD will provide improved screening outcomes for women with dense breasts. The review by Jalalian concurs with earlier studies (predating this review) which found possible tendency of breast density to affect the CAD performance in the detection of cancer

(Obenauer et al., 2006.) Ho and Lam (2003) found a decrease in sensitivity from 93% (fatty breasts) to 64% (very dense breasts).

3.4.4. Screening frequency

Most screening programmes (including European programs, the BSA program and Breast Screen Aotearoa) recommend screening by mammography with double reading every two years for asymptomatic women. American programs tend to screen asymptomatic women annually using a single reader strategy. Data is limited and mixed on the optimal frequency for performing mammography for all women as well as those with more dense breasts. Annual screening is associated with more harms and costs than screening every two years, and the difference in absolute benefits between annual and biennial screening is small. While some data suggest benefit for annual screening for some women (eg, premenopausal), there is limited information on women with mammographically dense breasts. Our search found one systematic review (Nelson et al., 2016) investigating frequency of screening in women with high dense breast density.

Nelson et al. (2016) undertook a large review of English-language systematic reviews, randomised trials, and observational studies. This review provides an update on the harms of breast cancer screening, including false-positive mammography results, over-diagnosis, anxiety, pain during procedures, and radiation exposure, and how these adverse effects vary by age, risk factor, screening interval, and screening modality. Most studies included in this review had designs for which quality rating criteria are not available, which limited data synthesis. Quality (eg, internal validity, sample size, consistency etc) of the studies was assessed when possible.

Based on two post-intervention US studies (Hubbard et al., 2011 and Kerlikowske et al., 2011), 10-year cumulative rates of false-positive mammography results and biopsies were higher with annual compared to biennial screening (61% vs. 42% and 7% vs. 5%, respectively), including for women with heterogeneously or extremely dense breasts, those aged 40–49 years, and those using combination hormone therapy. The quality of these two studies are high, with good applicability and consistency; however, they do not report on all risk factors. Kerlikowske et al. (2011) included 11,474 women with breast cancer and 922,642 without. Hubbard et al. (2011) had a study population of 169,456.

No further commentary was provided by Nelson et al. on the implications of these studies so it is difficult to make any conclusions with regards to screening frequency and dense breasts. These findings are also reflected by the American Cancer Society (2018), which state that there is not enough evidence to make a recommendation for or against yearly MRI screening for women who have "extremely" or "heterogeneously" dense breasts as seen on a mammogram. They also do not have any recommendations regarding mammogram frequency for women with more dense breasts.

3.4.5. Summary: supplemental testing and masking

DBT, MRI, MBI and ultrasound are screening options that may be considered in addition to mammography for women with dense breasts. Women with dense breast tissue show improved CDR with these supplemental testing modalities. While supplemental testing is useful for improving CDR, it does increase false positive and recall rates, which can lead to further testing including biopsies, increased anxiety, inconvenience, and additional cost. Furthermore, it is important to recognise that this is a rapidly evolving field with new imaging techniques regularly being developed (such as optical mammography). Consensus on which additional modality is best

has not yet been reached and there is no best method for measuring masking. Each supplemental imaging modality provides trade-offs via their advantages and disadvantages.

There is no evidence to determine best screening frequencies, although some studies suggest annual screening in high risk women, including those who have more dense breasts. To be able to define meaningful clinical outcomes of women with dense breasts, well-designed, long-term prospective, comparative studies of supplemental imaging are needed. As DBT becomes more common place as a screening tool, studies will need to evaluate if additional testing is still required for women with dense breasts if research complexities associated with the definition of 'dense breasts' are overcome (i.e., studies compare BIRADS 1 to BIRADS 4). Further research is also needed to understand what information women and healthcare professionals need to be informed as the long-term effect on morbidity and mortality related to these supplemental imaging tests is unclear.

4. ASSESSMENT OF EVIDENCE AND PRESENTATION OF RESULTS: THE IMPACT OF BREAST DENSITY ON CLINICAL OUTCOMES

Mandatory dense breast tissue notifications have gained momentum in the United States since Connecticut passed the first notification law in 2009, which required women to be told breast density findings. Since approximately 50% of all women over the age of 40 years have heterogeneously or extremely dense breast tissue, notification laws impact a large number of women. This may have far-reaching consequences for women's understanding of breast cancer risk and the impact on this understanding on health-seeking behaviour, including feeling less informed about screening-related participation, concern about the lower sensitivity of mammography in women with dense breasts and how this affects individual women's decision to continue participation or re-enter a screening program post-diagnosis and treatment and anxiety.

The role of notification is contentious. Some researchers reported that notification promotes women's awareness of breast density and can be beneficial (Cappello, 2013) whereas others have argued notifications may inflate risk perceptions without improving women's health (Ho et al., 2013). Although the American College of Radiology (ACR, 2014) does not oppose notification laws, a 2014 ACR position paper expressed concern that notifications may unduly increase anxiety about breast cancer risk. This may also encourage consumer demand for (and private practice provision of) widespread breast cancer screening by imaging techniques with lower specificity than mammography (eg, ultrasound and/or MRI) before RCTs have established whether the use of such screening modalities improves long-term health outcomes for women with dense breast tissue. There is also concern that notification could increase screening disparities, as costs will prohibit some women but not others from receiving additional tests. In 2017, the ACR updated its position statement to say that the provision of information about breast density may help inform dialogue between women and health practitioners.

Chapter 4 of this report investigates systematic reviews and narrative literature reporting on:

- physical health outcomes for women who have received information about their breast density, and
- mental health outcomes for women who have received information about their breast density.

The discussion for each area of interest includes a description of the number of articles and a summary of the results from all studies. Detailed study tables provide additional material about study population, methodology, intervention, comparator and key results.

Overall, the literature in this area is scarce and is mainly focused in the United States. Available literature is mainly in the form of observation studies and of low quality.

4.1. Physical health outcomes

Information about tumour characteristics (type, size and grade), stage and volume-specific incidence patterns of breast cancer diagnosis can over time provide evidence of a more or less effective screening program. Also, information about long-term improvements in health outcomes are critical for determining whether the use of a screening technique (or approach to screening) should be recommended.

Given the relatively recent advent of breast density notification, the follow-up for studies reporting on breast density notification and physical health outcomes has not been sufficiently long enough to draw conclusions about the relationship between breast density notification and the impact on the stage/volume of breast cancer diagnosis. We also do not know whether long-term health outcomes related to breast cancer differ for women whose only risk factor for breast cancer is having more dense breasts compared to other average-risk women. That is, we do not yet know if knowing breast density improves health outcomes compared to not knowing or the mechanism by which this would occur.

Our review returned very few studies that investigated long-term physical health outcomes.

Systematic reviews

No systematic reviews identified.

Narrative literature reviews

No literature reviews identified.

Observational studies

Two studies: Richman, Asch, Bendavid, Bhattacharya, & Owens (2017); Sanders, King, & Goodman (2016)

Key findings about notification and physical health outcomes

There is insufficient evidence to draw conclusions on the impact of breast density (where this is the only risk factor) and long-term clinical health outcomes, or the impact of breast density notifications on physical health outcomes. No studies reported on outcomes such as mortality or interval cancer rates in asymptomatic women with dense breasts and no other moderate or strong risk factors for breast cancer. The findings demonstrate that breast density notification may drive an increase in supplemental imaging and as a result, it is associated with an increased detection of breast cancer. However, it is unclear if this association indicates earlier/improved detection of cancers or an over-diagnosis of cancers.

Our literature review reports on two articles discussing the changes in breast cancer diagnosis following the enactment of breast density notification legislation.

Richman et al. (2017) examined the breast cancer stage at diagnosis after the enactment of breast density notification legislation in Connecticut, compared to changes among women in control states. The study included 466,930 women, with 25,592 living in Connecticut. Legislation was associated with a significant 1.38 percentage point (95%CI 0.12 to 2.63) increase in the proportion of women in Connecticut versus control states who had localised invasive cancer at the time of diagnosis, and a significant 1.12 percentage point (95%CI –2.21 to –0.08) decline in the proportion of women with DCIS at diagnosis. Breast density notification legislation was not significantly associated with a change in the proportion of women in Connecticut versus control states with regional-stage (–0.09 percentage points, 95%CI –1.01 to 1.02) or metastatic disease (–0.24, 95%CI –0.75 to 0.28). County-level analyses and analyses limited to women younger than 50 years found no statistically significant associations. Breast density notification legislation was associated with a small increase in women diagnosed with localised invasive breast cancer. The authors concluded it is not known whether the findings reflect potentially beneficial early detection or potentially harmful overdiagnosis associated with breast density notification.

Sanders et al. (2016) assessed the impact of the New Jersey breast density legislation on imaging volumes and breast cancer diagnosis at one of the state's largest breast centres. A retrospective

chart review was performed to determine changes in imaging and intervention utilization and modality of cancer diagnosis after enactment of the legislation. Screening ultrasound increased significantly after the implementation of the breast density legislation, by 651% (1,530 vs 11,486). MRI utilisation increased by 59.3% (2,595 vs 4,134). A total of 1,213 cancers were included in the final analysis, 592 in the first time period and 621 after legislation implementation. Breast cancer was most commonly detected on screening mammography, followed by diagnostic mammography with ultrasound for a palpable lump, in both time periods. Of the 621 cancers analysed, 26.1% (n = 162) were found in women aged 50 years or younger. Results demonstrated that with respect to how malignancies were detected, age and average mammographic density were both statistically significant (*p*=.002). The authors demonstrated that the number of supplemental ultrasound and MRI examinations increased after the implementation of breast density notification legislation. Evidence on whether diagnosis of additional breast cancers identified by supplemental tests leads to improved clinical outcomes was not evaluated in this study.

To be able to provide informed policy and practice it is essential that the effects of breast density notification on physical health outcomes are understood; research is needed in this area.

4.2. Mental health outcomes

One of the concerns with reporting breast density to women is that it may result in increased negative psychological outcomes. Negative mental health outcomes may arise from notification due to increased anxiety about the relationship between having dense breasts and breast cancer or fear of developing cancer. However, without research that examines whether women's awareness of their breast density is associated with cognitive and emotional outcomes prior to implementation of breast density notification, it is impossible to say whether breast density notifications make women with more dense breasts more anxious relative to women with less dense breasts, or whether they were more anxious to begin with (Manning, Albrecht, Yilmaz-Saab, Shultz, & Purrington, 2016). Women with more dense breasts are also more likely to be recalled from screening, which can also increase anxiety, although this is related to a clinical screening outcome (a positive mammogram) and not related to reporting of breast density.

This literature review reports on one systematic review, one literature review and seven observational studies that examined the potential psychological effects of breast density notification on women. Specific areas were:

- overall impact on mental health, and
- breast density knowledge and awareness.

The articles included in our literature review were:

Systematic reviews

One review: Melnikow et al. (2016)

Narrative literature reviews

One review: Santiago-Rivas, Benjamin, & Jandorf (2016)

Observational studies

Seven studies: Manning et al. (2017); Moothathu et al. (2017); Kressin, Gunn, & Battaglia (2016); Manning et al. (2016); Rhodes et al. (2015); Trinh et al. (2015); Yeh, Schnur, Margolies, & Montgomery (2015); Manning et al. (2013)

Key findings about notification and mental health outcomes

While there is some association between notifying women about their breast density and negative mental health outcomes (eg, increased anxiety about developing breast cancer) in women, the identified studies do not indicate a consistent and significant relationship. However, this could also signal that women generally have a poor understanding of the summary letter or a lack of knowledge of the relationship between breast density and cancer risk. There is also a limited body of evidence in this area, including a lack of studies that assess the mental health outcomes of notification in women with more dense breasts only, and cohort studies following women before and after the implementation of legislation (with a long-term follow up) to understand how the notifications impact on screening behaviour.

Two American studies reported on ethnic differences in emotional responses to breast density notification. Both studies found African American women to have more breast density-related anxiety compared to European women, however socioeconomic status and knowledge partially accounted for the effect of ethnicity on psychological response.

A small number of studies examined the association between breast density awareness or knowledge (as a result of breast density notification) and women's responses to breast cancer screening. The studies indicate that breast density notification may increase women's engagement in screening but further research to determine this relationship is needed.

4.2.1. Overall mental health

Five articles reported on overall mental health outcomes associated with knowledge of breast density. Inconsistent results were reported.

Systematic review and literature review

Our search returned one systematic review related to the impact of breast density knowledge on mental health outcomes (Melnikow et al., 2016). No pooled analysis relating to mental health outcomes was completed in this review. Information about Melnikow et al.'s systematic review methodology is discussed in section 3.4.2.

Melnikow et al. (2016) cited a Canadian RCT that examined the effect of notifying women if they had more or less dense breasts and the provision of additional advice about breast density as a risk factor and advice on supplemental testing. The trial was conducted in 2007, and although the date is outside of our review's Terms of Reference, it has been included as there are no other RCT studies that discussed mental health outcomes related to notification. In the RCT, women randomly assigned to the intervention group (n=285) received a report advising them of their breast density with letters summarising their mammography results and a pamphlet on breast cancer risk factors, including density. Supplemental testing was not recommended in the notifications. Women randomly assigned to the control group (n=333) were notified of mammography results without information on breast density. No statistically significant differences were found in the psychological outcomes, such as preoccupation with breast cancer, breast cancer fear, and psychological distress at either the four-week or six-month follow-up points. The authors concluded that breast density notification was not associated with negative psychological outcomes.

Melnikow et al. (2016) noted that the subjectivity and variability of breast density classification (using BIRADS, for example) may result in negative outcomes for women. Reclassification from one category to another, for example from dense to not-dense, may undermine a woman's confidence in the screening process and create uncertainty for women and physicians. The opposite reclassification may result in unnecessary worry for the woman or prompt unnecessary supplemental tests. No studies have examined this association in more detail, however.

Observational studies

Manning et al. (2016) examined cognition and emotions related to breast density knowledge among women in Michigan before implementation of the state's breast density notification law, with a focus on between-ethnicity differences. The study sample included survey responses from 182 (62%) African American women (146 classified as BIRADS 1-2, and 36 as BIRADS 3-4) and 113 (38%) European American women (69 classified as BIRADS 1-2, and 44 classified as BIRADS 3-4). Overall, European American women were significantly more likely to have dense breasts, be wealthy, highly educated, married, and to report a family history of breast cancer. The distribution of physical, social and emotional anxiety related to breast density was negatively skewed for both African American and European American women: 63% of all women reported no physical anxiety (eg, having trouble sleeping), 67% no social anxiety (eg, noticeably withdrawing from other people), and 47% no emotional anxiety (eg, being unhappy or depressed) related to thoughts about breast density. That is, more than half of participants were not affected adversely by their knowledge of breast density, although a significant proportion (approximately a third to a half) were affected. It is not clear what information was provided to women about breast density, breast cancer risk and screening.

African American women indicated greater physical (1.49 vs. 1.25, p<.01) and social (1.47 vs. 1.28, p<.05) dimensions of breast density-related anxiety, and less breast cancer worry ("How often do you worry about breast cancer?", measured on a 5-point scale; 2.34 vs. 2.72, p<.01). Further multivariate analyses found that these differences were not mediated by breast density status (i.e. breast density did not influence results) but were instead attributable to the effects of demographic covariates (eg, income, education, marital status and family history of breast cancer) rather than ethnicity itself. For example, given that African American women had lower education and income levels compared to European American women, and also given that lower income and education were associated with more anxiety, the results suggest that these particular covariates may account for the between-ethnic group differences in breast density-related anxiety independent of actual breast density. Conversely, European American women indicated greater breast cancer risk knowledge (p<.01), breast density knowledge (p<.01) and breast cancer risk perception (p<.05) than African American women. These differences were found to be influenced by racial group membership, with no significant impact of breast density status.

A follow-on study (Manning et al., 2017) examined differences in emotional responses and cognition between African American (n = 241, 53%) and European American (n = 211, 47%) women who received breast density notifications (i.e. classified as BIRADS 3-4). African American women generally reported more negative psychological responses (physical, emotional, and social) and greater anxiety ("How anxious do you get when you think about how dense your own breasts are?") to receiving breast density notifications regardless of prior breast density awareness. African American women also had more favourable perceptions related to talking to their physicians about the breast density notifications. Generally, ethnicity-related perceptions, socio-economic status, and related knowledge partially accounted for the effect of ethnicity on psychological response.

In Manning et al.'s (2017) study, ethnicity-related perceptions and SES partially accounted for the differences in behavioural intentions such as seeking breast cancer screening and discussing breast cancer risk with a physician. Between-ethnicity differences in emotional responses to breast density notifications did not explain differences in women's intentions to discuss breast density notifications with their physicians. The authors noted that the adoption of breast density notification laws may result in a narrowing of ethnic disparities if it motivates women to have a discussion with their health care provider; however, ethnic differences in behavioural responses to the notifications may exacerbate disparities in breast cancer if African American women are less likely to discuss the notifications with physicians compared to European American women.

Moothathu et al. (2017) conducted a survey of 950 women (classified as having heterogeneously or extremely dense breasts) in Connecticut to determine breast density awareness and attitudes towards supplemental breast ultrasound testing, following the implementation of the state's breast density notification legislation. The study reported that 43% of survey respondents who were aware of their breast density also expressed increased anxiety about developing breast cancer due to having dense breast tissue. Additionally, women who had a prior breast ultrasound were statistically significantly more likely to report anxiety related to breast density awareness than women who had not had a prior ultrasound (44% vs. 32%, p=.002)

Yeh et al. (2015) conducted an online study to explore women's responses to the wording of breast density notifications, including perceived risk and three types of screening intentions (for future mammograms, and for future ultrasounds covered or not covered by insurance; N = 184; mean age = 49.4 years, SD = 8.07). Results indicated that the relationship between perceived lifetime breast cancer risk and the three screening intention outcomes were mediated by the level of anxiety women experienced after reading the dense breast tissue notification. In other words, given the same level of risk for two women, the woman who experiences more anxiety after reading the notification is more likely to have increased motivation for screening. No other predictor was found to increase all three screening intentions. Conversely, women who preferred to make active decisions, those who found the notification text complex, and those who were averse to ambiguous information demonstrated a decrease in screening intentions following the notification text, after controlling for breast cancer risk. The authors noted that psychological factors predicted screening intentions more consistently than demographic factors.

4.2.2. Breast density knowledge and awareness

Two articles (six studies) reported on overall mental health outcomes associated with knowledge and awareness of breast density.

Reporting of breast density appears to increase knowledge and awareness of breast density as a risk factor for breast cancer; however, the impact of this increased knowledge on positive or negative mental health outcomes or choices regarding screening participation is not well-described in the literature, as few studies specifically describe or provide a long-term follow-up of women's responses to screening participation following breast density notification. Of those studies that did report notification + knowledge + response, it appears that notification may increase engagement with screening.

Systematic review and literature reviews

In the same RCT discussed above, Melnikow et al. (2016) reported that, at four weeks follow-up, significantly more women in the intervention group (i.e., those who had received information advising them of their breast density and information on breast cancer risk factors, including density) had increased knowledge of breast density compared to the control group, who did not receive additional information (25% compared to 8%, respectively; p<.001). Women who had received the additional information were more likely to perceive themselves as having elevated breast cancer risk. These differences did not persist at six-months follow-up.

Santiago-Rivas et al. (2016) reviewed literature on breast density knowledge and breast density awareness. The review included five cross-sectional studies that used surveys for data collection. Results from these five studies are described below and are more fully explained in Table 25.

Breast cancer awareness results reported by Santiago-Rivas et al. (2016)

Two of the included studies assessed breast cancer awareness. Results from a national survey of 1,506 American women administered to women aged 40 to 74 years using an online service reported that 57.5% of participants responded "yes" to the following item: "Have you ever heard of something called breast density?" (Rhodes et al., 2015). Women who participated in a small study (N = 77) conducted at a breast clinic responded to the item "Do you know what breast density is?" by using a scale from 1 (I have never heard about it) to 5 (I know exactly what it is). Results showed that the average response to this item was 3.64 (SD = 1.29; Manning et al., 2013). It is not clear whether the reported results from either study increased the previous level of knowledge.

Breast density knowledge results reported by Santiago-Rivas et al. (2016)

Five studies in Santiago et al.'s review assessed breast density knowledge (for example, "does having dense breasts mask the ability of a mammogram to correctly detect breast cancer?"). Generally, studies reported on overall awareness and knowledge of breast density in the study population (rather than testing knowledge before and after provision of specific information or notification of breast density assessments). The review found that a relatively low proportion of women knew their own density status, and there was a general lack of knowledge regarding the association between breast density and breast cancer risk. Overall, Santiago-Rivas et al. (2016) concluded that there is insufficient evidence to determine a pattern of breast density knowledge and awareness in women, however increased breast density knowledge seemed to be associated with sociodemographic and screening history factors, such as race, ethnicity, household income, and history of diagnostic evaluation after a mammogram. For example, two of the three studies that assessed breast density knowledge by race or ethnicity found that, on average, White women had significantly more knowledge about breast density than non-White women. The authors also noted that their review findings suggest a need to inform women about breast density in general.

Rhodes et al. (2015) assessed study participants' knowledge of breast density by asking whether "having breasts that are mostly dense on a mammogram puts a woman at increased risk of breast cancer". Slightly over half of respondents (53.2%) agreed with this statement. The authors also tested a multivariate model and found no significant associations between the selected variables (i.e. income, education, or screening history) and knowledge on the impact of breast density on breast cancer risk. The authors noted that breast density awareness was lower among black and Hispanic women, however there was no statistically significant association between ethnicity and breast density knowledge.

Manning et al. (2013) evaluated breast density knowledge and reported similar results to Rhodes et al. (2015). Manning et al. reported that over half of respondents (58.4%) did not know their own breast density. Participants indicated on a scale of 1 (strongly agree) to 5 (strongly disagree) for "women with more dense breasts are at greater risk for getting breast cancer" with a median value of 3.26. The authors noted a statistically significant difference in breast density awareness and knowledge by race, with greater awareness reported by white women than black women and more accurate breast density definitions by white women.

Women recruited at a breast clinic after a normal mammogram examination (N = 344; mean age = 45.71 years) reported on their knowledge of breast density as a risk factor for breast cancer. A total of 62.0% reported they knew about breast density as a risk factor if their health care provider had spoken to them about breast density. A further 32.6% reported having discussed breast density with their health care provider and 18.3% were told they had dense breasts after they were provided a description of breast density (Santiago-Rivas et al., 2016). The authors also reported that knowledge of breast density as a risk factor was higher among those with first-degree relatives who had previously had breast cancer.

In another study reported by Santiago-Rivas et al. (2016), women (aged \geq 31 years) responded to a survey at an academic facility (n = 105) and a county hospital (n = 132) serving women with high and lower socioeconomic status, respectively. Women were asked: "Do you know your breast density?" A greater percentage of women recruited at the academic facility (23%) answered "yes" to this item, compared with those recruited at the county hospital (5%). Most of the participants who answered "no" also reported they would want to know their breast density (94% and 79%, respectively; Trinh et al., 2015). This study did not statistically analyse the differences in breast density knowledge by ethnicity; however, the authors noted that most of the women recruited at the academic facility were White (69%) whereas most of the women recruited at the county hospital were Hispanic (51%).

Results from a study conducted online to explore how women respond to the wording of breast density notifications (N = 184; mean age = 49.4 years, SD = 8.07) indicated that women perceived significantly greater lifetime breast cancer risk after notification of more dense breasts (M = 27.82, SE = 1.53) than prior to notification (M = 19.79, SE = 1.29, p < .001; Yeh et al., 2015).

Table 25: Studies reporting	g on breast density knowleds	ge and awareness, as reported	in Santiago-Rivas et al., 2016
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Study	Sample	Study design	Measures	Results
Rhodes et al. (2015)	N = 1506; L = 11.8%; B = 12%; W = 70.6%; O = 5.5; Online study of screening age women (age = 55.2%)	Cross-sectional	Knowledge of the masking effect of BD: "If a woman has dense breasts, what impact does this have on the ability of a mammogram to correctly detect cancer? (Easier to see cancer/does not impact/more difficult to see cancer/I don't know) Awareness: "Have you ever heard of something called BD?" (yes/no) Knowledge of impact on breast cancer risk: "Having breasts that are mostly dense on a mammogram" does or does not put a woman at increased risk of breast cancer	Knowledge of the masking effect of BD (correct response): W 73.1%, B 58.0%, L 77.1%, O 67.3% Awareness (yes): W 65%, B 48.5%, L 22.9%, O 54.1% Knowledge of impact on breast cancer risk (correct response): W 57.5%, B 65.5%, L 66.8%, O 51.9% Knowledge of the masking effect of BD multivariate model: household income OR = 1.10, 95%Cl 1.05-1.15; education OR = 1.22, 95%Cl 1.05- 1.42; legislation status OR = 3.82, 95%Cl 1.56-9.32; past biopsy OR = 2.16, 95%Cl 1.38-3.38; Awareness multivariate: L (compared with W) L: OR = 0.23, 95%Cl 0.13-0.40, $p < .001$; B: OR = 0.57, 95%Cl 0.35-0.93; household income OR = 1.07, 95%Cl, 1.03-1.11; education OR = 1.19, 95%Cl 1.09- 1.30; diagnostic evaluation OR = 2.64, 95%Cl 1.94-3.58; hormonal therapy OR = 1.69, 95%Cl 1.21-2.38
Trinh et al. (2015)	Academic facility; 39% were aged 31-50 years, 50% were 51-70 years, 11% were >70 years; <i>n</i> = 105; L = 8%, B = 3%. W = 69%; A = 15%; O = 5% County hospital; women after/waiting for their screening	Cross-sectional	Knowledge: "Do you know your BD?" (yes/no) Interest in knowledge: "Would you like to know your BD?	Knowledge: 23% yes in academic facility; 5% yes in county hospital (<i>p</i> < .0001) Interest: 94% in academic facility and 79% in county hospital (<i>p</i> < .01)

Study	Sample	Study design	Measures	Results
	mammography appointments; 47% were aged 31-50 years, 59% were 51-70 years, 8% were >70 years; <i>n</i> = 132; L = 51%; B = 3%, W = 20%; A = 21%; O = 5%			Willingness to pay for the supplemental tests: 22% the county hospital and 70% in the academic facility for ultrasound ($p < .0001$); 20% and 65%, respectively, for contrast-enhanced spectral mammography ($p < .0001$)
Yeh et al. (2015)	N = 184 (213); L = 9; B = 16; W = 163; O = 9	Cross-sectional	Knowledge: If participants had been told by their physicians that they had dense breast tissue	Knowledge: 16.8% of women had already been told by their physicians that they had dense breast tissue
O'Neill et al. (2014)	N = 344; L = 29; B = 24; W = 235; A = 14; O = 11; with a recent screening mammogram at a tertiary care centre (age = 45.71 years)	Cross-sectional	Knowledge of the masking effect of BD: "If a woman has dense breasts, what impact does this have on the ability of a mammogram to correctly detect cancer? (Easier to see cancer/does not impact/more difficult to see cancer/I don't know) Awareness: "Have you ever heard of something called BD?" (yes/no) Knowledge of impact on breast cancer risk: "Having breasts that are mostly dense on a mammogram" does or does not put a woman at increased risk of breast cancer	Knowledge of the masking effect of BD (correct response): W 73.1%, B 58.0%, L 77.1%, O 67.3%. Awareness (yes): W 65.0%, B 48.5%, L 22.9%, O 54.1% Knowledge of impact on breast cancer risk (correct response): W 57.5%, B 65.5%, L 66.8%, O 51.9% Knowledge of the masking effect of BD multivariate mode: household income OR = 1.10, 95%CI 1.05-1.15; education OR = 1.22, 95%CI 1.05- 1.42; legislation status OR = 3.82, 95%CI 1.56-9.32; past biopsy OR = 2.16, 95%CI 1.38-3.38; Awareness multivariate L (compared with W) L: OR = 0.23, 95%CI 0.13-0.40, $p <$.001, B: OR = 0.57, 95%CI 0.35-0.93; household income OR = 1.07, 95%CI 1.03-1.11; education OR = 1.19, 95%CI 1.09-1.30; diagnostic evaluation OR = 2.64, 95%CI 1.94-

Study	Sample	Study design	Measures	Results
				3.58; hormonal therapy OR = 1.69, 95%Cl 1.21-2.38
Manning et al. (2013)	N = 76; B = 54.5% (42); W = 33.8% (26); O = 10.4% (8); clinic attendees for whom further screening was prescribed following a suspicious screening or diagnostic mammogram (age = 51.28 years)	Cross-sectional	Awareness: "Do you know what BD is?" 1 (I have never heard about it) to 5 (I know exactly what it is); "Do you know how dense your own breasts are?" (yes/no); if yes 1 (entirely fat) to 4 (extremely dense) Accuracy: Define BD in their own words Risk factor knowledge "Older women are at greater risk for getting breast cancer," "Women with female relatives who have breast cancer are more likely to get breast cancer;" "There is a gene that makes some women more likely to get breast cancer," "Women with more dense breasts are at greater risk for getting breast cancer." 1 (I strongly disagree) to 5 (I strongly agree)	Awareness: All sample: $M = 364$, $SD = 129$; W ($M = 4.28$, $SD = 0.94$), B ($M = 3.29$, $SD = 1.31$), $t(64) = 3.11$, $p < .01$, $d = 0.87$. Accuracy: All sample: $M = 2.42$, $SD = 0.97$; W ($M = 2.77$, $SD = 0.93$), B ($M = 2.27$, $SD = 0.96$), $t(67) = 2.07$, $p < .05$, $d = 0.53$ Correlation accuracy and knowledge: All sample: $r = 0.35$, $p < .01$; W ($r = 0.46$, $p < .05$), B (not significant) Risk factor knowledge: All sample: M = 3.26, $SD = 1.19$; by race (not significant) Knowledge own BD: All samples: 33.8%; by race (not significant)

Abbreviations: BD, breast density; *N*/*n* sample size; B, Black; W, White; L, Latina; O, Other; A, Asian/Asian American; OR, odds ratio; *M*, mean; *SD*, standard deviation; *r*, Pearson correlation coefficient; *d*, Cohen's d.

Observational studies

Our literature search returned seven observational studies that assessed factors such as knowledge, awareness and understandability relating to breast density notifications. These studies were all carried out in the United States following implementation of breast density notification legislation. In these studies, the authors examined women's responses to receiving breast density notifications with six of the papers also assessing demographic variables.

Manning et al. (2016) reported that European American women were more likely to report knowing how dense their breasts were compared with African American women (42% vs 15%, p<.0001). European American women also had greater breast cancer risk knowledge (0.68 vs. 0.54, p<.001), breast density knowledge (3.85 vs. 2.85, p<.001) and breast cancer risk perception (39.74 vs 32.26, p<.05) compared to African American women. Women with less education and lower income also had less knowledge about breast cancer risk and breast density risk. These findings reflect those noted in Santiago-Rivas et al.'s (2016) literature review: that sociodemographic factors may impact on knowledge about and understanding of breast density and cancer risk.

A follow-on study (Manning et al., 2017) examined differences in cognition and emotional response between African American and European American women who received breast density notifications. Most women (n=266, 59%) reported no prior awareness of breast density; however, significantly more European American women reported prior awareness compared with African American women (58% vs. 26%, respectively; p<.01).

The text and advice provided in notification of density may affect a woman's ability to understand the message, and therefore how she responds to it. Kressin, Gunn, & Battaglia (2016) measured the readability and understandability of dense breast notifications across US states. The authors assessed the required components of dense breast notifications for each state, including whether the notification informed the recipient of masking bias, density as a risk factor, and supplemental imaging. Readability was measured using the Flesch-Kincaid reading grade level in MS Word (range: theoretical lower bound, -3.4; no upper bound) and the Dale-Chall readability grade score (range, ≤ 4 to ≥ 16). Understandability was assessed using the Patient Education Materials Assessment Tool (PEMAT; range, 1% to 100%). Flesch-Kincaid readability levels ranged from grades 7 to 19.4 (M = 10.5).

Most of the advice provided exceeded the recommended readability level (grades 7-8; *NB* about 20% of the population reads below a grade 5 level). Dale-Chall readability grade scoring produced slightly higher scores overall (grade range: 9-10 to 13-15). All dense breast notifications scored poorly on understandability (PEMAT; range, 11%-33%). The authors reported that only three states' dense breast notifications readability level was at the grade 8 level or below. Kressin et al. discussed the impact of having dense breast notifications with poor understandability, due to the uncertainty women face about supplemental testing and disparities in breast cancer related to low health literacy. The study was limited by its analysis of the text only, with no data on outcomes such as anxiety, supplemental testing or additional cancers detected (Kressin et al., 2016). This study demonstrates that a deficit in women's understandability of dense breast notifications may create uncertainties for women attempting to make personalised decisions about supplemental testing and may exacerbate disparities in breast cancer screening related to low health literacy.

Moothathu et al., (2017) conducted a survey of 950 women in Connecticut to determine breast density awareness and attitudes towards supplemental breast ultrasound testing, following the implementation of the state's breast density notification legislation. Almost all surveyed women

(92%) were aware of their breast density, and 77% reported having a prior screening ultrasound. Of those who responded as not having a prior screening ultrasound, 28% (56/203) indicated it was because their physician had never discussed it with them, and 26% (53/203) stated it was because they were not familiar with the test. Other less common reasons were dislike of undergoing medical tests (3%, 7/203), a physician stating it was not needed (9%, 19/ 203), lack of time (2%, 5/203), and concern over insurance reimbursement and costs (3%, 6/203).

Moothathu et al., (2017) also reported that identifying as European and having higher education were significantly associated (p<.05) with knowledge of personal breast density (93% and 95%, respectively) and having a prior screening breast ultrasound (79% and 80%, respectively). Women with less than a college degree (82%) were significantly more likely to rely exclusively on their provider's recommendation regarding obtaining screening ultrasound (p<.05). The authors concluded that breast density awareness is strongly associated with higher education, higher income, and identifying as European.

Our search also returned studies from Rhodes et al. (2015), Manning et al. (2013); Trinh et al. (2015) and Yeh et al. (2015). The findings of these papers have been described in the literature review above by Santiago-Rivas et al. (2016).
5. NOTIFICATION AND REPORTING

Reporting of breast density assessment is common in some jurisdictions, particularly the United States (where it is required by law in 31 states). In contrast, BSA's 2016 position statement states that:

"until such time that more evidence is available on how breast density should be best assessed and managed, and evidence supports clinical pathways for women, BSA programs should not routinely record breast density or provide supplemental screening for women with dense breasts".

Chapter 5 of this report discusses our findings on notification and reporting of breast density to women and health practitioners. Specific topics are:

- Lessons from jurisdictions where breast density information is reported to women, including acceptability of reporting (or not) and reporting protocols, and
- Advice and support that women and health practitioners want and need if density is reported.

Key findings about notification and reporting of breast density

No studies identified what information women require to be included in or additional to a breast density notification letter. Legislation has been implemented at an individual state level in the United States (as opposed to federal legislation) and this has resulted in variations in the language of the notifications, which can impact on the quality of care delivered.

The studies highlight that where breast density notification occurs, it is critical for women and providers to be informed of the meaning of the information in the notification, and how it should influence their approach to breast screening. This relies on providers being confident in communicating breast density information and emphasises the need for health providers' education and evidence-based guidelines for the management of women with dense breasts.

5.1. Notification and reporting in other jurisdictions

This section provides an overview of the developments in breast density notification legislation (namely in the United States and Western Australia). The legislation has typically been implemented with the goal of empowering women's decision-making and improving the quality of breast screening, however these benefits are yet to be realised in recent studies.

5.1.1. Notification and reporting in the United States

In the United States, successful lobbying by advocacy groups has seen changes in the law (beginning in Connecticut in 2009). There is no current federal legislation stipulating what can and cannot be reported. The Breast Density and Reporting Act 2017 was introduced to the Senate in October 2017, and as at July 2018, has been referred to the Committee on Health, Education, Labor and Pensions. If passed, the bill would set a minimum standard for dense breast tissue notification after mammograms and recommend women discuss options with their physician to see if additional breast cancer screening is needed. The lack in federal legislation has resulted in some inconsistencies in reporting across states in the United States.

Summary reports typically include some, or all the following information about breast density:

- 1. scientific knowledge about breast density and screening
- 2. the effect of breast density in masking the presence of breast cancer on a mammogram (based on individual woman's breast density assessment), and
- 3. that individuals with more dense breasts should talk with their physicians about any questions or concerns regarding the summary and whether they would benefit from any additional tests.

For more detail on what each US state's notification is required to contain, see Table 26 overleaf.

As at July 2018, breast density notification laws have been (or are planned to be) put into effect in 35 states in the United States. However, concerns are being raised in the literature about breast density notification laws limiting a broader understanding and discussion of personal risk, the legislation bringing the probability of greater clinical uncertainty and increased liability for radiologists and primary care physicians, and for women additional tests leading to an increased likelihood of false-positive results, unnecessary biopsies and over-diagnosis.

5.1.2. Notification and reporting in Western Australia

In the BSA program, only the Western Australia BSA program reports breast density. BreastScreen WA advises women with dense breasts to consult their GP to discuss the significance of breast density findings, to have a clinical examination and receive further advice about their breast cancer risk. This literature review did not identify any further information that is reported in Western Australia's breast density letter.

5.1.3. Notification and reporting in New Zealand

Breast Screen Aotearoa does not measure breast density or provide notification to women as part of the BSA program, as the harms of extra screening may outweigh the benefits. Additionally, the Royal Australian and New Zealand College of Radiologists released a position statement in 2016, which stated that:

> "the receipt of breast density information may create undue anxiety about the risk and worry that mammography may have missed a breast cancer in women with dense breasts. For women with fatty breasts, it may convey a false sense of security."

5.1.4. Notification and reporting in European countries

No European countries currently have legislated breast density notifications for women. The European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies released a position paper on breast cancer screening in 2017. The EUSOBI did not present a view on breast density notifications.

State	Who receives information	Informs woman her breasts are dense (BIRADS 3-4)	Includes personal breast density category	Masking effect mentioned	Density as a risk factor mentioned	Supplemental imaging tests mentioned ¹	Insurance mandate to cover additional testing
Alabama	Dense ²	Yes	No	Yes	Yes	Yes	No
Arizona	Dense	Yes	No	Yes	Yes	No	No
California	Dense	Yes	No	No	Yes	No	No
Colorado	Dense	Yes	No	No	Yes	No	No
Connecticut	All, general info. If dense, supplemental imaging info	No	No	Yes	No	Yes, if dense	Yes - If dense, US; if high risk, US or MRI. All women, 3D
Delaware	All ²	Yes	Yes	Yes	Yes	Yes	No
Florida	Dense	Yes	No	Yes	Yes	No	No
Hawaii	Dense	Yes	No	Yes	Yes	Yes	No
lowa	All	Yes	Yes	TBD	Yes	TBD	No
Kentucky	Dense	Yes	No	Yes	Yes	No	Yes – all women, 3D
Louisiana	All	No	No	Yes	Yes	Yes	No
Maryland	All	No	No	Yes	Yes	No	Yes – all women, 3D
Massachusetts	Dense	Yes	Yes	Yes	Yes	Yes	No
Michigan	Dense	Yes	No	Yes	Yes	Yes	No
Minnesota	Dense	Yes	No	Yes	Yes	No	No

 Table 26: Information provided on breast density notifications in legislated states in the US

State	Who receives information	Informs woman her breasts are dense (BIRADS 3-4)	Includes personal breast density category	Masking effect mentioned	Density as a risk factor mentioned	Supplemental imaging tests mentioned ¹	Insurance mandate to cover additional testing
Missouri	All	No	No	Yes	Yes	Yes	No
Nebraska	All	Yes	Yes	Yes	Yes	No	No
Nevada	All	Yes	Yes	No	Yes	No	No
New Jersey	All	No	No	Yes	Yes	No	If extremely dense or as determined by health care provider, not modality specific
New York	Dense	Yes	No	Yes	Yes	Yes	Yes - all women, screening (all modalities) + diagnostic breast imaging
North Carolina	Dense	Yes	Yes	Yes	Yes	No	No
Ohio	Dense	Yes	No	Yes	Yes	No	No
Oklahoma	Dense	Yes	Yes	Yes	Yes	No	No
Oregon	Extremely Dense	Yes	No	Yes	Yes	Yes	No
Pennsylvania	All	Yes	Yes	Yes	Yes	No	Yes – all women, 3D
Rhode Island	Dense	Yes	Yes	Yes	Yes	Yes	No
South Carolina	"Where applicable"	Yes	No	No	Yes	No	No
Tennessee	Dense	Yes	No	No	Yes	No	No

State	Who receives information	Informs woman her breasts are dense (BIRADS 3-4)	Includes personal breast density category	Masking effect mentioned	Density as a risk factor mentioned	Supplemental imaging tests mentioned ¹	Insurance mandate to cover additional testing
Texas	All	No	No	Yes	Yes	Yes	Yes - all women, 3D
Vermont	Dense	Yes	Yes	Yes	Yes	No	No
Virginia	Dense	Yes	No	Yes	Yes	Yes	No
Washington ³	Dense	Yes	Yes	No	Yes	No	Yes – all women, 3D
Wisconsin	Dense	Yes	No	Yes	Yes	No	No

State	Who receives information	Informs woman her breasts are dense (BIRADS 3-4)	Includes personal breast density category	Masking effect mentioned	Density as a risk factor mentioned	Supplemental imaging tests mentioned ¹	Insurance mandate to cover additional testing
Western Australia	Dense	Yes	Unknown	Unknown	Unknown	Unknown	Unknown

¹ "Supplemental imaging tests mentioned" indicates state inform law requires the notification to mention imaging tests that might be added to mammography (generally or by modality).

² Dense refers to women with dense breast tissue (i.e., BIRADS 3-4). "All" means every woman receives some notification post-mammogram.

³ To be enacted 1/1/2019

Source: (Dense Breast-info, 2018; Durning, 2017)

5.2. Information that women want and acceptability of reporting

We searched for literature that would provide information about women's and health practitioner attitudes towards dense breast notifications and what requirements they have from them. At February 2018, no studies had specifically asked women what they need from breast density notification; however, five articles discussed challenges and associated improvements that could be made to the notification letters, and we identified five articles that discussed information requirements for women or health practitioners. It is important to note that all the studies described in this literature review are from the United States and Europe, and therefore they may not be suitable to be generalised to the Australian context.

The US Preventive Services Task Force stated, in its update of the 2009 recommendation for breast cancer, that critical questions remain about how best to report on and manage the association between breast density, breast cancer risk and breast cancer diagnosis, and to support women with increased breast density.

Health practitioner education is critical for breast density notification laws to positively impact breast cancer outcomes. Health practitioners in the United States reportedly have variable knowledge of the breast density laws and what this means for clinical practice. In some states, this has resulted in inconsistencies in referral for supplemental tests. For example, Slanetz et al. (2015) noted that some Connecticut clinicians refer 100% of women and others refer none. These inconsistencies may result in reduced access to supplemental testing for women defined as having a high risk of breast cancer or unnecessary screening for women with a low to average risk of breast cancer.

One study investigated physician awareness of breast density legislation and its impact on primary care practice (Khong et al., 2015). The study included 77 survey responses from Internal Medicine (39%), Family Medicine (47%) and Obstetric-Gynaecology (9%) outpatient physicians in California. Roughly half of those surveyed (49%) reported no knowledge of the breast density notification legislation. Seventy-five percent of those surveyed would also be interested in more specific education on the subject. The authors concluded that due to a reasonably low level of awareness among physicians, there may need to be more physician education for density notification laws to have a significant impact on patient care.

A similar study surveyed 96 radiologists to assess their knowledge about breast density legislation as well as perceived practice changes resulting from the enactment of breast density legislation (Lourenco et al., 2017). Sixty-nine percent felt that breast density notification increased women's anxiety about breast cancer, but also increased women's (74%) and provider (66%) understanding of the effect of breast density on mammographic sensitivity. The authors also concluded that clinicians would benefit from further education about breast density legislation and management of women with dense breasts.

Slanetz et al. (2015) notes that the legislation is an opportunity to strengthen the patient-provider relationship, by encouraging a discussion about the risks and benefits of screening, regardless of breast density. The way in which breast density information is communicated to women is important to ensure that all women sufficiently understand the information. As discussed in section 4.2.1, Manning et al. (2017) reported on the emotional responses and ethnic differences for women who received breast density notifications. The authors stated that African American women are less likely to have prior awareness of their breast density due to a lack of physician

communication, however the notifications provide an opportunity for such communication to take place. In the review by Sullivan et al. (2015), the authors concluded that for jurisdictions with legislated density notification, there is a need for evidence-based guidelines to assist the woman and physician in making the decision to have supplemental testing.

REFERENCES

American College of Radiology. (2014). "ACR statement on reporting breast density in mammography reports and patient summaries." Retrieved March 2018, from http://www.acr.org/About-Us/Media-Center/Position-Statements/Position-Statements-Folder/Statement-on-Reporting-Breast-Density-in-Mammography-Reports-and-Patient-Summaries.

Antoni, S., A. J. Sasco, I. Dos Santos Silva and V. McCormack (2013). "Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis." Breast Cancer Research and Treatment 137(2): 337-347.

Assi, V., N. J. Massat, S. Thomas, J. MacKay, J. Warwick, M. Kataoka ... S.W. Duffy (2015). "A casecontrol study to assess the impact of mammographic density on breast cancer risk in women aged 40-49 at intermediate familial risk: Impact of mammographic density on breast cancer risk." International Journal of Cancer 136(10): 2378–2387.

Astley, S., E. Harkness, J. Sergeant, P. Stavrinos, R. Warren, M. Wilson, A. Brentnall, J. Cuzick, A. Howell and G. Evans (2016). "Proffered Paper: A comparison of four methods of mammographic density measurement in the UK Predicting Risk Of Cancer At Screening (PROCAS) study – on behalf of the PROCAS Study team." European Journal of Cancer 61: S6.

Astley, S. M., E. F. Harkness, J. C. Sergeant, J. Warwick, P. Stavrinos, R. Warren ... D. G. Evans (2018). "A comparison of five methods of measuring mammographic density: a case-control study." Breast Cancer Research 20(1)

Bae, J. M. and E. H. Kim (2016). "Breast Density and Risk of Breast Cancer in Asian Women: A Metaanalysis of Observational Studies." Journal of Preventive Medicine and Public Health 49(6): 367– 375.

BCSC Data Explorer. NCI-funded Breast Cancer Surveillance Consortium. (2013). "Breast Cancer Surveillance Consortium " Retrieved March 2018, from http://breastscreening.cancer.gov.

Berg, W. and J. Pushkin (2017). "In defense of breast density notification laws." Contemporary OB/GYN 62(3): 10-13.

Berg, W. A., J. D. Blume, A. M. Adams, R. A. Jong, R. G. Barr, D. E. Lehrer . . . E. B. Mendelson (2010). "Reasons women at elevated risk of breast cancer refuse breast MR imaging screening: ACRIN 6666." Radiology 254(1): 79-87.

Berg W.A., J. D. Blume, J. B. Cormack, E. B. Mendelson, D. Lehrer, M. Böhm-Vélez ... K. Boparai (2008). "Combined Screening with Ultrasound and Mammography Compared to Mammography Alone in Women at Elevated Risk of Breast Cancer: Results of the First-Year Screen in ACRIN 6666." Journal of the American Medical Association 299(18): 2151-2163.

Berg, W. A., Z. Zhang, D. Lehrer, R. A. Jong, E. D. Pisano, R. G. Barr, M. Böhm-Vélez, M. C. Mahoney, W. P. Evans and L. H. Larsen (2012). "Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk." Journal of the American Medical Association 307(13): 1394-1404.

Bertrand, K. A., R. M. Tamimi, C. G. Scott, M. R. Jensen, V. S. Pankratz, D. Visscher, A. Norman, F. Couch, J. Shepherd and B. Fan (2013). "Mammographic density and risk of breast cancer by age and tumor characteristics." Breast Cancer Research 15(6): R104.

Boyd, N. F., G. S. Dite, J. Stone, A. Gunasekara, D. R. English, M. R. McCredie, G. G. Giles, D. Tritchler, A. Chiarelli and M. J. Yaffe (2002). "Heritability of mammographic density, a risk factor for breast cancer." New England Journal of Medicine 347(12): 886-894.

Boyd, N. F., H. Guo, L. J. Martin, L. Sun, J. Stone, E. Fishell, R. A. Jong, G. Hislop, A. Chiarelli and S. Minkin (2007). "Mammographic density and the risk and detection of breast cancer." New England Journal of Medicine 356(3): 227-236.

Boyd, N. F., J. M. Rommens, K. Vogt, V. Lee, J. L. Hopper, M. J. Yaffe and A. D. Paterson (2005). "Mammographic breast density as an intermediate phenotype for breast cancer." The Lancet Oncology 6(10): 798-808.

Brem, R. F., M. J. Lenihan, J. Lieberman and J. Torrente (2015). "Screening breast ultrasound: past, present, and future." American Journal of Roentgenology 204(2): 234-240.

Brem, R. F., R. C. Ruda, J. L. Yang, C. M. Coffey and J. A. Rapelyea (2016). "Breast-specific γ -imaging for the detection of mammographically occult breast cancer in women at increased risk." Journal of Nuclear Medicine 57(5): 678-684.

Brandt, K. R., C. G. Scott, L. Ma, A. P. Mahmoudzadeh, M. R. Jensen, D. H. Whaley, F. F. Wu, S. Malkov, C B. Hruska and A. D. Norman (2016). "Comparison of clinical and automated breast density measurements: implications for risk prediction and supplemental screening." Radiology 279(3): 710-719.

BreastScreen Australia. 2016. Position Statement on Breast Density and Screening. DOH, Canberra.

Brisson, J., A. S. Morrison and N. Khalid (1988). "Mammographic parenchymal features and breast cancer in the breast cancer detection demonstration project." JNCI: Journal of the National Cancer Institute 80(19): 1534-1540.

Buchberger, W., S. Geiger-Gritsch, R. Knapp, K. Gautsch and W. Oberaigner (2018). "Combined screening with mammography and ultrasound in a population-based screening program." European Journal of Radiology 101: 24–29.

Burkett, B. J. and C. W. Hanemann (2016). "A Review of Supplemental Screening Ultrasound for Breast Cancer: Certain Populations of Women with Dense Breast Tissue May Benefit." Academic radiology 23(12): 1604-1609.

Busana, M. C., A. Eng, R. Denholm, M. Dowsett, S. Vinnicombe, S. Allen and I. dos-Santos-Silva (2016). "Impact of type of full-field digital image on mammographic density assessment and breast cancer risk estimation: a case-control study." Breast Cancer Research 18(1): 96-108.

Cappello, N. M. (2013). "Decade of 'normal' mammography reports–the happygram." Journal of the American College of Radiology 10(12): 903-908.

Chae, E. Y., H. H. Kim, J. H. Cha, H. J. Shin and H. Kim (2013). "Evaluation of Screening Whole-Breast Sonography as a Supplemental Tool in Conjunction With Mammography in Women With Dense Breasts." Journal of Ultrasound in Medicine 32(9): 1573-1578.

Chowdhury, M., D. Euhus, M. O'Donnell, T. Onega, P. K. Choudhary and S. Biswas (2018). "Dosedependent effect of mammographic breast density on the risk of contralateral breast cancer." Breast Cancer Research and Treatment, in press.

Ciatto, S. and M. Zappa (1993). "A prospective study of the value of mammographic patterns as indicators of breast cancer risk in a screening experience." European Journal of Radiology 17(2): 122-125.

Colin, C., V. Prince and P.J. Valette (2013). "Can mammographic assessments lead to consider density as a risk factor for breast cancer?" European Journal of Radiology 82: 404-411.

Coop, P., A. Cowling, and B. Lawson (2016). "Tomosynthesis as a Screening Tool for Breast Cancer: A Systematic Review." Radiography 22(3): e190–95.

De Stavola, B., I. Gravelle, D. Wang, D. Allen, R. Bulbrook, I. Fentiman, J. Hayward and M. Chaudary (1990). "Relationship of mammographic parenchymal patterns with breast cancer risk factors and risk of breast cancer in a prospective study." International journal of epidemiology 19(2): 247-254.

Destounis, S., Arieno, A., Morgan, R., Roberts, C., & Chan, A. (2017a). Qualitative versus quantitative mammographic breast density assessment: Applications for the US and abroad. *Diagnostics*, 7(2), 30-63

Destounis, S., L. Johnston, R. Highnam, A. Arieno, R. Morgan and A. Chan (2017b). "Using volumetric breast density to quantify the potential masking risk of mammographic density." American Journal of Roentgenology 208(1): 222-227.

Devolli-Disha, E., S. Manxhuka-Kërliu, H. Ymeri and A. Kutllovci (2009). "Comparative accuracy of mammography and ultrasound in women with breast symptoms according to age and breast density." Bosnian Journal of Basic Medical Sciences 9(2): 131.

Duffy, S. W., O. W. Morrish, P. C. Allgood, R. Black, M. G. Gillan, P. Willsher, J. Cooke, K. A. Duncan, M. J. Michell and H. M. Dobson (2018). "Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer." European Journal of Cancer 88: 48-56.

Ellsworth, R., D. Decewicz, C. Shriver and D. Ellsworth (2010). "Breast cancer in the personal genomics era." Current Genomics 11(3): 146-161.

Eng, A., A. Gallant, J. Shepherd, V. McCormack, J. Li, M. Dowsett ... I. dos-Santos-Silva (2014). "Digital mammographic density and breast cancer risk: a case–control study of six alternative density assessment methods." Breast Cancer Research 16(5): 439-451.

Freer, P. E. (2015). "Mammographic breast density: impact on breast cancer risk and implications for screening." Radiographics 35(2): 302-315.

Gartlehner, G., K. J. Thaler, A. Chapman, A. Kaminski, D. Berzaczy, M. G. Van Noord and T. H. Helbich (2013). "Adjunct ultrasonography for breast cancer screening in women at average risk: a systematic review." International Journal of Evidence-Based Healthcare 11(2): 87-93.

Gartlehner, G., Thaler, K., Chapman, A., Kaminski-Hartenthaler, A., & Berzaczy, D. (2012). Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. Cochrane Database of Systematic Reviews 30(4).

Gierach, G. L., L. Ichikawa, K. Kerlikowske, L. A. Brinton, G. N. Farhat, P. M. Vacek, D. L. Weaver, C. Schairer, S. H. Taplin and M. E. Sherman (2012). "Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium." Journal of the National Cancer Institute 104(16): 1218-1227.

Gram, I. T., Y. Bremnes, G. Ursin, G. Maskarinec, N. Bjurstam and E. Lund (2005). "Percentage density, Wolfe's and Tabár's mammographic patterns: agreement and association with risk factors for breast cancer." Breast Cancer Research 7(5): R854.

Habel, L. A., J. A. Lipson, N. Achacoso, J. H. Rothstein, M. J. Yaffe, R. Y. Liang ... W. Sieh (2016). "Case-control study of mammographic density and breast cancer risk using processed digital mammograms." Breast Cancer Research 18(1): 53-60

He, W., A. Juette, E. R. Denton, A. Oliver, R. Martí and R. Zwiggelaar (2015). "A review on automatic mammographic density and parenchymal segmentation." International Journal of Breast Cancer 2015.

Hendrick, R. E. (2010). "Radiation doses and cancer risks from breast imaging studies." Radiology 257(1): 246-253.

Ho, W. and P. Lam (2003). "Clinical performance of computer-assisted detection (CAD) system in detecting carcinoma in breasts of different densities." Clinical Radiology 58(2): 133-136.

Holbrook, A. and M. S. Newel (2015). "Alternative screening for women with dense breasts: breast-specific gamma imaging (molecular breast imaging)." American Journal of Roentgenology 204(2): 252-256.

Holland, K., C. H. van Gils, R. M. Mann and N. Karssemeijer (2017). "Quantification of masking risk in screening mammography with volumetric breast density maps." Breast Cancer Research and Treatment 162(3): 541-548.

Hooley, R. J. (2017). "Breast Density Legislation and Clinical Evidence." Radiologic Clinics of North America 55(3): 513-526.

Houssami, N. and R. M. Turner (2016). "Rapid review: estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts." The Breast 30: 141-145.

Hruska, C. B. (2017). "Molecular Breast Imaging for Screening in Dense Breasts: State of the Art and Future Directions." American Journal of Roentgenology 208(2): 275-283.

Hubbard, R. A., K. Kerlikowske, C. I. Flowers, B. C. Yankaskas, W. Zhu and D. L. Miglioretti (2011). "Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study." Annals of Internal Medicine 155(8): 481-492.

Huo, C., G. Chew, K. Britt, W. Ingman, M. Henderson, J. Hopper and E. Thompson (2014). "Mammographic density—a review on the current understanding of its association with breast cancer." Breast Cancer Research and Treatment 144(3): 479-502.

iCAD (2018). "iReveal." from http://www.icadmed.com/icad-announces-launch-of-ireveal-breast-density-analysis-solution.html.

Jalalian, A., S. B. Mashohor, H. R. Mahmud, M. I. B. Saripan, A. R. B. Ramli and B. Karasfi (2013). "Computer-aided detection/diagnosis of breast cancer in mammography and ultrasound: a review." Clinical Imaging 37(3): 420-426.

Jeffers, A. M., W. Sieh, J. A. Lipson, J. H. Rothstein, V. McGuire, A. S. Whittemore and D. L. Rubin (2017). "Breast Cancer Risk and Mammographic Density Assessed with Semiautomated and Fully Automated Methods and BIRADS." Radiology 282(2): 348–355.

Kataoka, M., A. Antoniou, R. Warren, J. Leyland, J. Brown, T. Audley and D. Easton (2009). "Genetic models for the familial aggregation of mammographic breast density." Cancer Epidemiology and Prevention Biomarkers 18(4): 1277-1284.

Kavanagh, A. M., G. B. Byrnes, C. Nickson, J. N. Cawson, G. G. Giles, J. L. Hopper, D. M. Gertig and D. R. English (2008). "Using mammographic density to improve breast cancer screening outcomes." Cancer Epidemiology and Prevention Biomarkers 17(10): 2818-2824.

Kerlikowske, K., R. A. Hubbard, D. L. Miglioretti, B. M. Geller, B. C. Yankaskas, C. D. Lehman, S. H. Taplin and E. A. Sickles (2011). "Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study." Annals of Internal Medicine 155(8): 493-502.

Kerlikowske, K., L. Ma, C. G. Scott, A. P. Mahmoudzadeh, M. Jensen, B. L. Sprague ... J. A. Shepherd (2017). "Combining quantitative and qualitative breast density measures to assess breast cancer risk." Breast Cancer Research 19(1): 97-106.

Kerlikowske, K., W. Zhu, A. N. Tosteson, B. L. Sprague, J. A. Tice, C. D. Lehman and D. L. Miglioretti (2015). "Identifying women with dense breasts at high risk for interval cancer: a cohort study." Annals of Internal Medicine 162(10): 673-681.

Kim, B.-K., Y. H. Choi, T. L. Nguyen, S. J. Nam, J. E. Lee, J. L. Hopper, J. Sung and Y.-M. Song (2015). "Mammographic density and risk of breast cancer in Korean women." European Journal of Cancer Prevention 24(5): 422-429.

Kolb, T. M., J. Lichy and J. H. Newhouse (2002). "Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations." Radiology 225(1): 165-175.

Kotsuma, Y., Y. Tamaki, T. Nishimura, M. Tsubai, S. Ueda, K. Shimazu, S. J. Kim, Y. Miyoshi, Y. Tanji and T. Taguchi (2008). "Quantitative assessment of mammographic density and breast cancer risk for Japanese women." The Breast 17(1): 27-35.

Kressin, N. R., C. M. Gunn and T. A. Battaglia (2016). "Content, readability, and understandability of dense breast notifications by state." Journal of the American Medical Association 315(16): 1786-1788.

Kriege, M., C. T. Brekelmans, I. M. Obdeijn, C. Boetes, H. M. Zonderland, S. H. Muller, T. Kok, R. A. Manoliu, A. P. E. Besnard and M. M. Tilanus-Linthorst (2006). "Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer." Breast Cancer Research and Treatment 100(1): 109-119.

Krishnan, K., L. Baglietto, C. Apicella, J. Stone, M. C. Southey, D. R. English ... J. L. Hopper (2016). "Mammographic density and risk of breast cancer by mode of detection and tumor size: a casecontrol study." Breast Cancer Research 18(1): 63-76

Kuhl, C. K., S. Schrading, K. Strobel, H. H. Schild, R.-D. Hilgers and H. B. Bieling (2014). "Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximumintensity projection—a novel approach to breast cancer screening with MRI." Journal of Clinical Oncology 32(22): 2304-2310.

Lång K., I. Andersson, A. Rosso, A. Tingberg, P. Timberg and S. Zackrisson "Performance of One-View Breast Tomosynthesis as a Stand-Alone Breast Cancer Screening Modality: Results from the Malmo Breast Tomosynthesis Screening Trial, a Population-Based Study." European Radiology 26(1): 184–90. Lee, C. P. L., H. Choi, K. C. Soo, M.-H. Tan, W. Y. Chay, K. S. Chia, J. Liu, J. Li and M. Hartman (2015). "Mammographic breast density and common genetic variants in breast cancer risk prediction." PloS One 10(9): e0136650.

Leong, L. C., A. Gogna, R. Pant, F. C. Ng and L. S. Sim (2012). "Supplementary breast ultrasound screening in Asian women with negative but dense mammograms—a pilot study." Annals of the Academy of Medicine-Singapore 41(10): 432.

Lindström, S., C. M. Vachon, J. Li, J. Varghese, D. Thompson, R. Warren, J. Brown, J. Leyland, T. Audley and N. J. Wareham (2011). "Common variants in ZNF365 are associated with both mammographic density and breast cancer risk." Nature Genetics 43(3): 185.

Lokate, M., P. H. Peeters, L. M. Peelen, G. Haars, W. B. Veldhuis and C. H. van Gils (2011). "Mammographic density and breast cancer risk: the role of the fat surrounding the fibroglandular tissue." Breast Cancer Research 13(5): R103.

Lourenco, A. P. and M. B. Mainiero (2016). "Incorporating Imaging Into the Locoregional Management of Breast Cancer." Seminars in Radiation Oncology 26(1): 17-24.

Lucas, N. P., P. Macaskill, L. Irwig and N. Bogduk (2010). "The development of a quality appraisal tool for studies of diagnostic reliability (QAREL)." Journal of Clinical Epidemiology 63(8): 854-861.

Manning, M., T. L. Albrecht, Z. Yilmaz-Saab, J. Shultz and K. Purrington (2016). "Influences of race and breast density on related cognitive and emotion outcomes before mandated breast density notification." Social Science & Medicine 169: 171-179.

Manning, M., T. L. Albrecht, Z. Yilmaz-Saab, L. Penner, A. Norman and K. Purrington (2017). "Explaining between-race differences in African-American and European-American women's responses to breast density notification." Social Science & Medicine 195: 149-158.

Masala, G., D. Ambrogetti, M. Assedi, B. Bendinelli, S. Caini and D. Palli (2017). "Mammographic breast density and breast cancer risk in a Mediterranean population: a nested case-control study in the EPIC Florence cohort." Breast Cancer Research and Treatment 164(2): 467–473.

Maskarinec, G., L. Dartois, S. Delaloge, J. Hopper, F. Clavel-Chapelon and L. Baglietto (2017). "Tumor characteristics and family history in relation to mammographic density and breast cancer: The French E3N cohort." Cancer Epidemiology 49: 156–160.

McCormack, V. A. and I. dos Santos Silva (2006). "Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis." Cancer Epidemiology and Prevention Biomarkers 15(6): 1159-1169.

Melnikow, J., J. J. Fenton, E. P. Whitlock, D. L. Miglioretti, M. S. Weyrich, J. H. Thompson and K. Shah (2016). "Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force." Annals of Internal Medicine 164(4): 268-278.

Moothathu, N. S., L. E. Philpotts, S. H. Busch, C. P. Gross, L. H. Staib and R. J. Hooley (2017). "Knowledge of Density and Screening Ultrasound." The Breast Journal 23(3): 323-332.

Mousa, D. A., E. Ryan, C. Mello-Thoms and P. Brennan (2014). "What effect does mammographic breast density have on lesion detection in digital mammography?" Clinical Radiology 69(4): 333-341.

Nagao, Y., Y. Kawaguchi, Y. Sugiyama, S. Saji and Y. Kashiki (2003). "Relationship between mammographic density and the risk of breast cancer in Japanese women: a case-control study." Breast Cancer 10(3): 228-233.

Nagata, C., T. Matsubara, H. Fujita, Y. Nagao, C. Shibuya, Y. Kashiki and H. Shimizu (2005). "Mammographic density and the risk of breast cancer in Japanese women." British Journal of Cancer 92(12): 2102.

National Screening Unit. 2016. *Breast Density Information Sheet*. Ministry of Health, Wellington.

Nelson, H. D., M. Pappas, A. Cantor, J. Griffin, M. Daeges and L. Humphrey (2016). "Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation." Annals of Internal Medicine 164(4): 256-267.

Nguyen, T. L., Y. K. Aung, C. F. Evans, G. S. Dite, J. Stone, R. J. MacInnis ... J. L. Hopper (2017). "Mammographic density defined by higher than conventional brightness thresholds better predicts breast cancer risk." International Journal of Epidemiology 46(2), 652–661.

Nguyen, T. L., Y. K. Aung, C. F. Evans, C. Yoon-Ho, M. A. Jenkins, J. Sung, ... Y. M. Song (2015). "Mammographic density defined by higher than conventional brightness threshold better predicts breast cancer risk for full-field digital mammograms." Breast Cancer Research 17(1): 142–150.

Nguyen, T. L., D. F. Schmidt, E. Makalic, G. S. Dite, J. Stone, C. Apicella, M. Bui, R. J. MacInnis, F. Odefrey and J. N. Cawson (2013). "Explaining variance in the cumulus mammographic measures that predict breast cancer risk: a twins and sisters study." Cancer Epidemiology and Prevention Biomarkers 22(12): 2395-2403.

O'Flynn, E. A. M., A. E. W. Ledger and N. M. deSouza (2015). "Alternative screening for dense breasts: MRI." American Journal of Roentgenology 204(2): W141-149.

Obenauer, S., C. Sohns, C. Werner and E. Grabbe (2006). "Impact of breast density on computeraided detection in full-field digital mammography." Journal of Digital Imaging 19(3): 258.

Ohuchi, N., A. Suzuki, T. Sobue, M. Kawai, S. Yamamoto, Y.-F. Zheng, Y. N. Shiono, H. Saito, S. Kuriyama, E. Tohno, T. Endo, A. Fukao, I. Tsuji, T. Yamaguchi, Y. Ohashi, M. Fukuda and T. Ishida "Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial." The Lancet 387(10016): 341-348.

Olsen, A., K. Bihrmann, M. Jensen, I. Vejborg and E. Lynge (2009). "Breast density and outcome of mammography screening: a cohort study." British Journal of Cancer 100(7): 1205.

Parisky, Y., A. Sardi, R. Hamm, K. Hughes, L. Esserman, S. Rust and K. Callahan (2003). "Efficacy of computerized infrared imaging analysis to evaluate mammographically suspicious lesions." American Journal of Roentgenology 180(1): 263-269.

Park, B., H. M. Cho, E. H. Lee, S. Song, M. Suh, K. S. Choi ... J. K. Jun (2018). "Does breast density measured through population-based screening independently increase breast cancer risk in Asian females?" Clinical Epidemiology 10: 61–70.

Park, I. H., K. Ko, J. Joo, B. Park, S.-Y. Jung, S. Lee, Y. Kwon, H.-S. Kang, E. S. Lee and K. S. Lee (2014). "High volumetric breast density predicts risk for breast cancer in postmenopausal, but not premenopausal, Korean women." Annals of Surgical Oncology 21(13): 4124-4132.

Passaperuma, K., E. Warner, K. A. Hill, A. Gunasekara and M. J. Yaffe (2010). "Is mammographic breast density a breast cancer risk factor in women with BRCA mutations?" Journal of Clinical Oncology 28(23): 3779-3783.

Patterson, S. K. and M. A. Roubidoux (2014). "Update on new technologies in digital mammography." International Journal of Women's Health 6: 781-788.

Pereira, S. M. P., V. A. McCormack, S. M. Moss and I. dos Santos Silva (2009). "The spatial distribution of radiodense breast tissue: a longitudinal study." Breast Cancer Research 11(3): R33.

Pettersson, A., R. E. Graff, G. Ursin, I. dos Santos Silva, V. McCormack, L. Baglietto, C. Vachon, M. F. Bakker, G. G. Giles and K. S. Chia (2014). "Mammographic density phenotypes and risk of breast cancer: a meta-analysis." JNCI: Journal of the National Cancer Institute 106(5).

Pike, M. C., M. Krailo, B. Henderson, J. Casagrande and D. Hoel (1983). "Hormonal risk factors, breast tissue age and the age-incidence of breast cancer." Nature 303(5920): 767.

Pollán, M., N. Ascunce, M. Ederra, A. Murillo, N. Erdozáin, J. E. Alés-Martínez and R. Pastor-Barriuso (2013). "Mammographic density and risk of breast cancer according to tumor characteristics and mode of detection: a Spanish population-based case-control study." Breast Cancer Research 15(1): R9.

Rauh, C., C. Hack, L. Häberle, A. Hein, A. Engel, M. Schrauder, P. Fasching, S. Jud, A. Ekici and C. Loehberg (2012). "Percent mammographic density and dense area as risk factors for breast cancer." Geburtshilfe und Frauenheilkunde 72(8): 727.

Ravert, P. K. and C. Huffaker (2010). "Breast cancer screening in women: An integrative literature review." Journal of the American Academy of Nurse Practitioners 22(12): 668-673.

Ray, K. M., E. R. Price and B. N. Joe (2015). "Breast density legislation: mandatory disclosure to patients, alternative screening, billing, reimbursement." American Journal of Roentgenology 204(2): 257-260.

Rhodes, D. J., C. B. Hruska, S. W. Phillips, D. H. Whaley and M. K. O'connor (2011). "Dedicated dualhead gamma imaging for breast cancer screening in women with mammographically dense breasts." Radiology 258(1): 106-118.

Rhodes, D. J., C. B. Hruska, A. L. Conners, C. L. Tortorelli, R. W. Maxwell, K. N. Jones, A. Y. Toledano and M. K. O'Connor (2015A). "Journal club: molecular breast imaging at reduced radiation dose for supplemental screening in mammographically dense breasts." American Journal of Roentgenology 204(2): 241-251.

Rhodes, D. J., C. Radecki Breitkopf, J. Y. Ziegenfuss, S. M. Jenkins and C. M. Vachon (2015B). "Awareness of breast density and its impact on breast cancer detection and risk." Journal of Clinical Oncology 33(10): 1143-1150.

Rice, M. S., K. A. Bertrand, T. J. VanderWeele, B. A. Rosner, X. Liao, H. O. Adami and R. M. Tamimi, (2016). "Mammographic density and breast cancer risk: a mediation analysis." Breast Cancer Research 18(1): 94-107.

Richman, I., S. M. Asch, E. Bendavid, J. Bhattacharya and D. K. Owens (2017). "Breast density notification legislation and breast cancer stage at diagnosis: early evidence from the SEER registry." Journal of General Internal Medicine 32(6): 603-609.

Rose, S. L., A. L. Tidwell, L. J. Bujnoch, A. C. Kushwaha, A. S. Nordmann and R. Sexton Jr (2013). "Implementation of breast tomosynthesis in a routine screening practice: an observational study." American Journal of Roentgenology 200(6): 1401-1408.

Rosenberg, R. D., B. C. Yankaskas, L. A. Abraham, E. A. Sickles, C. D. Lehman, B. M. Geller, P. A. Carney, K. Kerlikowske, D. S. Buist and D. L. Weaver (2006). "Performance benchmarks for screening mammography." Radiology 241(1): 55-66.

Saadatmand, S., M. M. Tilanus-Linthorst, E. J. Rutgers, N. Hoogerbrugge, J. C. Oosterwijk, R. A. Tollenaar, M. Hooning, C. E. Loo, I.-M. Obdeijn and E. A. Heijnsdijk (2013). "Cost-effectiveness of screening women with familial risk for breast cancer with magnetic resonance imaging." Journal of the National Cancer Institute 105(17): 1314-1321.

Sanders, L. M., A. B. King and K. S. Goodman (2016). "Impact of the New Jersey breast density law on imaging and intervention volumes and breast cancer diagnosis." Journal of the American College of Radiology 13(10): 1189-1194.

Santiago-Rivas, M., S. Benjamin and L. Jandorf (2016). "Breast density knowledge and awareness: a review of literature." Journal of Primary Care & Community Health 7(3): 207-214.

Sari, A. A., M. Mobinizadeh and M. Azadbakht (2013). "A systematic review of the effects of diffuse optical imaging in breast diseases." Iranian Journal of Cancer Prevention 6(1): 44.

Sartor, H., K. Lång, A. Rosso, S. Borgquist, S. Zackrisson, and P. Timberg (2016). "Measuring mammographic density: comparing a fully automated volumetric assessment versus European radiologists' qualitative classification." European Radiology 26(12): 4354–4360.

Scheel, J. R., J. M. Lee, B. L. Sprague, C. I. Lee and C. D. Lehman (2015). "Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts." American Journal of Obstetrics & Gynecology 212(1): 9-17.

Shepherd, J. A., K. Kerlikowske, L. Ma, F. Duewer, B. Fan, J. Wang, S. Malkov, E. Vittinghoff and S. R. Cummings (2011). "Volume of mammographic density and risk of breast cancer." Cancer Epidemiology and Prevention Biomarkers 20(7): 1473-1482.

Shermis, R. B., K. D. Wilson, M. T. Doyle, T. S. Martin, D. Merryman, H. Kudrolli and R. J. Brenner (2016). "Supplemental breast cancer screening with molecular breast imaging for women with dense breast tissue." American Journal of Roentgenology 207(2): 450-457.

Shen, S., Y. Zhou, Y. Xu, B. Zhang, X. Duan, R. Huang, B. Li, Y. Shi, Z. Shao and H. Liao (2015). "A multi-centre randomised trial comparing ultrasound vs mammography for screening breast cancer in high-risk Chinese women." British Journal of Cancer 112(6): 998.

Skaane P., A. I. Bandos, R. Gullien, E. B. Eben, U. Ekseth, U. Haakenaasen, M. Izadi ... S. Hofvind (2013). "Prospective Trial Comparing Full-Field Digital Mammography (FFDM) versus Combined FFDM and Tomosynthesis in a Population-Based Screening Programme Using Independent Double Reading with Arbitration." European Radiology 23(8): 2061–71.

Stone, J., J. Ding, R. M. Warren, S. W. Duffy and J. L. Hopper (2010). "Using mammographic density to predict breast cancer risk: dense area or percentage dense area." Breast Cancer Research 12(6): R97.

Sung, J., Y. M. Song, J. Stone, K. Lee, J. I. Jeong and S. S. Kim (2010). "Genetic influences on mammographic density in Korean twin and family: the Healthy Twin study." Breast Cancer Research and Treatment 124(2): 467-474.

Tamimi, R. M., S. E. Hankinson, G. A. Colditz and C. Byrne (2005). "Endogenous sex hormone levels and mammographic density among postmenopausal women." Cancer Epidemiology and Prevention Biomarkers 14(11): 2641-2647.

Torres-Mejía, G., B. De Stavola, D. S. Allen, J. J. Pérez-Gavilán, J. M. Ferreira, I. S. Fentiman and I. dos Santos Silva (2005). "Mammographic features and subsequent risk of breast cancer: a comparison of qualitative and quantitative evaluations in the Guernsey prospective studies." Cancer Epidemiology and Prevention Biomarkers 14(5): 1052-1059.

Trieu, P. D. Y., C. Mello-Thoms, J. K. Peat, T. D. Do and P. C. Brennan (2017). "Risk Factors of Female Breast Cancer in Vietnam: A Case-Control Study." Cancer Research and Treatment 49(4): 990–1000.

Trinh, L., D. M. Ikeda, K. K. Miyake, J. Trinh, K. K. Lee, H. Dave, K. Hanafusa and J. Lipson (2015). "Patient awareness of breast density and interest in supplemental screening tests: comparison of an academic facility and a county hospital." Journal of the American College of Radiology 12(3): 249-255.

Vacek, P. M. and B. M. Geller (2004). "A prospective study of breast cancer risk using routine mammographic breast density measurements." Cancer Epidemiology and Prevention Biomarkers 13(5): 715-722.

Vachon, C. M., K. R. Brandt, K. Ghosh, C. G. Scott, S. D. Maloney, M. J. Carston, V. S. Pankratz and T. A. Sellers (2007). "Mammographic breast density as a general marker of breast cancer risk." Cancer Epidemiology and Prevention Biomarkers 16(1): 43-49.

Vachon, C. M., C. C. Kuni, K. Anderson, V. E. Anderson and T. A. Sellers (2000). "Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States)." Cancer Causes & Control 11(7): 653-662.

van der Waal, D., T. M. Ripping, A. L. M. Verbeek and M. J. M. Broeders (2017). "Breast cancer screening effect across breast density strata: A case-control study: Screening effect across breast density strata." International Journal of Cancer 140(1): 41–49.

van Gils, C. H., J. Otten, A. Verbeek, J. Hendriks and R. Holland (1998). "Effect of mammographic breast density on breast cancer screening performance: a study in Nijmegen, The Netherlands." Journal of Epidemiology & Community Health 52(4): 267-271.

Wanders, J. O., K. Holland, W. B. Veldhuis, R. M. Mann, R. M. Pijnappel, P. H. Peeters, C. H. van Gils and N. Karssemeijer (2017). "Volumetric breast density affects performance of digital screening mammography." Breast Cancer Research and Treatment 162(1): 95-103.

Wang, A. T., C. M. Vachon, K. R. Brandt and K. Ghosh (2014). "Breast density and breast cancer risk: a practical review." Mayo Clinic Proceedings 89(4): 548-557.

Weigel, S., W. Heindel, J. Heidrich, H. W. Hense and O. Heidinger (2017). "Digital mammography screening: sensitivity of the programme dependent on breast density." European Radiology 27(7): 2744–2751.

Weigert, J. and S. Steenbergen (2012). "The Connecticut experiment: the role of ultrasound in the screening of women with dense breasts." The Breast Journal 18(6): 517-522.

Wellings, E., L. Vassiliades and R. Abdalla (2016). "Breast Cancer Screening for High-Risk Patients of Different Ages and Risk-Which Modality Is Most Effective?" Cureus 8(12): e945.

Winkel, R. R., M. von Euler-Chelpin, M. Nielsen, P. Diao, M. B. Nielsen, W. Y. Uldall and I. Vejborg (2015). "Inter-observer agreement according to three methods of evaluating mammographic density and parenchymal pattern in a case control study: impact on relative risk of breast cancer." BMC Cancer 15(1): 274-288.

Winkel, R. R., M. von Euler-Chelpin, M. Nielsen, K. Petersen, M. Lillholm, M. B. Nielsen ... I. Vejborg (2016). "Mammographic density and structural features can individually and jointly contribute to breast cancer risk assessment in mammography screening: a case–control study." BMC Cancer 16(1): 414-426.

Winkler, N. S., S. Raza, M. Mackesy and R. L. Birdwell (2015). "Breast density: clinical implications and assessment methods." Radiographics 35(2): 316-324.

Wolfe, J. N. (1976). "Risk for breast cancer development determined by mammographic parenchymal pattern." Cancer 37(5): 2486-2492.

Yaghjyan, L., G. A. Colditz, B. Rosner and R. M. Tamimi (2015a). "Mammographic breast density and breast cancer risk: interactions of percent density, absolute dense, and non-dense areas with breast cancer risk factors." Breast Cancer Research and Treatment 150(1): 181–189.

Yaghjyan, L., A. Pettersson, G. A. Colditz, L. C. Collins, S. J. Schnitt, A. H. Beck ... R. M. Tamimi (2015b). "Postmenopausal mammographic breast density and subsequent breast cancer risk according to selected tissue markers." British Journal of Cancer 113(7): 1104–1113.

Yankaskas, B. C., S. Haneuse, J. M. Kapp, K. Kerlikowske, B. Geller, D. S. Buist and B. C. S. Consortium (2010). "Performance of first mammography examination in women younger than 40 years." JNCI: Journal of the National Cancer Institute 102(10): 692-701.

Yeh, V. M., J. B. Schnur, L. Margolies and G. H. Montgomery (2015). "Dense breast tissue notification: Impact on women's perceived risk, anxiety, and intentions for future breast cancer screening." Journal of the American College of Radiology 12(3): 261–266.

Ziv, E., J. Tice, R. Smith-Bindman, J. Shepherd, S. Cummings and K. Kerlikowske (2004). "Mammographic density and estrogen receptor status of breast cancer." Cancer Epidemiology and Prevention Biomarkers 13(12): 2090-2095.

APPENDIX A: QUALITY ASSESSMENT FOR EACH INCLUDED STUDY

AMSTAR2 Tool for systematic reviews and meta-analysis

Bae and Kim (2016) - A Review of Supplemental Screening Ultrasound for Breast Cancer: Certain Populations of Women with Dense Breast Tissue May Benefit

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	
4	Did the review authors use a comprehensive literature search strategy?	Yes	Yes followed PRISMA protocol
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	
7	Did the review authors describe the included studies in adequate detail?	Yes	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	No – risk was not well discussed
9	Did the review authors report on the sources of funding for the studies included in the review?	No	
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	3/6 studies included, provided summary size effect (sES)

	AMSTAR2 TOOL QUESTION	Answer	Comment
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Risk of bias was not well discussed
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Limitation and risk of individual studies were not discussed
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	I2 was calculated and discussed
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	No	Appeared to be a convenience sample of studies, this was not justified
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	No	
4	Did the review authors use a comprehensive literature search strategy?	No	
5	Was there duplicate study selection and data extraction?	No	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	No	
7	Did the review authors describe the included studies in adequate detail?	Yes	Additional files described the study well
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	This work was supported in part by the National Institutes of Health, National Cancer Institute, the Breast Cancer Research Foundation and the Department of Defense, KAB was supported by the Nutritional Epidemiology of Cancer Training Grant.

Bertrand et al. (2013) - Mammographic density and risk of breast cancer by age and tumor characteristics

	AMSTAR2 TOOL QUESTION	Answer	Comment
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Individual studies were report o for bias and confounders
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Tests of heterogeneity were complete d by cancer subtype
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Discussed ethnicity, varied study designs and populations
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Authors have no competing interests, all funding declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	
4	Did the review authors use a comprehensive literature search strategy?	Yes	
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	No	Exclusion criteria: not in English, as well as any published before 2005 due to tomosynthesis only becoming clinically available after this point. Studies were also excluded if they compared DBT to film-screen mammography, since current screening standards use digital breast mammography.
7	Did the review authors describe the included studies in adequate detail?	Yes	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	
9	Did the review authors report on the sources of funding for the studies included in the review?	No	

Coop et al. (2016) - Tomosynthesis as a screening tool for breast cancer: A systematic review

	AMSTAR2 TOOL QUESTION	Answer	Comment
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Some meta-analysis performed where possible
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?		
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	N/A	None to report

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	RCTs, with either individual or cluster randomisation, and prospective, controlled non-randomised studies with a low risk of bias and a sample size of at least 500 participants. In addition to studies eligible for efficacy, we considered any controlled, non- randomised study with a low risk of bias and a study size of at least 500 participants for the assessment of harms. Our population of interest were women between the ages of 40 and 75 years who were at average risk for breast cancer.
4	Did the review authors use a comprehensive literature search strategy?	Yes	
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	
7	Did the review authors describe the included studies in adequate detail?	N/A	No studies were found
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	

Gartlehner et al. (2013) - Adjunct ultrasonography for breast cancer screening in women at average risk: a systematic review

	AMSTAR2 TOOL QUESTION	Answer	Comment
9	Did the review authors report on the sources of funding for the studies included in the review?	No	
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	No studies were found
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	No studies were found
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	N/A	No studies were found
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	No studies were found
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A	No studies were found
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	

Houssami & Turner (2016) - Rapid review: Estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	
3	Did the review authors explain their selection of the study designs for inclusion in the review?		(a) evaluated tomosynthesis (also referred to as 3D-mammography) for population screening in comparison with standard digital mammography, and (b) provided data on BC detection (detection data or rates and/or incremental BC detection from tomosynthesis) or allowed its calculation, in women with dense breasts.
4	Did the review authors use a comprehensive literature search strategy?	No	This was based on a previous systematic review, but not provided in this rapid review
5	Was there duplicate study selection and data extraction?	No	No information regarding duplicate studies
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	

	AMSTAR2 TOOL QUESTION	Answer	Comment
7	Did the review authors describe the included studies in adequate detail?	Yes	However, how density was defined by each study was not provided
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	N. Houssami receives research support through a National Breast Cancer Foundation (Australia)
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	For paired data, pooled estimate (and 95%CI) of the incremental effect on detection was calculated using a random effects model for proportions using the Wilson (score) method. For data from independent groups of participants, the pooled difference in proportions (and 95%CI) was calculated using random effects modelling estimated with the DerSimonian and Laird method. Forest plots were also provided
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Limited information given
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	

	AMSTAR2 TOOL QUESTION	Answer	Comment
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts declared

Melnikow et al. (2016) - Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	
3	Did the review authors explain their selection of the study designs for inclusion in the review?		Good-quality diagnostic accuracy studies, RCTs and observational studies
4	Did the review authors use a comprehensive literature search strategy?	Yes	
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	
7	Did the review authors describe the included studies in adequate detail?	Yes	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Summary of evidence tables provided
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	Agency for Healthcare Research and Quality.
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	

	AMSTAR2 TOOL QUESTION	Answer	Comment
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	All conflicts were declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	RCTs, observational studies of screening cohorts, and systematic reviews of screening with mammography (film, digital, tomosynthesis) and other modalities (MRI, ultrasound, CBE alone or in combination) were included
4	Did the review authors use a comprehensive literature search strategy?	Yes	
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	
7	Did the review authors describe the included studies in adequate detail?	Yes	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Summary of evidence tables provided
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	Agency for Healthcare Research and Quality

Nelson et al. (2016) - Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis

	AMSTAR2 TOOL QUESTION	Answer	Comment
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	A random-effects model was used to combine relative risks (RRs) as the effect measure of the meta-analyses, while incorporating variation among studies.
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	The presence of statistical heterogeneity among the studies was assessed by using the standard Cochran's chi-square test, and the magnitude of heterogeneity by using the I 2 statistic.
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	All conflicts declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	Yes	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Studies partaking in the DENSNP consortium
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	case –controlled design
4	Did the review authors use a comprehensive literature search strategy?	No	
5	Was there duplicate study selection and data extraction?	N/A	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	N/A	
7	Did the review authors describe the included studies in adequate detail?	Yes	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes however, they were unable to account for all the biases
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	National Cancer Institute
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Random effects model
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Undertook a fully adjusted model
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	

Petterson et al. (2014)- Mammographic Density Phenotypes and risk of Breast Cancer: A Meta-analysis

	AMSTAR2 TOOL QUESTION	Answer	Comment
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	All author declarations declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	No	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	
4	Did the review authors use a comprehensive literature search strategy?	No	
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	
7	Did the review authors describe the included studies in adequate detail?	No	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	No funding declared
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	

Sari et al. (2013). - A Systematic Review of the Effects of Diffuse Optical Imaging in Breast Diseases
	AMSTAR2 TOOL QUESTION	Answer	Comment
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No conflicts declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	No	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	No	No – but they did say included studies using either ABUS or handheld US (HHUS) as an adjunct to screening mammography that were not in male patients, reader studies, case reports, and review articles.
4	Did the review authors use a comprehensive literature search strategy?	No	
5	Was there duplicate study selection and data extraction?	Yes	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	
7	Did the review authors describe the included studies in adequate detail?	Yes	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	National Institutes of Health (grant 1R01CA151326).
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	

Scheel et al. (2015) - Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts

	AMSTAR2 TOOL QUESTION	Answer	Comment
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	All conflicts declared

	AMSTAR2 TOOL QUESTION	Answer	Comment
1	Did the research questions and inclusion criteria for the review include the components of the PICO?	No	
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The BCSC is a National Cancer Institute-funded collaborative network of population-based mammography registries with linkages to pathology and/or tumor registries
3	Did the review authors explain their selection of the study designs for inclusion in the review?	No	
4	Did the review authors use a comprehensive literature search strategy?	No	
5	Was there duplicate study selection and data extraction?	No	
6	Did the review authors provide a list of excluded studies and justify the exclusion?	N/A	
7	Did the review authors describe the included studies in adequate detail?	No	
8	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	
9	Did the review authors report on the sources of funding for the studies included in the review?	Yes	National Cancer Institute-funded Breast Cancer Surveillance Consortium cooperative agreements
10	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No	Not enough detail provided to know
11	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	

Yankaskas et al. (2010) - Performance of First Mammography Examination in Women Younger Than 40 Years

	AMSTAR2 TOOL QUESTION	Answer	Comment
12	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Some study limitations were provided which may have provided bis
13	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	
14	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	
15	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	

SIGN criteria for RCTs

Ohuchi et al. (2016) - Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial

	INTERNAL VALIDITY			
1.1	The study addresses an appropriate and clearly focused question.	Yes 🗹	Can't say 🗆	No 🗆
1.2	The assignment of subjects to treatment groups is randomised.	Yes 🗹	Can't say 🗆	No 🗆
1.3	An adequate concealment method is used.	Yes 🗹	Can't say 🗆	No 🗆
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes 🗆	Can't say 🗆	No 🗹
1.5	The treatment and control groups are similar at the start of the trial.	Yes 🗹	Can't say 🗆	No 🗆
1.6	The only difference between groups is the treatment under investigation.	Yes 🗆	Can't say 🗹	No 🗆
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes 🗹	Can't say 🗆	No 🗆
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	2% of participants were lost to follow-up - No information about which arm these women were in is provided.	NA	NA
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes 🗹	Can't say 🗆	No 🗆
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes 🗹	Can't say 🗆	No 🗆 NA 🗆

	OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise bias?	High quality (++)□ Acceptable (+)☑ Low quality (-)□ Unacceptable – reject 0 □		
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes – study has good power and groups have no heterogeneity		
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes		