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Review

Are mammographic density phenotypes associated with breast cancer treatment response and clinical outcomes? A systematic review and meta-analysis

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ABSTRACT

Mammographic density (MD) increases breast cancer (BC) risk, however, its association with patient outcomes is unclear. We examined the association of baseline MD (BMD), and MD reduction (MDR) following BC treatment with patient outcomes. Six databases (CINAHL, Scopus, PubMed, Web of Science, MEDLINE, and Embase) were used to identify relevant articles. The PRISMA strategy was used to extract relevant details. Study quality and risk of bias were assessed using the "Quality In Prognosis Studies" (QUIPS) tool. A Meta-analysis and pooled risk estimates were performed. Results showed that BMD is associated with contralateral breast cancer (CBC) risk (HR = 1.9; 95%CI: 1.3–3.0, p = 0.0007), recurrence (HR = 2.0; 95%CI: 1.0–4.0, p = 0.04), and mortality (HR = 1.4; 95%CI: 1.1–1.9, p = 0.003). No association was found between BMD and prognosis (HR = 3.2; 95%CI: 0.9–11.2, p = 0.06). Data on risk estimates (95% CI) from BMD for survival [RR: 1.75; 0.99–3.1 to 2.4; 1.4–4.1], ipsilateral BC [HR: 1; 0.6–1.6 to 3; 1.2–7.5], and treatment response (OR, 1.8; 0.98–3.3) are limited. MDR showed no association with mortality (HR = 0.5; 95%CI: 0.2–1.2, p = 0.13). MDR is associated with a reduced risk of recurrence [HR/RR: 0.35; 0.17–0.68 to 1.33; 0.67–2.65)], however data on MDR and outcomes such as mortality [HR/RR: 0.5; 0.27–0.93 to 0.59; 0.22–0.88], and CBC risk [RR/HR: 0.53; 0.24–0.84 to 1.3; 0.6–2.7] are limited. Evidence, although sparse, demonstrates that high BMD is associated with an increased risk of recurrence, CBC, and mortality. Conversely, MDR is associated with a reduced risk of BC recurrence, CBC, and BC-related mortality.

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1. Introduction

Mammographic density (MD) is a strong predictor of breast cancer (BC) risk and modifies the relationship between many traditional BC risk factors and BC risk [1]. Breast tissue comprises epithelial cells, stroma, and adipose tissue that determine the appearance of the breast on mammograms [2]. High (MD), the proportion of the breast containing radiographically opaque tissue is significantly associated with interval cancer due to high BC risk in dense tissue and the masking effect of MD [3]. Importantly, MD is modifiable [4], and changes following BC therapy [5–8]. Factors such as physical activity, diet, chemotherapies and endocrine therapies have been shown to change MD [5,7–10], with chemotherapies and endocrine therapies modulating MD through endogenous hormones [8,10]. It is well established that MD is associated with BC risk and is modifiable, however it is an open question as to whether MD at diagnosis (baseline BMD) and changes in MD following BC treatment has an impact on treatment outcomes and prognosis.

MD and changes in MD can be measured using qualitative and quantitative approaches. The qualitative approaches rely mainly on visual assessment and grading of MD into different categories, and include approaches proposed by Wolfe [11,12], Tabar [13], Boyd [14], the visual analogue scale (VAS),and the Breast Imaging Reporting and Data System (BI-RADS®) [12,15]. Prior to 2013, the fourth edition of BI-RADS® which classifies BD into quartiles was commonly used clinically. In 2013, the edition BIRADS® 5th was developed to account for the likelihood of the masking of BC by MD, increasing the potential for interrater variability [16,17]. To reduce subjective variability in MD assessment, objective quantitative tools were developed. Quantitative methods use computer-assisted software packages to calculate MD and these include area-based methods and volumetric approaches [18]. Area-based techniques utilize computer-assisted tools to perform tasks such as segmentation, thresholding, mathematical and statistical modelling to calculate percent mammographic density (PMD) and include the Laboratory for Individualized Breast Radiodensity Assessment (LIBRA), iReveal, Cumulus, Madena, and MedDensity [18,19]. To account for volume of dense tissue in the dense area, volumetric tools were proposed. Volumetric approaches comprising of Volpara™, Quantra™, and Cumulus V rely on physics-based algorithms to model the fibro-glandular tissue thickness and physical characteristics of the X-ray beam [15]. All methods have shown significant association between MD and BC risk and could be used to monitor changes in MD following treatment [20,21].

Many studies have investigated the association between MD and prognosis as well as treatment outcomes [2,5,6,8,22–46]. However, these studies have generated different data for the association between MD phenotypes and patient outcomes. Evidence shows that 20–30% variation in MD is concomitant with variation in BC incidence [47], and that there are ethnic variations in response to treatment and mortality from BC [48,49]. However, it is unclear whether the MD versus outcome relationship is confounded by MD phenotype used or ethnic differences. Importantly, there is a lack of understanding of the impact of MD changes on the course and outcomes of BC treatment. Despite the gaps above, there has been no review of the literature to establish the true impact of BMD and MDR following cancer treatment on outcomes for women diagnosed with, or treated for BC. This emphasises the need for a detailed analysis of published studies to establish the relationship between MD and treatment outcomes. Therefore, the objective of this review was to examine the relationship between BMD, which is a woman's MD at diagnosis, and outcomes from BC. The review also aims to investigate the association between MDR following BC treatment and treatment outcomes such as survival, mortality, recurrence, and pathological complete response (pCR). The findings of the review may lead to the identification of MD phenotypes that can be used to improve the discriminatory power of current BC treatment outcome prediction models. If current models' prediction abilities can be improved, we would more reliably identify BC-affected women who may develop adverse events such as contralateral BC and recurrence and better inform choices of treatment options to reduce deaths from BC.

2. Materials and methods

2.1. Search strategy

A search protocol was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to extract articles published to date. Articles were identified using CINAHL, Scopus, PubMed, Web of Science, MEDLINE, and Embase databases. To access additional articles, a further search was conducted using Google scholar, the University of Sydney library database, and reference lists of published articles were manually scrutinized. The search was conducted in English language. All search terms were identified earlier by a rapid scoping search strategy. Search terms were combined with “AND” or “OR” and included “Breast density” AND “Treatment response” OR “Treatment outcome” OR “Prognosis” OR “Survival rate” OR “Recurrence” OR “Disease free survival” OR “Progression free survival” OR “Clinical outcome”.

2.2. Inclusion and exclusion criteria

Articles were considered relevant for inclusion if they assessed the association between BMD and BC treatment outcome, or between MDR and treatment outcome. Randomized controlled trials (RCTs), nested case control studies, case control studies, longitudinal studies, and case only studies were considered for inclusion. Only articles published in English language were deemed eligible for inclusion. Articles that did not fulfil the above-mentioned criteria were excluded. Literature reviews, posters, conference articles, editorial, and case reports were also excluded.

2.3. Data synthesis and quality assessment

In terms of study selection, two authors (IK) and (EE) independently evaluated the articles for relevance to the review. Any disagreement was resolved through deliberation, and where a consensus could not be reached, a third reviewer (WR) was asked to arbitrate. All articles were independently reviewed by IK and EE for quality and risk of bias using the “Quality In Prognosis Studies” (QUIPS) tool which comprises of six main domains with 28 questions [50]. To assess the consistency of rating between the two

reviewers, interrater agreement assessment was calculated using a quadratic weighted kappa (κ_W) for each domain and for the overall quality.

Questions of each domain were independently answered by the reviewers as "yes", "partially", or "no". Any disagreement in rating was discussed, and if no agreement was reached after deliberation, another reviewer (WR) was asked to arbitrate. The overall rating of each domain was then coded based on these responses, as a high (+++), moderate (++), or low (+) risk of bias. Studies were considered to be high quality if all domains were scored as having a low risk of bias, or at least four domains were scored as low risk. Studies were deemed to be of moderate quality if all domains were scored as having a moderate risk of bias, or at least three domains showed moderate risk of bias. Studies were considered to be low quality if all domains were scored as high risk of bias or at least four domains had a high level of bias. Each of these articles was reviewed based on the population intervention comparator outcomes (PICO) method (Table 1). The following data were extracted from studies reviewed: year of publication, study design, characteristics of study sample (sample size, age, menopause status), MD information (methods of MD assessment, measured BMD, magnitude of MDR, duration between baseline mammogram and other follow-up mammograms), type of treatment, related findings, adjustments, and patient outcomes (survival, mortality, treatment response, recurrence contralateral BC, prognosis). Survival was defined as the number of years lived following BC diagnosis, and mortality as death due to BC. Treatment response was defined as the absence of cancer tissue after treatment. Recurrence denotes the return of BC after treatment, and prognosis as the possible outcome following treatment.

2.3.1. Statistical analysis

A meta-analysis with pooled risk estimate for each BC outcome was performed using the NCSS statistical software. This analysis requires two variable inputs for each study including Log Hazard Ratio (HR) and the standard error (SE logHR). Due to the variability in the measure of risk estimates between studies, and because a majority of studies used HR or Relative risk (RR) as a measure of risk estimate, odds ratios (ORs) of some studies were converted to RR using the formula $\mathbf{RR{=}OR/(1\text{-}P_{ref}) + (P_{ref} * OR)}$, where $\mathbf{P_{ref}}$ is "the prevalence of the disease in the outcome group". The standard error of log HR was manually calculated using the formula: $\mathbf{(SE\ log\ HR) = \sqrt{(1/E1 + 1/E2)}}$, where **E1** is "the number of events in high MD group", and **E2** is "the number of events in low MD group" [51]. In some studies, the variables required for pooled analysis were not reported, therefore pooled estimates could not be computed. Instead, summaries of these studies were presented as forest plots, which were generated using Microsoft Excel. A few studies were excluded from the analysis, because they did not report the risk estimates (HR/RR) of outcome measures. The statistical heterogeneity among the studies was tested using the Cochran's Q test.

3. Results

The search strategy yielded 6,764 articles from the selected databases, and seven additional publications were recognised through Google scholar, the University of Sydney library, and the reference lists of articles obtained from databases. Of these, 6,365 articles were excluded based on their titles, 349 articles were duplicates, and 57 publications were considered for further assessment. Of these 57 articles assessed, 29 were deemed eligible for review, and the 28 remaining articles were excluded, because they were not full-texts (n = 4), assessed the association between MD and outcome measures such as cosmetics (breast appearance following surgery), metastatic BC, and nodal status, which are not relevant to the review (n = 10), or were posters, conference proceedings, and commentary papers (n = 14). Of the 29 studies reviewed, 20 articles used BMD as a marker of prognosis and treatment outcomes, and nine articles assessed the association between MDR and treatment outcomes (Fig. 1).

Of the 20 studies that investigated the association between BMD and treatment outcomes as well as prognosis (Tables 2–5) [2,22–27,30–32,35–37,40–46], 70% were retrospective observational cohort studies (ROCSs) [2,23–27,31,32,35,37,41,42,44,46], 5% were case only studies (COS) [30], 10% were case control studies (CCS) [22,36], and 15% were nested case control studies (NCCS) [40,43,45]. Eight studies were conducted in the USA [23,26,31,37,40,43,45,46], four in Sweden [22,24,30,42], two in Finland [2,32], and single studies were conducted in Canada [25], Taiwan [36], Peru [35], Saudi Arabia and Egypt [27], the UK [44], and Denmark [41]. These studies were published between 2004 and 2017, and their sample size ranged from 241 to 48,052 participants (Total: 86,297; Mean = 4,315). Two of the studies were mainly based on postmenopausal women [22,30], seven studies included both premenopausal and postmenopausal women [2,25,27,32,40,42,46], and the remaining 12 studies did not provide information about menopausal status. Half of the studies assessed MD in women who had surgery in combination with chemotherapy, immunotherapy and radiotherapy [23,25,26,30,31,36,37,42,43,46]. Five studies assessed MD in women who had no surgery but were treated with chemotherapy and interventions such as, immune therapies, radiotherapy, and endocrine therapies [2,27,32,35,45]. One study investigated patients treated mainly with radiotherapy [40]. The four remaining

Table 1
Inclusion criteria for eligible studies based on PICO methodology.

Characteristics	Criteria
Study year	Studies published up to March 2019
Study design	Randomized controlled trials (RCTs)
	Nested case control studies
	Case control studies
	Cohort studies
	Longitudinal studies
	Case only studies
Population	Female breast cancer patients at all ages
Interventions	Surgery
	Chemotherapies
	Endocrine therapies
	Radiotherapy
Comparator	Relationship between BMD or MDR induced by cancer treatments with patient outcomes
Outcomes	Survival, mortality, recurrence, prognosis, treatment response, Contralateral risk

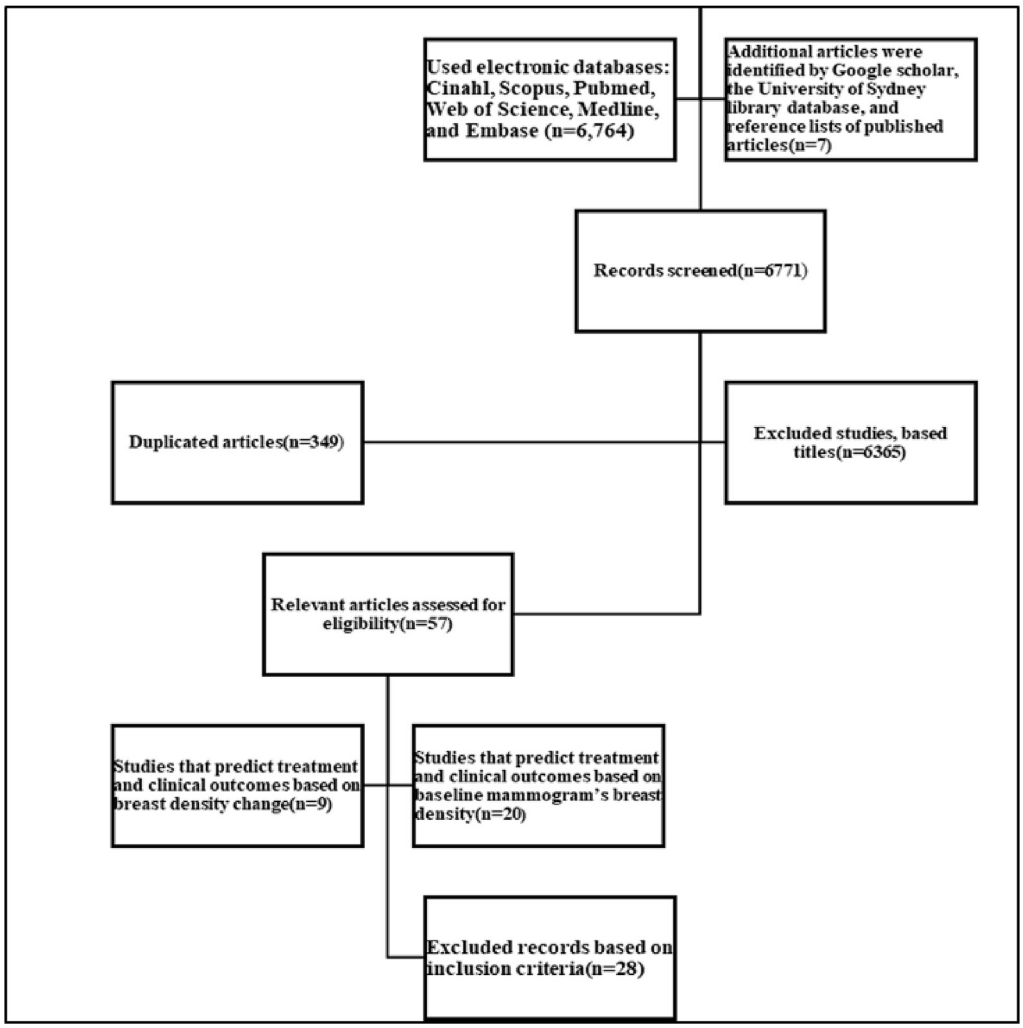

Fig. 1. Flow diagram showing the search results.

articles did not report the treatment interventions used [22,24,41,44]. In all, 14 articles had an unequal distribution of MD categories described by visual MD measurements at baseline [2,22–24,26,27,30–32,35–37,42,44], and the majority of the studies measured density at diagnosis [2,22,23,25,27,30–32,40,42,43,45]. Thirteen studies used visual approaches for MD assessment [2,24,25,27,31,32,35,37,41,42,44–46], five employed area based methods [22,30,36,40,43], and two utilised a combination of different methods, such as volumetric, visual, and area based methods [23,26]. Percent MD (PMD) was the main MD phenotype used by these studies [22,23,26,30,36,40,43]. Only six studies assessed the reliability of MD measurement and showed reliable MD measures (Interclass correlation coefficient ≥ 0.8) [2,22,23,25,30,31]. All but five of these studies performed MD assessment using the contralateral breast [22,30,36,43,44], three used both breasts [23,40,41], and one used the ipsilateral breast [31]. Follow-up periods were expressed as medians ranging from 1 to 11 years in eight studies [23,31,36,37,41–44], and as means (6.4–12.9 years) in five studies [2,24,32,40,46]. Three studies had a mean follow-up period of 9 years [22,25,30], and the remaining 4 studies did not report the follow-up duration [26,27,35,45].

The association between BMD and survival outcomes (overall survival and BC specific survival) was assessed in three studies [22,24,44], mortality endpoint in five [24,40–42,46] (Table 2), recurrence outcomes in five (Table .3) [25,26,30,36,43], contralateral BC in four studies (Table 4) [23,31,37,45], treatment response in two (Table 5) [27,35], and prognosis in two studies (Table 5) [2,32]. BMD was associated with an increased risk of mortality in three studies involving the European population [24,41,42], and a reduced risk in two studies from an American population [40,46]. Survival varied by tumour characteristics, with tumour size (>20 mm) [42,46], tumour grade (grade III), lymph node positivity, estrogen hormone receptor negative (ER-), and progesterone hormone receptor negative (PR-), and all these features were associated with poor survival [42]. All but one of these studies assessed BMD at diagnosis [42]. Information about menopausal status was only reported by one study which recruited more postmenopausal participants [42]. High BMD was associated with an increased risk of BC recurrence in four studies that measured BMD using area-based subjective and semi-automated approaches [25,30,36,43], and no association was observed in one study that explored excision rate as an outcome using both subjective (BI-RADS® 4th edition) and volumetric breast density measurement methods [26]. Among the studies on recurrence, three involved pre- and post-menopausal women, and one was based on postmenopausal women [30]. BMD was associated with an increased risk of contralateral breast cancer (CBC) in all four studies using visual MD

Table 2
Characteristics of studies that assessed the association between baseline mammographic density and survival as well as mortality.

Authors, Year	Study Design	Study Population and Country	Age, Menopausal Status,	Type of Intervention	BMD Measurement/ Time	MD Assessment Method, Inter-observer Variability Assessment, Region of Interest	Follow-up Period	Patient Outcomes	Related Significant Finding	Adjustments
Chiu et al., [24] 2010	ROCS	n:15685, Sweden	45 to 59 Yrs.	Not reported	12.7% (High MD), MD was measured at the beginning of screening.	Tabar's method	Mean: 25 Yrs.	Survival, Mortality	BC specific survival (no association), Mortality (positive association with dense breast)	Age, Tumour size, Node status, Grade, and BMI
Eriksson et al. [22] 2013	CCS	n:1400, Sweden	62 Yrs. (post-meno. only)	Not reported	PMD <25%: 75.3% PMD ≥25%: 24.6% MD was measured at diagnosis	Cumulus, Intra-observer reliability assessment was applied, CB	5 Yrs.	Survival	MD is negatively associated with overall survival	Age, BMI, HRT use, Tumour size and Lymph node metastasis.
Maskarinec et al. [40] 2013	NCCS	n:607, USA	63.3 Yrs. (79.7%, post-meno.)	RT	High PMD, n:303 Low PMD, n:304 ,MD was measured at diagnosis	Cumulus, Bilateral breasts	Mean: 12.9 Yrs.	Mortality	MD is negatively associated with mortality	RT
Olsson et al. [42] 2014	ROCS	n:619, Sweden	56.7 ± 7.0 Yrs., (89.3%, post-meno.)	Surgery ET Chemo. RT	BI-RADS4:34.6% BI-RADS2,3:50.4% BI-RADS1:15%, MD was measured at diagnosis	BI-RADS® 4th edition	Median: 7.8 Yrs.	mortality	MD is positively associated with mortality	Age, Tumour size, Grade, ER status, PR status, Diagnostic period. BMI Mode of detection
Porter et al [44] 2007	ROCS	n:759(SDC:455, IC:304) UK	(50–64) Yrs.	Not reported	51% had BI-RADS 4,3 (SDC), 70% had BI-RADS 4,3(IC), MD was measured at screened mammograms	BI-RADS® 4th edition, CB	Median: 9 Yrs.	Survival	No significant association is found between MD and BC specific survival	Not reported
Olsen et al [41]. 2009	ROCS	n:48,052, Denmark	(50–69) Yrs.	Not reported	54% had BI-RADS 4,3 breasts, and 46% had BI-RADS1,2, MD was measured at screened mammograms	BI-RADS® 4th edition, Bilateral breasts	Median: 11 Yrs.	Mortality	MD is positively associated with mortality	Age
Weaver et al. [46] 2012	ROCS	n:9,232, USA	59 ± 13 Yrs. (74.6%, post-meno.)	Surgery, RT Chemo. ET	BI-RADS 4 = 9.9% BI-RADS 3 = 43.5% BI-RADS 2 = 40.5%, BI-RADS 1 = 6.1%, MD was measured on mammograms conducted before diagnosis.	BI-RADS® 4th edition	Mean: 6.6 Yrs.	Mortality	MD is negatively associated with mortality	Site, Age at and year of diagnosis, American Joint Committee on Cancer stage, BMI, Mode of detection, Treatment, and Income

Abbreviations: HRT, hormonal replacement therapy; ROCS; retrospective observational cohort study; CCS, case control study; CB, contralateral breast; MD, mammographic density; Post-meno., postmenopausal; AIs, aromatase inhibitors; RFS, recurrence free survival; NCCS, nested case control study; BMI, body mass index; ER, estrogen receptor status; PMD, percent mammographic density; RT, radiotherapy; Chemo., chemotherapy; DCIS, ductal carcinoma in situ; IBC, ipsilateral breast cancer; CBC, contralateral breast cancer; Pre-meno., premenopausal; VLD, very low breast density; MID, mixed breast density; BI-RADS®, breast imaging reporting and data system; LRR, locoregional recurrence; LDR, local disease recurrence; COS, case only study; ET, endocrine therapy; IB, ipsilateral breast; PR, progesterone receptor; IC, interval cancers; SCD, screened cancers detected; HER2, human epidermal growth receptor2, NPI, Nottingham prognostic index; NAC, neoadjuvant chemotherapy; BCS, breast conserving surgery; pCR, pathological complete response.

assessment methods, and population was mainly American [23,31,37,45]. Menopausal status was only provided in one study that included both pre- and post-menopausal women [37]. BMD was associated with a reduced survival in one case control study that involved only postmenopausal women and measured MD at diagnosis using cumulus software [22]. No association was found between BMD and breast cancer specific survival in two studies that employed visual approaches [24,44]. BMD was positively associated with poor prognosis in two studies that used tumour grade and lymph node [2] or Nottingham Prognostic Index (NPI) [32] as prognostic markers. These studies were on a Finnish population with small sample size (n = 278) using Boyd MD scale. Of the two available studies on the association between BMD and treatment response [27,35], one involving a Saudi population reported that low BMD improves treatment response [27], and the other on a Peruvian population found no association [35]. Data on the time of MD measurement and menopause status were not reported by the Peruvian study [35]. All the 20 studies considered a range of possible confounders that influence the relationship between BMD and the previously mentioned outcomes, and none of these studies attempted to investigate the association between different MD phenotypes and treatment outcomes [2,22–27,30–32,35–37,40–46].

Forest plots demonstrating the association between BMD and outcomes measures (mortality, recurrence, contralateral breast cancer risk, and prognosis) are shown in Fig. 2. The pooled estimates (PE) showed that high BMD was significantly associated with an increased risk of developing CBC (HR = 1.9; 95%CI: 1.3–3.0,

Table 3
Characteristics of studies that assessed the association between baseline mammographic density and recurrence.

Authors, Year	Study Design	Study Population and Country	Age, Menopausal Status,	Type of Intervention	BMD Measurement/ Time	MD Assessment Method, Inter-observer Variability Assessment, Region of Interest	Follow-up Period	Patient Outcomes	Related Significant Finding	Adjustments
Cil et al. [25], 2009	ROCS	n:335, Canada	33-87 Yrs., (the majority post-meno.)	Surgery	Higher MD:38.5% Intermediate MD:31.9% Low MD:29.6%, MD was measured at diagnosis	Wolfe Classification method, Intra-observer reliability assessment was applied.	7 Yrs.	LDR	MD is positively associated with LDR	Age, Menopausal status, RT
Eriksson et al. [30] 2013	COS	n:1774, Sweden	62.9 Yrs. (post-meno. only)	Surgery HRT Chemo. RT ET	PMD <25%: 74.9% PMD ≥25%: 25.1% MD was measured at diagnosis	Cumulus, Intra-observer reliability assessment was applied, CB	10 Yrs.	LDR LRR	MD is positively associated with LDR, LRR	Age, BMI, HRT use, Mode of detection, Tumour size, Lymph node metastasis, ER status, PR status, and Grade
Huang et al. [36] 2016	CCS	n:242 (case:121, control:121), Taiwan	51.4(28–89) Yrs.	Surgery Chemo. Targeted therapy RT Adjuvant ET	32.2% had MD<50% (control group), 43% had MD>50% (case group), MD was measured before diagnosis	Cumulus, CB	Median for Cases: 84 mts., Median for control = 92.9 mts.	LRR	MD is positively associated with LRR	Dense breasts (PMD >50%), Positive margin, Adjuvant RT, Adjuvant chemo.
PARK et al., [43] 2009	NCCS	n:253(cases:117 had recurrence, control:136 no recurrence),USA	The majority >50 Yrs.	Surgery RT	Both groups have similar baseline MD, between 25% and 50%, MD was measured at diagnosis	Cumulus, CB	Median: 7.7 Yrs.	LRR	MD is positively associated with LRR	BMI
Edwards et al. [26] 2016	ROCS	n:655, USA	(42–71) Yrs.	Surgery	BI-RADS4 = 8% BI-RADS3 = 34% BI-RADS2 = 41.2%, BI-RADS1 = 16.8%, MD was measured closes to the time of diagnosis	BI-RADS® 4th edition and Volpara,	Not reported	Excision rate after BCS	The rate of unnecessary margins is not associated with MD	Age, Presence of DCIS, Multifocality, and Resection of additional margins at initial BCS

Abbreviations: HRT, hormonal replacement therapy; ROCS; retrospective observational cohort study; CCS, case control study; CB, contralateral breast; MD, mammographic density; Post-meno., postmenopausal; AIs, aromatase inhibitors; RFS, recurrence free survival; NCCS, nested case control study; BMI, body mass index; ER, estrogen receptor status; PMD, percent mammographic density; RT, radiotherapy; Chemo., chemotherapy; DCIS, ductal carcinoma in situ; IBC, ipsilateral breast cancer; CBC, contralateral breast cancer; Pre-meno., premenopausal; VLD, very low breast density; MID, mixed breast density; BI-RADS®, breast imaging reporting and data system; LRR, locoregional recurrence; LDR, local disease recurrence; COS, case only study; ET, endocrine therapy; IB, ipsilateral breast; PR, progesterone receptor; IC, interval cancers; SCD, screened cancers detected; HER2, human epidermal growth receptor2, NPI, Nottingham prognostic index; NAC, neoadjuvant chemotherapy; BCS, breast conserving surgery; pCR, pathological complete response.

p = 0.0007), recurrence (HR = 2.0; 95%CI: 1.0–4.0, p = 0.04), and mortality (HR = 1.4; 95%CI: 1.1–1.9, p = 0.003). No heterogeneity was found in studies on CBC (p = 0.345), recurrence (p = 0.65), and mortality (p = 0.90). BMD did not show any association with prognosis (HR = 3.2; 95%CI: 0.9–11.2, p = 0.06), and there was no heterogeneity between studies (p = 0.92). Figs. 3 and 4 are forest plots showing risk estimates of survival and ipsilateral BC risk from MD. The pooled estimate could not be computed for survival, ipsilateral BC, and treatment response due to insufficient number of outcome events. Range of risk estimates were: survival (HR/RR: 1.75; 95%CI: 0.99–3.1 to 2.43; 95%CI:1.44–4.1) [22,24], ipsilateral breast cancer risk (IBC) (HR/RR: 1; 95%CI: 0.6–1.6 to 1.7; 95%CI: 1–2.9 to 3; 95%CI: 1.2–7.5) [23,31,37], and only one of the two studies on treatment response provided risk estimates (OR, 1.8; 95% CI: 0.98–3.3) [27]. In summary, evidence supports that BMD is significantly associated with an increased risk of BC recurrence, CBC, and mortality [23–25,30,31,36,37,40–46], but not prognosis [2,32]. However, there is a limited evidence for the association of BMD with survival, IBC risk, and treatment response [22–24,27,31,35,37,44].

The association between MDR and treatment outcomes was assessed in nine studies (Table .6) [5–8,28,33,34,38,39]. These studies were published between 2012 and 2017. Of these, there were four ROCSs [5–7,39], four CCSs [28,33,34,38], and one randomized controlled trial (RCT) [8]. A majority of these studies were from Sweden [5,28,34] and Korea [6,7,39]. The mean sample size of these studies was 792.5 (Range: 80–1,740), and most of the participants (n = 4,579) were older than 45 years [5,6,8,28,34]. Three of the nine studies were mainly based on postmenopausal women [5,8,34], two studies included pre- and post-menopausal participants [7,28], and the remaining four did not provide menopausal information [6,7,33,38]. Tamoxifen (TAM) was the common intervention associated with MDR in these studies. TAM was the single treatment in five studies [5,7,33,34,39], combined with aromatase inhibitors (AIs) in two studies [6,8], or with chemotherapy and radiotherapy in two studies [28,38].

A majority of the nine studies reported median follow-up periods ranging from 2 to 14.2 years [5–8,34,38,39]. Among these studies, MD was commonly measured using Cumulus [5,6,28,33,34,38], with PMD phenotype used in four studies [6,28,33,38] and absolute dense area (AD) in three studies [5,33,34]. BI-RADS® and Boyd methods were employed in two studies [8,39] and volumetric breast density of MRI was used in one study [7]. PMD and AD at baseline ranged from 26%–37.6% [6,7,28,33,38] and from 25 to 36.5 cm^2 respectively [5,33,34]. The reported magnitude of MDR after treatments ranged from −2% to −6.2% for PMD [6,7,28,33,38] and −5 to −6 cm^2 for AD [5,33,34]. Visual assessment-based studies reported reduction using lower MD

Table 4
Characteristics of studies that assessed the association between baseline mammographic density and the risk of contralateral breast cancer.

Authors, Year	Study Design	Study Population and Country	Age, Menopausal Status,	Type of Intervention	BMD Measurement/ Time	MD Assessment Method, Inter-observer Variability Assessment, Region of Interest	Follow-up Period	Patient Outcomes	Related Significant Finding	Adjustments
Habel et al. [23] 2010	ROCS	n:935, USA	60% > 55 Yrs.	Surgery RT	67.27% had high MD assessed by Wolfe method, 30.7% had MD>50% assessed by Planimetry, 48.4% had high MD assessed by BI-RADS® classification method, MD was measured at diagnosis	BI-RADS® 4th edition, Planimetry, and Wolfe method, Intra-observer reliability assessment was applied by experts, Bilateral breasts	Median: 8 Yrs.	The risk of a subsequent BC or a subsequent invasive cancer	MD is positively associated with the risk of subsequent contralateral breast invasive cancer, contralateral breast DCIS. No association was found with subsequent ipsilateral BC.	Diagnosis year, Age, BMI, and RT, ET
Habel et al. [31] 2004	ROCS	n:504, USA	The majority >50 Yrs.	Surgery RT	6.6% had higher percent breast density, MD was measured at diagnosis	Wolfe method and, Planimetry, Intra-observer reliability assessment was applied, IB	Median: 11 Yrs.	The risk of a subsequent BC or a subsequent invasive cancer	MD is positively associated with the risk of subsequent contralateral breast invasive cancer, contralateral breast DCIS, and, subsequent ipsilateral BC.	RT, Age, and BMI
Hwang et al. [37] 2007	ROCS	n:3,274, USA	30–80 Yrs.	Surgery RT	BI-RADS3 = 45% BI-RADS 2: 41% BI-RADS4 = 9.8%, MD was measured at pre-diagnostic mammograms	BI-RADS® 4th edition	Median: 39 mts.	Risk of subsequent cancer	MD is positively associated with the risk of subsequent contralateral breast invasive cancer, contralateral breast DCIS. No association is found with subsequent ipsilateral BC.	Age and RT
Raghavendra et al. [45] 2017	NCCS	n:680(cases: 229 CBC, control: 451 do not have CBC), USA	56 Yrs.	Chemo. ET	Cases: BI-RADS1.2 = 39.3% BI-RADS3,4 = 60.7% Control: BI-RADS1.2 = 48.3%, BI-RADS3,4 = 51.7%, MD was measured at the time of diagnosis	BI-RADS® 4th edition	Not reported	Risk of developing CBC	MD is positively associated with the risk of developing CBC	BMI, Tumour, Histologic subtype, chemo., and ET

Abbreviations: HRT, hormonal replacement therapy; ROCS; retrospective observational cohort study; CCS, case control study; CB, contralateral breast; MD, mammographic density; Post-meno., postmenopausal; AIs, aromatase inhibitors; RFS, recurrence free survival; NCCS, nested case control study; BMI, body mass index; ER, estrogen receptor status; PMD, percent mammographic density; RT, radiotherapy; Chemo., chemotherapy; DCIS, ductal carcinoma in situ; IBC, ipsilateral breast cancer; CBC, contralateral breast cancer; Pre-meno., premenopausal; VLD, very low breast density; MID, mixed breast density; BI-RADS®, breast imaging reporting and data system; LRR, locoregional recurrence; LDR, local disease recurrence; COS, case only study; ET, endocrine therapy; IB, ipsilateral breast; PR, progesterone receptor; IC, interval cancers; SCD, screened cancers detected; HER2, human epidermal growth receptor2, NPI, Nottingham prognostic index; NAC, neoadjuvant chemotherapy; BCS, breast conserving surgery; pCR, pathological complete response.

ratings of readers following interventions [8,39]. Six studies assessed the reliability of MD assessment approaches [6,8,28,33,34,38], and all articles measured BD either before or after BC diagnosis. Contralateral breasts were commonly selected for MD measurements [5–8,28,33,34,38]. More than two follow-up mammograms tracking MDR were reported in four articles [5,8,33,34]. The duration between the time of intervention administration and the last follow-up mammogram ranged from 1 to 6 years.

MDR was assessed with BCspecific survival in one study [5], mortality in two [33,34], recurrence in four [6–8,39], and CBC risk in three (Table 6) [8,28,38]. MDR was found to improve BC specific survival in one large study involving postmenopausal women [5]. This study did not assess the reliability of MD assessment. MDR was associated with a reduced risk of mortality in two studies [33,34], the risk of developing CBC in two studies [28,38], and BC recurrence in three studies [6,7,39]. A majority of these studies included pre-menopausal and postmenopausal women [6,7,28,33,38,39], and considered the effect of common prognostic factors on the association between MD and CBC [6,7,28,33,34,38,39]. The relationship between MDR and outcome measures such as mortality and CBC were not affected by MD phenotype or ethnic differences. Reductions in different MD phenotypes (PMB, volumetric and BI-RADS® 4th edition) were consistently associated with a reduced risk of recurrence in Koreans (Table 6). One randomized clinical trial reported no association between MDR and recurrence as well as CBC risk in a Dutch population [8]. However, this trial did not account for any important confounders that could affect the relationship between MD and outcomes measured. Furthermore, the trial was based on postmenopausal women and subjective MD assessment.

Pooled estimate showed no association between MDR and mortality (HR = .5; 95%CI: 0.2–1.2; p = 0.13), and there was no heterogeneity between studies (p = 0.84) (Fig. 5). Because of insufficient data for the number of events, pooled estimates for recurrence and CBC could not be computed, however summaries of the results are presented in forest plots (Figs. 6 and 7). The reported risk (HR) estimates for recurrence ranged from 0.35 (95% CI: 0.17–0.68) to 0.87 (95%CI: 0.45–1.68) and RR varied from 0.87 (95% CI: 0.77–0.94) to 1.33; (95%CI: 0.67–2.65) [6,7,39]. For CBC, the RR

Table 5
Characteristics of studies that assessed the association between baseline mammographic density and prognosis as well as treatment response.

Authors, Year	Study Design	Study Population and Country	Age, Menopausal Status,	Type of Intervention	BMD Measurement/ Time	MD Assessment Method, Inter-observer Variability Assessment, Region of Interest	Follow-up Period	Patient Outcomes	Related Significant Finding	Adjustments
Masarwah et al. [32] 2016	ROCS	n:278, Finland	58.8(32–86) Yrs. (66.3%, Post-meno.)	Chemo. Targeted therapy RT Adjuvant ET	Low risk NPI: VLD= (4.5%) MID= (95.5%) Intermediate risk NPI: VLD=(53.3%) MID=(46.7%) High risk NPI: VLD= (100%), MD was measured at diagnosis	Boyd method	Mean: 8.03 Yrs.	Prognosis	MD is positively associated with prognosis	HER2 status, NPI and VLD
Masarwah et al. [2] 2015	ROCS	n:278, Finland	Median: 58(32–86) Yrs. (66.3% post-meno.)	Chemo. RT Tamoxifen AIs	18.6% had MD> 50%, MD was measured at diagnosis	Boyd method, Intra-observer reliability assessment was applied by two experts	Mean: 6.4 Yrs.	Prognosis	MD is positively associated with prognosis	Age, BMI, and Menopausal status
Elsamany et al. [27] 2015	ROCS	n:241, Saudi Arabia, Egypt	The majority >55 Yrs. (61.4%, pre-meno.)	NAC	High MD = 67% Low MD = 34%, MD was measured at the time of diagnosis	Wolfe method	Not reported	Treatment response	MD is negatively associated with treatment response	BMI, HER2 positive receptor, Clinical stage
Castaneda et al. [35] 2014	ROCS	n:494, Peru	49 (24–82) Yrs.	NAC	BI-RADS1 = 16.9%, BI-RADS2 = 22% BI-RADS3 = 35.7% BI-RADS4 = 25.1%	BI-RADS® 4th edition	Not reported	Treatment response	No association is found with MD	Not reported

Abbreviations: HRT, hormonal replacement therapy; ROCS; retrospective observational cohort study; CCS, case control study; CB, contralateral breast; MD, mammographic density; Post-meno., postmenopausal; AIs, aromatase inhibitors; RFS, recurrence free survival; NCCS, nested case control study; BMI, body mass index; ER, estrogen receptor status; PMD, percent mammographic density; RT, radiotherapy; Chemo., chemotherapy; DCIS, ductal carcinoma in situ; IBC, ipsilateral breast cancer; CBC, contralateral breast cancer; Pre-meno., premenopausal; VLD, very low breast density; MID, mixed breast density; BI-RADS®, breast imaging reporting and data system; LRR, locoregional recurrence; LDR, local disease recurrence; COS, case only study; ET, endocrine therapy; IB, ipsilateral breast; PR, progesterone receptor; IC, interval cancers; SCD, screened cancers detected; HER2, human epidermal growth receptor2, NPI, Nottingham prognostic index; NAC, neoadjuvant chemotherapy; BCS, breast conserving surgery; pCR, pathological complete response.

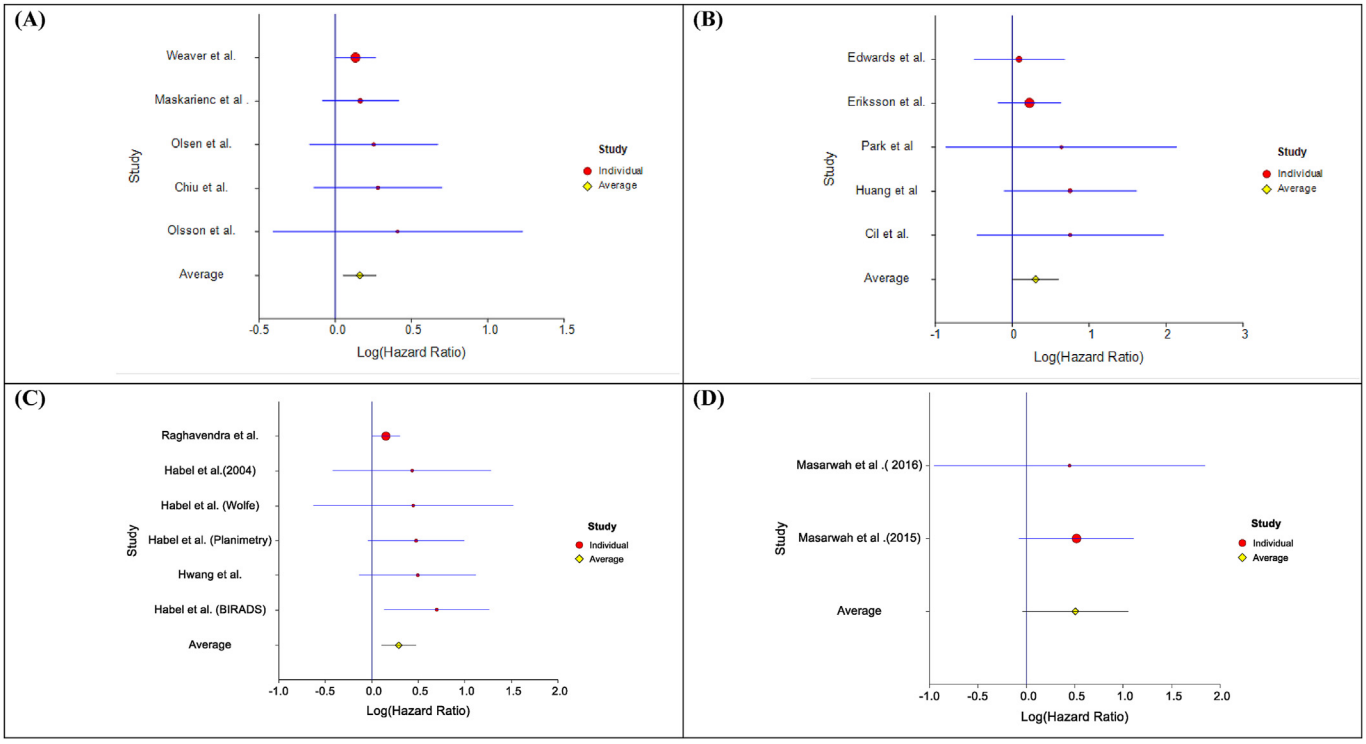

Fig. 2. Forest plots showing a summary of studies on the relationship between BMD and breast cancer outcomes with pooled estimates: (**A**) mortality; (**B**) recurrence; (**C**) contralateral breast cancer risk; (**D**) prognosis.

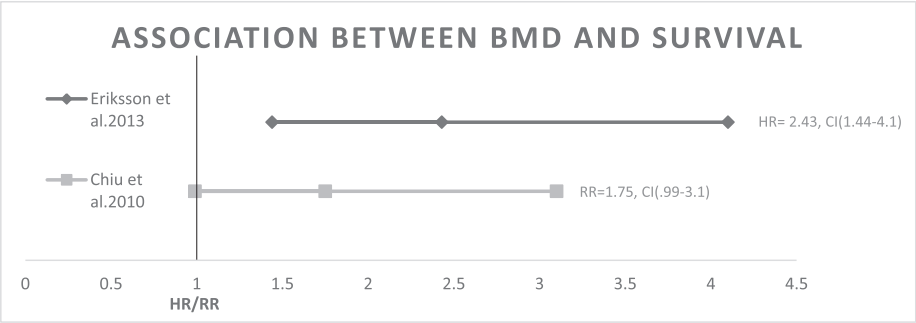

Fig. 3. Forest plot showing risk estimates (95%CI) for the relationship between BMD and survival from breast cancer.

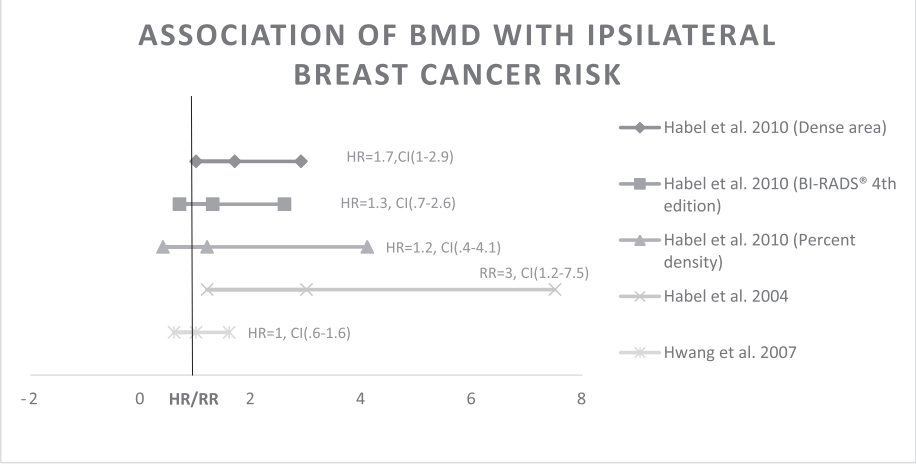

Fig. 4. Forest plot showing risk estimates (95%CI) for the relationship between BMD and ipsilateral breast cancer (IBC).

ranged from 0.53 (95%CI: 0.24–0. 84) to 0.74 (95%CI: 0.4–1.01), and one study reported a HR of 1.3 (95%CI: 0.6–2.7). In summary, there is limited literature on the relationship between MDR and treatment outcomes, however available evidence shows that MDR is associated with a reduced risk of recurrence, mortality, and CBC [8,28,38], and an increased chance of survival from BC [5].

The overall quality of the studies reviewed is presented in Table 8. None of the reviewed studies were rated as low quality study. Forty-eight percent of the studies were deemed to be of high quality[2,7,22,26–28,30,31,33,36,38,41,42,46], and 51.8% were considered to be of moderate quality [5,6,8,23–25,32,34,35,37,39,40,43–45]. A majority of studies (86.2%) had a moderate risk of bias in the domain related to study attrition where no information was reported about the characteristics of ineligible participants as well as important differences between eligible and non-eligible patients [2,5–8,23–25,27,30–40,42–46]. A high risk of bias was observed in two studies in terms of study confounding and statistical analysis and reporting [8,35] (Table 8). Based on the quality of studies reviewed, a cohort study design appeared to be the most suitable for assessing the relationship between BMD and BC outcomes, and a case-control study would better capture the association between MDR and BC outcomes. The overall weighted Kappa (interrater agreement) of risk of bias for the included studies was 0.71 (CI: 0.48–0.85). (Table 7).

4. Discussion

Current literature demonstrates a paucity of evidence and conflicting results for the use of MD for assessing breast cancer treatment outcome. The conflicting evidence could be explained by several factors including MBD assessment methods, study design, sample selection, time of BMD measurement, and adjustment for possible confounders. A better understanding of these factors and their impact is needed in order to effectively use information extracted from radiological images for BC prognosis and the monitoring of treatment efficacy.

The limited evidence for the association between BMD and patient survival is based on postmenopausal women, and only one [22] of the three studies [22,24,44] on this subject found that higher BMD is associated with poor survival outcome. Whether BMD and survival relationship is confounded by menopausal status is unclear, however larger tumour size, nodal involvement, higher tumour grade, and ER and PgR negativity appear to be significant confounding factors influencing BMD versus survival relationship [40]. Therefore, studies accounting for these factors may provide a better understanding of the relationship between BMD and survival.

The literature on relationship between BMD and mortality is contradictory. An increased risk of mortality with higher MBD was evident after adjustments for BMI at diagnosis, HRT at baseline, and mode of detection [24,41,42], whilst a reduced risk of death from cancer was found following radiotherapy, chemotherapy, and surgical interventions [40,46]. Such inverse associations suggest that BMD may be a marker of mortality following surgical or therapeutic interventions. It should be noted that the studies reporting increased mortality and BMD relationship attributed mortality to BC [24,41], even though it has been shown that comorbidities such

Table 6
Characteristics of studies that assessed the association between breast density changes and breast cancer treatment outcomes.

Authors, Year	Study Design	Study Population (n), Country	Age, Menopausal Status	Type of Intervention, Follow-up Period	BMD Measurement/ Time	MD Assessment Method, Inter-observer Variability Assessment, Region of Interest	Magnitude of MD Reduction	Number of Included Follow-up Mammograms/ Duration Between Baseline Image and Follow-up Images	Patient Outcomes	Related Significant Finding	Adjustments
Andersson et al. [5] 2017	ROCS	n:1740, Sweden	50–74 Yrs., post-meno only	Tamoxifen, 15 Yrs.	Mean dense area(cm^2): 25 (HRT user), Mean dense area (cm^2): 22 (Non-HRT), MD was measured on pre-diagnostic and post-diagnostic mammograms.	Cumulus, CB	Mean reduction dense area(cm^2): −5 (HRT users with and without tamoxifen)	1-8 follow-up mammograms, 5 Yrs.	BC specific survival	MDR is positively associated with survival	Age, and BMI at baseline
Kim et al. [6] 2012	ROCS	n:1,065, Korea	49.1 (24–77) Yrs.	Tamoxifen and AIs, Median: 67.7 mts.	35.77 ± 13.94%, MD was measured on pre-diagnostic and post-diagnostic mammograms	Cumulus, inter-observer variability assessment was applied, CB	Mean PMDR: −5.9%	One follow-up mammogram, Mean: 13.1 (8–20) mts.	Recurrence(RFS)	MDR is negatively associated with recurrence	Tumour size, Lymph node positivity, High Ki-67 (≥10%)
Li et al. [34] 2013	CCS	n:974 (cases: 474 tamoxifen group. Control: 500 non-tamoxifen group), Sweden	50 -74 Yrs., (Post-meno only)	Tamoxifen, median:14.2 Yrs.	Absolute dense area (DA): median: 27.4 cm^2 MD was measured on mammograms obtained before and after surgery	Cumulus, inter-observer variability assessment was applied, CB	DA reduction: −5.3 ± 13.4 cm^2 for tamoxifen-treated group; DA reduction: −3.7 ± 12.4 cm^2 for the no-tamoxifen group.	At least one follow-up mammogram, 3 Yrs.	Mortality	MDR is negatively associated with mortality.	Age, Time between baseline and follow-up mammograms, HRT, ER status, Tumour size, Number of metastatic nodes, Grade/ Tamoxifen use, RT, Chemo.
Nyante et al. [33] 2015	CCS	n:698 (cases: 446, control: 252), USA	59 Yrs.	Tamoxifen,	26.2 ± 16.3%, 36.5 ± 21.5 cm^2 (case group), 30.0 ± 17.4%, 41.0 ± 27.9 cm^2 (control group), MD was measured on mammograms obtained before and after diagnosis	Cumulus, inter-observer variability assessment was applied, CB	PMDR: −3.1 ± 7.6%, −6.0 ± 12.3 cm^2 (cases), −5.2 ± 9.3%, −8.7 ± 14.8 cm^2 (control).	Multiple films were included, nearly 1 Yrs.	Mortality	MDR is negatively associated with mortality and better prognosis	Baseline MD, Age, Tamoxifen use duration, ER status, PR status, BMI, Chemo., RT.
Sandberg et al. [28] 2013	CCS	n:422 (cases: 211 CBC, control: 211UBC), Sweden	The majority >45 Yrs. (Most of them post-meno.)	Endocrine therapy, Chemo, RT, Mean:8.25 Yrs.	Mean PMD: 28%, MD was measured at mammograms close to diagnosis	Cumulus, inter-observer variability assessment was applied, CB	Mean PMDR: −3.13%(Cases) −4.75%(Control)	One follow-up mammogram, Mean time: 1.6 Yrs. (Max. 5 Yrs.)	Risk of developing CBC	MDR is negatively associated with the risk of developing CBC	Age and Calendar period of first diagnosis, Adjuvant therapy and Follow-up time, Non-dense area
Kim et al. [7] 2014	ROCS	n:80, Korea	44(27–68) Yrs., (the majority pre-meno)	Tamoxifen, Median: 48 mts.	Observer1: 29.9 ± 9.3% Observer2: 23.3 ± 5.9%, MD was measured at preoperative MRI breasts	Volumetric MRI breast density assessment method, CB	Volumetric MRI breast density reduction: Observer1: −2.0 ± 8.4% Observer2: −6.2 ± 19.5%	One MRI follow-up was included, The interval between the baseline and follow-up MRI examinations. Median: 21 mts.	Recurrence	MDR is negatively associated with recurrence	Age, BMI, Menopausal status, Chemo. Tamoxifen usage duration
Ko et al. [39] 2013	ROCS	n:1,066, Korea	45.3 ± 7.6 Yrs.	Tamoxifen, Median: 61.3 mts.	BI-RADS 1,2: 13.2% BI-RADS 3: 47.1% BI-RADS 4: 39.5%, MD was measured on preoperative and postoperative mammograms	BI-RADS® 4th edition	99.4% of MD individuals downgraded by 1 grade, 6% of MD individuals downgraded by 2 grades.	One follow-up mammogram, Median: 19 mts.	Recurrence	MDR is negatively associated with recurrence	Age, BMI, Tumour size, lymph node status, ER status, PR status, and (HER2) status

(*continued on next page*)

Table 6 (*continued*)

Authors, Year	Study Design	Study Population (n), Country	Age, Menopausal Status	Type of Intervention, Follow-up Period	BMD Measurement/ Time	MD Assessment Method, Inter-observer Variability Assessment, Region of Interest	Magnitude of MD Reduction	Number of Included Follow-up Mammograms/ Duration Between Baseline Image and Follow-up Images	Patient Outcomes	Related Significant Finding	Adjustments
Knight et al. [38]. 2014	CCS	n:710 (cases: 253 CBC, control:269 UBC), USA	46 ± 6 Yrs.	Chemo., Tamoxifen, and RT, Median: almost 8 Yrs.	Mean PMD: 37.6 ± 18.1% (Cases), Mean PMD: 35.8 ± 18.3% (Control), MD was measured on mammograms close to diagnosis	Cumulus, inter-observer variability assessment was applied, CB	Cases: Mean PMDR: −6.2% Control: Mean PMDR: −7.8%	One follow-up image, Median: 1Yr.	Risk of CBC	MDR is negatively associated with the risk of developing CBC	Age Menopausal status Family history of BC, BMI, Race, Study design, age at menarche, Number of pregnancies, Chemo, RT, tamoxifen
Van Nes et al. [8] 2015	RCT	n:378(181 tamoxifen, 197 exemestane), Netherlands	The majority > 50 Yrs. (post-meno. only)	Exemestane. Tamoxifen, Median: 6 Yrs.	75% of patients in both arms had a breast density score less than 50%. MD was measured on preoperative mammograms	Boyd method, Inter-observer variability assessment was applied, CB	Increase MD:17% Stable MD:62% Decrease MD: 21%	3 follow-up mammograms, 3 Yrs.	LRR, and CBC	No association is found between MDR and LRR as well as the risk of developing CBC	Not reported

Abbreviations: HRT, hormonal replacement therapy; ROCS; retrospective observational cohort study; CCS, case control study; CB, contralateral breast; MD, mammographic density; Post-meno, postmenopausal; AIs, aromatase inhibitors; PMDR, percent mammographic density reduction; MDR, mammographic density reduction; RFS, recurrence free survival; DA, dense area; BMI, body mass index; ER, estrogen receptor status; PMD, percent mammographic density; RT, radiotherapy; Chemo., chemotherapy; PMDR, percent mammographic density reduction; MD, mammographic density; UBC, unilateral breast cancer; CBC, contralateral breast cancer; Pre-meno., premenopausal; MRI, magnetic resonance imaging; Her2, human epidermal growth factor receptor 2; BI-RADS®, breast imaging reporting and data system; BC, breast cancer; RCT, randomized controlled trial; LRR, locoregional recurrence.

as hypertension, diabetes mellitus, and stroke are significant causes of death in breast cancer affected individuals [40]. The absence of adjustments for these comorbidities and the lack of sufficient cancer mortality events in the studies make it difficult to establish with certainty the MD versus mortality relationship [24,40–42].

The literature shows that high BMD is associated with an increased risk of BC recurrence [25,30,36,43]. Only one study reported the absence of this association [26], and this can be partially explained by methodological differences, where mastectomy specimens were used to assess the BMD versus recurrence relationship [26], as opposed to BMD scores from mammogram in studies that found high recurrence rates in women with dense breasts [25,30,36,43]. A few hypotheses have been provided to explain high recurrence in dense breasts: the ability of dense breasts to restrict drug delivery to the tumour site [52,53], the presence of residual tumour volumes in extremely dense breasts compared to fatty breasts [26], and high risk of cancer in dense breast women [36]. We found that BMI and radiotherapy impacted the BMD and recurrence relationship [25,43], where high BMI and absence of radiotherapy increased recurrence rates. However, these were not accounted for in 40% of the studies assessing BMD versus recurrence relationship [26,30,36], and this should be considered in future studies.

Like recurrence outcome, the literature on the association between BMD and CBC is sparse, however high BMD was consistently shown to be associated with an increased risk of developing CBC, [23,31,37,45]. No association was found between an increase in BMD and the risk of subsequent IBC [23,31,37]. This could be explained by the small numbers of IBC in published studies [23,31], and a lack of surgical margin information [37]. Many of these studies were limited by the lack of adjustment for confounding factors affecting BMD and CBC risk including BMI [37] and hormonal replacement therapy (HRT) [45]. These factors are independently associated with risk and could bias the outcome relationship.

Evidence for the relationship between BMD and prognosis is also limited [2,32], but available data generally indicate that very low BMD is independently associated with an increased risk of having a poor prognosis, regardless of the molecular subtypes of BC [2,32]. However, factors such as tumour features including human epidermal growth factor receptor (HER2) status [2,32], tumour size, and lymph node positivity [2], were found to confound the association between BMD and prognosis. This suggests that these tumour-related factors should be adjusted for when using MD as a predictor of prognosis. Interestingly, the combination of BMD data with other prognostic factors, such as human epidermal growth factor receptor 2 (HER2), and Nottingham prognostic index (NPI) was found to improve the prognosis [32], suggesting that the addition of MD data into current clinico-pathologic models may improve the discriminatory power of these models, and this needs to be explored.

In terms of treatment response, we found limited and conflicting data: BMD improved pathologic complete response (pCR) [27] and no association between BMD and pCR for women with advanced disease [35]. The differences in BMD measures used to assess pCR may have contributed to these conflicting results. Whilst Elsamany et al. [27] considered very low MD in both early and advanced stage cancer, Castaneda et al. [35] examined the association between high MD and pCR in locally advanced disease. In addition, Castaneda et al. [35] defined pCR based on the cancer cellularity, which does not sufficiently reflect complete response [35], and may be the reason for the non-significant relationship with BMD. The association between very low BMD and pCR following neoadjuvant chemotherapy was confounded by BMI, which is an independent predictor of treatment response [27].

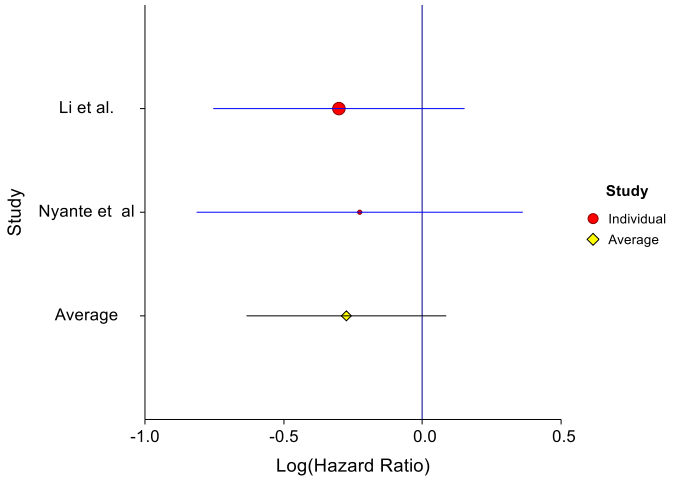

Fig. 5. Forest plot showing risk estimates (95%CI) for the relationship between MDR and mortality with pooled results.

These findings suggest that BMI should be considered for predicting pCR and that the combination of MD and demographic factors such as BMI with clinico-pathologic factors may improve the assessment of treatment response.

If very low MD improves pCR, it is probable that MDR may be associated with better outcome from breast cancer. We found consistently that MDR was associated with reduced risk of CBC, recurrence, and death from BC regardless of the MD phenotype used or population studied (Table 6), albeit there was limited number of studies that investigated each of these outcome measures. Only one study has explored the association between MDR and survival following tamoxifen therapy in postmenopausal women and reported a better outcome for women with a reduced MD [5]. Unsurprisingly, very subtle MDR was observed in some tamoxifen users, too minimal to impact patient outcomes. Although tamoxifen users with significant MDR experienced a reduction in the risk of death and an improvement in survival, the paucity of evidence supporting these findings makes it difficult to draw conclusions [5,33,34]. Published studies are further limited by short follow-up intervals, making it difficult to track density changes. It appears BMD is another important factor to consider [33], given that participants with low BMD experienced small reductions that might not be sufficient to induce change in mortality. We found that the studies reporting MDR to be associated with a reduced risk of recurrence were based on the Korean population [6,7,39], the only RCT showing no reduction in recurrence rate was based on a Dutch cohort [8]. The findings of this RCT can be explained by the use of Exemestane in postmenopausal women. Exemestane has no effect on MD, particularly in postmenopausal

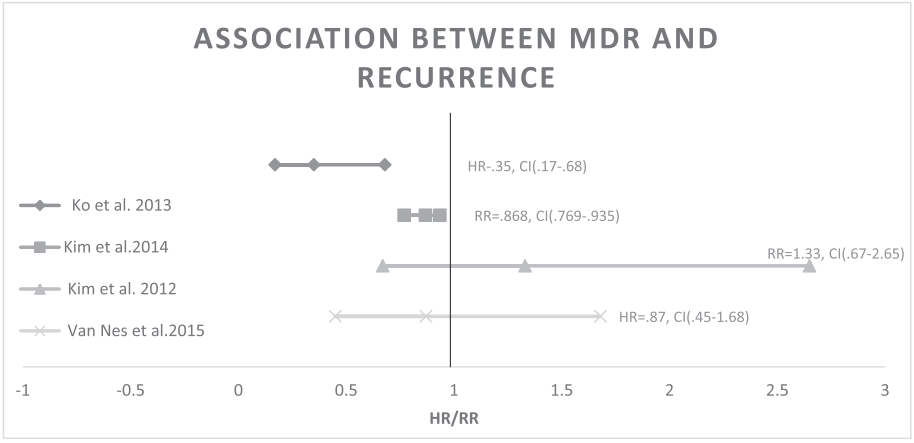

Fig. 6. Forest plot showing risk estimates (95%CI) for the relationship between MDR and BC recurrence.

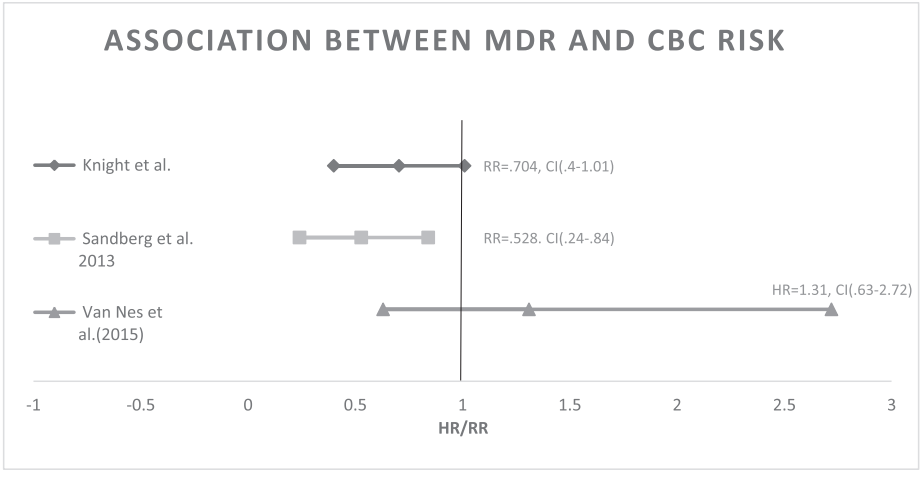

Fig. 7. Forest plot showing risk estimates (95%CI) for the relationship between MDR and contralateral breast cancer.

Table 7
Interrater assessment of each domain as well as overall quality.

Domains	Study participation	Study attrition	Prognostic measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall quality
Interrater agreement (κ_w) 95%CI	0.88; 0.76–0.94	0.71; 0.46 –0.85	0.93; 0.86–0.97	0.92; 0.84–0.96	0.87; 0.74–0.94	0.63; 0.34–0.81	0.71; 0.48 –0.85

* κ_w = weighted Kappa.
*95%CI: 95% confidence interval.

Table 8
Quality assessment of the included studies using the QUIPS tool.

Authors	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall quality of study
Eriksson et al. (2013) [22]	+	+	+	++	+	+	H
Porter et al. (2007) [44]	++	++	++	+	++	++	M
Chiu et al. (2010) [24]	++	++	++	+	++	+	M
Maskarinec et al. (2013) [40]	++	++	+	+	++	+	M
Weaver et al. (2012) [46]	+	++	++	+	+	+	H
Olsen et al. (2009) [41]	++	+	++	+	+	+	H
Olsson et al. (2014) [42]	++	++	++	+	+	+	H
Park et al. (2008) [43]	++	++	++	+	+	+	M
Eriksson et al.(2013) [30]	+	++	+	+	+	+	H
Huang et al. (2016) [36]	++	++	+	+	+	+	H
Cil et al. (2009) [25]	+	++	++	++	+	+	M
Edwards et al. (2016) [26]	+	+	+	+	+	+	H
Raghavendra et al. (2017) [45]	++	++	++	+	++	+	M
Hwang et al. (2007) [37]	+	++	++	++	++	+	M
Habel et al. (2004) [31]	++	++	+	+	+	+	H
Habel et al. (2010) [23]	++	++	+	+	++	+	M
Masarwah et al. (2016) [32]	+	++	++	++	++	+	M
Masarwah et al. (2015) [2]	+	++	+	++	+	+	H
Elsamany et al. (2015) [27]	+	++	++	+	+	+	H
Castaneda et al. (2014) [35]	++	++	++	+	+++	+++	M
Ko et al. (2013) [39]	+	++	++	++	+	+	M
Sandberg et al. (2013) [28]	++	+	+	+	+	+	H
Kim et al. (2013) [7]	+	++	+	+	+	+	H
Kim et al. (2012) [6]	+	++	++	++	++	+	M
Knight et al. (2018) [38]	++	++	+	+	+	+	H
Van Nes et al. (2015) [8]	++	++	++	+	+++	+++	M
Li et al. (2013) [34]	++	++	++	+	+	+	M
Andersson et al. (2016) [5]	+	++	++	+	++	+	M
Nyante et al. (2015) [33]	++	++	+	+	+	+	H

Abbreviations; H: High Quality Study, **M:** Moderate Quality study, **(+++):** High risk of bias, **(++):** Moderate risk of bias, **(+):** Low risk of bias.

women with already atrophying breast tissue and potentially weak hormone receptors to modulate MDR [4].

It is also possible that racial factors may be responsible for negative association between MDR and recurrence in the Korean population and should be explored further [6–8,39]. MDR (>10%) by tamoxifen independently was found to be associated with a reduced risk of CBC after adequate adjustments for important confounders [28,38], however postmenopausal status appeared to neutralise the association between MDR and CBC risk as shown in the only study involving postmenopausal women. The effect of menopause on MDR and CBC association may be due to difficulty in detecting MDR in this category of women [8]. Thus, differences in study methodologies and population characteristics may have contributed to some of the slight variability in results of published works and should be considered when interpreting MD and treatment outcome relationship.

Current models for assessing treatment response and predicting BC treatment outcome including CancerMath, PREDICT, NPI, and OncotypeDX are based on clinico-pathologic and/or genetic data. These models have demonstrated at best moderate discriminatory power (AUC: 0.55–0.77) [54–56]. Evidence from the current review suggests that MD data (BMD and MDR) provide information about BC treatment outcome [2,22,23,27,31,32,36,41,43,46]. It also suggests that incorporating MD information into current clinical models may improve the performance of the models. However, prior to integrating MD data into current models, it is important to address the limitations associated with the reliability and reproducibility of MD measurements and to better understand the MD phenotypes that best predict outcomes. Although none of the studies reviewed compared different MD phenotypes in terms of their ability to predict outcomes, a comparison across studies shows that some of these outcomes varied according to the MD phenotype used. For example, quantitative PMD of Cumulus showed a negative association between MD and survival [22] while

visual approaches found no association; a negative association between PMD and mortality was shown by Cumulus [40] whereas visual approaches showed a positive association [24,41,42] (Table 2). In contrast, regardless of the MD phenotype used or ethnic population studied, a mostly consistent association was observed between MD and outcome measures such as recurrence (Table 3) [25,30,36,43], and CBC [23,31,37,45], albeit the studies on CBC were from American populations (Table 4). These findings suggest that ethnicity may have little or no confounding effect on both BMD and MDR as surrogate markers for BC treatment outcome. However, large studies involving women from different ethnicities are needed to confirm these findings.

Visual and area based semi-automated methods were extensively used in the studies reviewed. The wide variability in MD assessment (K = 0.37–0.91) has been reported in the literature using visual approaches such as BI-RADS® [57,58]. Semi-automated approaches also introduce some subjectivity, which may reduce the reproducibility of MD measures. Therefore, it is important to mitigate the subjective variability associated with visual and semi-automated assessment of MD as this will reduce the reliability of MD data for prognosis and prediction of BC treatment outcome. These approaches only measure changes in the dense area following endocrine therapies, and do not account for the volume fibroglandular tissues, which may be more associated with the outcomes assessed [4]. Importantly, for MDR to be used as a surrogate marker of treatment outcome, we must identify measures or phenotypes that best demonstrate changes in MD, and in particular, changes in the fibroglandular tissue content, the major tissue influencing outcomes. PMD was the phenotype consistently associated with an increased risk of CBC. Although other phenotypes have shown associations between MDR and improved outcomes, there is very limited evidence to draw definite conclusions. Three studies have shown that volumetric measures from mammograms and MRI detected changes in MD following endocrine therapies in women where area-based methods could not [59–61], however these studies did not explore patient outcome from such MD reduction. Therefore, further studies are needed to assess the relationship between volumetric density changes and patient outcomes. Alternatively, since volumetric tools require raw data, which may be difficult to extract, automated MD measurement approaches that account for area and depth information should be explored. Such approaches may more accurately assess MD reduction as a determinant of patient outcomes. Treatment interventions, duration of treatment, and treatment regimens may affect outcomes. Most of the studies reviewed are limited in that, they did not account for the effect of these factors on the association of MDR with treatment outcomes. Furthermore, almost all the studies explored associations with little emphasis on outcome prediction, making it difficult to establish whether or not MD is an independent or intermediate marker of treatment outcome.

A limitation of the review and meta-analysis is that only studies written in English language were reviewed and many of the studies reviewed did not provide data of the number of events in the outcome group, making it impossible to generate pooled risk estimates for some of the outcomes. Additionally, the impact of cancer intervention regimen and drug dosage on outcomes was not evaluated as many studies did not provide these data.

Many of the studies reviewed are retrospective observational studies, albeit these were of moderate to high quality. Nonetheless, this is the first systematic review and meta-analysis to investigate the role of MD may have on BC prognosis and the prediction of BC treatment outcome. Thus, the work provides the first integrated and comprehensive evidence for the potential applicability of MD as a marker of BC treatment outcome. Future works should explore the possible impact of age at diagnosis, molecular and histological subtypes of BC, tumour grade, size, shape, and site, and treatment intervention and regimen on the MD and treatment outcome relationship. The analysis should focus on whether BMD and MDR are outcome predictors rather than explore their associations with treatment outcomes. Future studies should also consider combining MD data with clinico-pathologic and genetic data for establishing BC treatment outcome prediction models. This may improve the predictive abilities of current clinical models and better inform follow-up strategies to facilitate early detection and management of adverse cancer events such as recurrence and CBC.

5. Conclusion

Evidence, although sparse, demonstrates that high BMD is associated with an increased risk of breast cancer recurrence, CBC, and mortality. Conversely, MDR is associated with a reduced risk of BC recurrence, CBC, and BC-related mortality. These findings paints a positive perspective for the utility of MD for assessing BC treatment outcomes or improving the performance of current BC treatment outcome prediction models.

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Declaration of interest

None.

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