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REVIEW

A review of the influence of mammographic density on breast cancer clinical and pathological phenotype

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Abstract

Purpose It is well established that high mammographic density (MD), when adjusted for age and body mass index, is one of the strongest known risk factors for breast cancer (BC), and also associates with higher incidence of interval cancers in screening due to the masking of early mammographic abnormalities. Increasing research is being undertaken to determine the underlying histological and biochemical determinants of MD and their consequences for BC pathogenesis, anticipating that improved mechanistic insights may lead to novel preventative or treatment interventions. At the same time, technological advances in digital and contrast mammography are such that the validity of well-established relationships needs to be re-examined in this context.

Methods With attention to old versus new technologies, we conducted a literature review to summarise the relationships between clinicopathologic features of BC and the density of the surrounding breast tissue on mammography, including the associations with BC biological features inclusive of subtype, and implications for the clinical disease course encompassing relapse, progression, treatment response and survival.

Results and conclusions There is reasonable evidence to support positive relationships between high MD (HMD) and tumour size, lymph node positivity and local relapse in the absence of radiotherapy, but not between HMD and LVI, regional relapse or distant metastasis. Conflicting data exist for associations of HMD with tumour location, grade, intrinsic subtype, receptor status, second primary incidence and survival, which need further confirmatory studies. We did not identify any relationships that did not hold up when data involving newer imaging techniques were employed in analysis.

Keywords Breast cancer · Mammographic density · Breast cancer pathology · Oestrogen receptor

Introduction

Breast cancer (BC) remains the most commonly diagnosed cancer and the second most common cause of cancer-related mortality in women worldwide. The American Cancer

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Society estimates that BC will account for 30% of new cancer cases and 15% of cancer deaths among females in 2019 [1]. Mammographic density (MD) has emerged as a major factor in clinical BC risk assessment. Currently, mammography is the modality used in routine clinical practice for screening and diagnosis, with digital mammography (DM) largely replacing screen film mammography (SFM) over the past decade. Mammography, however, is not ideal for breast density measurement due to accumulated low-level x-ray exposure. Alternative modalities have been extensively explored, most importantly Magnetic Resonance Imaging (MRI) and digital breast tomosynthesis [2, 3].

MD refers to the proportion of opaque (white) dense breast tissue compared to the radiolucent (dark) areas seen on mammography, attributable to the distinct radiographic attenuation properties of fibroglandular tissue (FGT) versus fat [4], and usually expressed as percent MD (PMD) which is calculated by dividing the dense area by the total breast area [5]. Interest in MD research started 40 years ago when Wolf and Egan et al. noted an increased risk of BC during follow-up of women with dense breasts; a finding suggested to be due to the masking effect of dense breast tissue on the detection of small tumours [6, 7]. Subsequent studies in the 1990s confirmed that, after adjustment for age and BMI, MD was an independent risk factor for BC, with a relative risk ranging from 1.8 to 6.0 in women with high MD (HMD) when compared to those with low MD (LMD). Published data indicate that MD is the most significant risk factor for BC after age and BRCA carrier status [8, 9]. Recently, Hopper et al. showed that, when adjusted for population characteristics, high PMD carried a higher population-based risk of BC than known gene mutations, family history or low parity [10, 11].

The MD–BC association is not confined to general populations but has also been demonstrable among patients with previous benign breast disease (BBD) and/or with high risk of BC due to other factors. In a study of 2666 patients with BBD, Ghosh et al. demonstrated that MD was independently associated with BC risk [12]. In a study of 206 BRCA mutation carriers, Mitchell et al. found that HMD was associated with higher BC risk [13]. Additionally, compared to women with no family history of BC, women with affected relatives were found to have higher PMD [14]. A recent study on 11,478 high-risk Chinese women demonstrated positive associations between MD and either later first full-term delivery or the woman's height, and inverse associations between MD, parity and longer breast feeding, factors known to modulate BC risk [15].

The higher risk of BC with HMD suggests an underlying pathobiological relationship rather than a simple masking effect alone, as previously hypothesised. Although it has been established beyond doubt that MD confers a degree of BC risk, it remains uncertain as to whether this conferred risk is stronger for, or confined to, specific clinicopathological patterns or subtypes of BC. Our understanding of the pathobiology of MD in relation to endogenous and exogenous oestrogen exposure, hormonal therapy response, both preventative and adjuvant, and the epidemiological aspects of MD has been extensively reviewed elsewhere [16–18], and suggests the hypothesis that MD could have stronger links to hormone-driven cancers.

In the first part of this article, we look in particular at developments in technology that may have had bearing on this field. We then move on to review current knowledge regarding the possible association of MD with the generation of specific clinical and pathological features of BC. Our aim is to establish the magnitude of any such association, explore its potential impact on or guidance for clinical management, and highlight controversies for future research.

Methods

Eligibility criteria

Studies eligible for this review included original research papers that were published in peer-reviewed journals and assessed the association between MD and clinicopathological features of BC, rather than the association between MD and overall BC risk. "Participants" (P) included female subjects of any age diagnosed with histopathologically proven BC, ductal or lobular, invasive or in situ. "Exposure" (E) was considered high mammographic density (HMD), while low mammographic density (LMD) was considered "comparator", as evaluated by screen film (SF) or digital mammography (DM), either prior to or at BC diagnosis and either in the unaffected contralateral or in the ipsilateral diseased breast. "Outcomes" (O) were pathologic and clinical tumour features. Pathologic features included gross primary pathology (size and location), presence of metastases (lymph node and distant), basic histopathology (presence of invasion, lymphovascular invasion (LVI), grade), molecular features (receptor expressions and intrinsic subtypes) and breast cancer events (local and distant recurrence, contralateral new tumours). Clinical features considered in the analysis that were available were age, menopausal status, BMI, method of detection and treatment.

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed where applicable. An electronic search of Medline (using the Ovid interface), and Web of Science databases, last updated on 31 December 2018, was performed. Titles (*field*) of journal articles, published in English (*language*), were searched for

three elements, with several (*keywords*) indicative of each element combined using the Boolean operators; (i) breast cancer (cancer* OR carcinoma* OR tumour* OR tumor* OR neoplasm*), AND (ii) mammographic density (mammograph* AND (density OR feature* OR pattern)), AND (iii) clinicopathologic feature (clinical OR patholog* OR characteristic* OR phenotype) or (in situ OR size OR site OR location) or (subtype OR receptor* OR basal OR luminal OR HER OR triple) or (recurren*) or (detection OR (screen AND interval)) or (second OR subsequent OR contralateral) or (prognos* OR outcome* OR survival). Search for (site OR location) was extended to the abstract (*field*) in Medline database, because search in title did not yield any article.

Study selection

All study citations identified from the original search were imported to Endnote library. Duplicates from overlapping database search, and common key words were removed. Titles and abstracts of the remaining articles were screened for eligibility, and articles for full-text review were identified, and eligible articles were selected. Bibliographies of selected articles were then screened, which resulted in additional eligible articles.

Data abstraction

Data selected for extraction are included in Tables 1, 2, 3, 4. Data common in all tables include author/year, participant number and age, method of image acquisition and MD measurement and whether adjustment for age and BMI were done. Outcomes, "gross and histopathology", "molecular pathology, age and menopausal status", "mode of detection" and "survival" were included in Tables 1, 2, 3 and 4, respectively.

Results and discussion

Study selection

The process of article identification, screening and selection are summarised in Fig. 1. The initial search resulted in 415 articles (200 from Medline, and 215 from Web of Science). After removing duplicates ($n=228$), titles and abstracts of 187 articles were screened for eligibility, generating a list of 124 appropriate for full-text review, which subsequently resulted in 82 papers to be included in this review. The bibliographies of these eligible articles were also examined for further suitable works, with the subsequent addition of 20 further publications, making a total of 102 eligible articles (Fig. 1).

Overview of study characteristics

Study design

This is a systematic review of observational studies investigating the association between MD and BC characteristics, rather than the association between MD and general BC risk. "Case only" study was the commonest study design. Control groups or "no BC subjects" were only considered when study subjects were nested from a relevant population-based cohort. The use of "case-only" design has been shown to minimise the standard error (i.e. the sample better represents the population) compared to case–control studies [19]. The vast majority of these studies have been retrospectively, rather than prospectively designed. Retrospective studies are at higher risk of confounding factors and bias, therefore qualifying as lower level of evidence than prospective studies. Additionally, two cross-sectional studies were observed.

Image acquisition

Evidence documenting the association between HMD and BC risk was largely based on SFM, which has been largely replaced by DM. The latter, having improved contrast resolution, results in PMD readings significantly lower than in SFM [20], although a study has demonstrated no difference in the reported BIRADS MD categories according to acquisition method [21]. Moreover, the more recent tomosynthesis technology, which allows 3-D reconstruction of the mammographic images, results in PMD readings significantly lower again than in DM, a difference that does result in a significant difference in BIRADS categorisation of cases [22].

Density measurement

Several MD assessment methods have been proposed over the last four decades, with moves from area-based to volumetric, from qualitative to semiquantitative to quantitative and from visual to semi-automated to fully automated methods. Studies which investigated clinicopathological patterns of BC in relation to MD have predominantly assessed area methods. Given their consideration of three-dimensional structure, volumetric methods can more accurately assess the volume of dense breast tissue, compared to area-based methods, which are inherently limited by their two-dimensional nature [23]. Several studies have assessed the agreement of these different methods. The dichotomous Danish MD classification used by Olsen et al. [24] has been compared to BIRADS, and yielded good agreement ($K=0.75$) [25]. Moshina et al. reported a "moderate" agreement ($K=0.5$)

Table 1 Association between high MD and pathologic features of BC

Study			Subjects		Methods					pathologic features				
References	Design		Age	Number	Image acquisition	MD measure	Time	Lat	Adjustment	Size	Lymph node (LN) status	Grade	Histology	LVI
Boyd et al. [126]	R	Case only	40–95	183	SFM	Wolfe's grades, V (4 categories)	Before diagnosis	CL	None	No association $P=0.75$	No association $P=0.92$			
Sala et al. [39, 127]	R	Nested case–control	NR	875 cases 2601 controls	NR	Wolfe's grades, V (4 categories)	Before diagnosis (within 3 m) –	NM	None	Larger P NR	–	Higher $P=0.016$	–	–
Roubidoux et al. [83]	R	Case only	34–86	121	SFM	BI-RADS, V (4 categories)	Before diagnosis (within 17 m)	NM	Age only	Larger $P<0.05$	+ve LN $P=0.08$	Higher $P<0.05$	–	–
Aiello et al. [49]	R	Case only	12.5% ≤ , rest > 50	546	SFM	BI-RADS, V (dichotomised: 1 and 2 vs. 3 and 4)	Before diagnosis (within 24 m)	NM	Age, BMI	Larger $P=0.003$	+ve LN OR 1.7	No association $P=0.47$	–	+ve LVI OR 2.1
Morishita et al. [128]	R	Case only	28–86	163	NR	BI-RADS, V (4 categories)	Time of diagnosis	NM	None	No association P NR	No association P NR	No association P NR	No association P NR	–
Fasching et al. [44]	P	Case only	Mean: 60.2	434	NR	BI-RADS, V (4 categories)	Time of diagnosis	NM	None	Smaller $P=0.032$	No association $P=0.78$	No association $P=0.62$	Lobular Hx $P=0.016$	No association $P=0.214$
Porter et al. [118]	R	Case only	50–64	759	NR	BI-RADS, V (4 categories)	IBC SBC	Before diagnosis (within 3 y) Time of diagnosis	CL	None	Larger $P=0.01$	No association $P=0.54$	No association $P=0.055$	No association $P=0.78$	No association $P=0.3$
Ghosh et al. [51]	R	Case only	≥ 40	286 cases	Digitised	CAM (continuous)	Before diagnosis (w 4 y)		IL	Age, BMI	Larger $P=0.06$	–	Lower $P=0.06$	No association $P=0.5$	–
Garnett et al. [129]	R	Case only	49–82	59 IDC 59 ILC	SFM	BI-RADS, V (4 categories)	Time of diagnosis (all are SBC)		NR	None				No association P NR	
Cil et al. [33]	R	Case only	33–87	335	NR	Wolfe's grade, V, 3cat	Time of diagnosis		IL	None	No association $P=0.21$	No association $P=0.96$	No association $P=0.78$	–	No association $P=0.33$
Nickson et al. [130]	R	Case only	50–69	1348	SFM	CAM, (6 categories: 4 lowest quintiles, 2 upper deciles)	Before diagnosis		NM	Age only	Larger $P<0.001$	–	–	–	–
Ding et al. [79]	R	Nested case–control	50–75	370 cases 1904 controls	Digitised	Cumulus, (4 categories: < 10, 10–24, 25–49, ≥ 50%)	Before diagnosis (within 3 y) –		CL	Age only	No association $P=0.381$	No association $P=0.396$	Lower $P=0.043$	–	No association $P=0.749$
Arora et al. [45]	R	Case only	27–91	1323	DM & SFM	BI-RADS, V (4 categories)	Time of diagnosis		NM	Age only	No association $P=0.58$	No association 0.85	No association $P=0.42$	Lobular $P=0.03$	LVI $P=0.07$
Pinker et al. [131]	R	Case only	> 49	185	DM & SFM	BI-RADS, V (4 categories)	Time of diagnosis		IL	None				Lobular P NR	

Table 1 (continued)

Study			Subjects		Methods					pathologic features				
References	Design		Age	Number	Image acquisition	MD measure	Time	Lat	Adjustment	Size	Lymph node (LN) status	Grade	Histology	LVI
Yaghjyan et al. [38]	P	Nested case–control	Mean: 60.2	1042 cases 1794 controls	Digitised	Cumulus, (4 categories: < 10, 10–24, 25–49, ≥ 50%)	Before diagnosis (within mean 4.8 y; 2–7) –	NM –	Age, BMI	Larger $P < 0.01$	No association $P = 0.5$	Higher G $P = 0.02$	No association $P = 0.24$	–
Heusinger et al. [82]	R	Case only	< 45–70	2410 cases	Digitised	CAM, (3 categories: tertiles over 10%)	Time of diagnosis	NM	Age only	Larger $P = 0.07$	No association P NR	No association P NR	–	–
Eriksson et al. [50, 69]	R	Case only	50–74	1747, 1774	Digitised	Cumulus, (continuous)	Before diagnosis (within median 50d)	CL	Age, BMI	Larger $P = 0.007$	No association $P = 0.581$	No association $P = 0.382$	No association $P = 0.23$	–
Eriksson et al. [132]	R	Case only	32–86	110	Digitised	Cumulus (continuous)	Before diagnosis (within 1 m)	CL	None	No association $P = 0.821$	No association $P = 0.379$	–	–	–
Bertrand et al. [32]	R	Nested case–control	Mean 57	3414 cases 7199 controls	Digitised	CAM (4 categories: ≤ 10, 10–25, 26–50, > 50%)	Before diagnosis (within mean 4.5 y; 0.5–17.6) –	CL	Age, BMI	Larger $P < 0.01$	+ve LN $P < 0.01$	No association P NR	No association P NR	–
Moshina et al. [133]	R	Case only	50–69	9126 cases	DM & SFM	Visual (3 categories: fatty, medium, dense)	Before diagnosis (within 2 y)	NM	Age only	Larger $P < 0.001$	+ve LN OR 1.26 $P < 0.001$	No association $P = 0.179$	–	–
Masarwah et al. [52]	R	Case only	32–86	270	DM, digitised	Visual (2 categories: > 25 vs. < 25)	Diagnosis	IL	Age, BMI	No association $P = 0.420$	No association $P = 0.277$	No association with MD category $P = 0.291$	No association $P = 0.795$	
						Visual (6 categories: Percentiles)				–	–	Lower G with higher Percentile $P = 0.019$	–	
Kim et al. [81]	R	Case only	NM	178	DM	BI-RADS, V (4 categories)	Time of diagnosis	CL	Age only	No association $P = 0.394$	No association $P = 0.442$	No association $P = 0.128$		No association $P = 0.331$
Maskarinec et al. [48]	P	Nested case–control	40–65	820 820	digitised	Cumulus (4 categories: < 10, 10–19, 2–49, ≥ 50%)	Before diagnosis (mean 1 y)		Age, BMI	No association $P = 0.58$	No association $P = 0.69$	No association $P = 0.58$		
Krishnan et al. [46][a]	R	Nested case–control	Mean 65 and 62	392 cases 1146 controls	Digitised	Cumulus, (continuous)	Before diagnosis (within mean 6 y; 5 y) –	CL	Age, BMI	Larger $P < 0.01$	+ve LN $P < 0.01$	No association $P = 0.98$		
Shaikh et al. [47]	Cross sectional		Mean 54	123	DM	Cumulus, (continuous)	Time of diagnosis	CL	Age, BMI	No association $P = 0.30$	No association $P = 0.67$	No association $P = 0.25$	No association $P = 0.94$	–
Strand et al. [74]	R	Case only	Mean 60.3	2012	Digitised	Automated (> 20% vs. < 20%)	Before diagnosis (within 3 y)	CL	Age, BMI	Larger $P < 0.05$	–	–	–	–

Table 1 (continued)

Study		Subjects		Methods					pathologic features				
References	Design	Age	Number	Image acquisition	MD measure	Time	Lat	Adjustment	Size	Lymph node (LN) status	Grade	Histology	LVI
Hwang et al. [88]	R Case only	Mean 54.3	969	SFM, DM	BI-RADS, V (4 categories)	Time of diagnosis	NR	None	No association $P=0.378$	No association $P=0.818$	No association $P=0.198$		

Study design—P prospective, R retrospective, cross sectional

MD measure—MD mammographic density, BIRADS breast imaging reporting and data systems, CAM computer-assisted method

Image acquisition—SFM screen film mammography, DM digital mammography

LVI lympho—vascular invasion

IBC Interval Breast Cancer, *SBC* Screen Breast Cancer

Time—timing of mammogram relative to diagnosis

Lat—laterality of mammogram with respect to the diseased breast, *IL* ipsilateral, *CL* contralateral, *NM* not mentioned, *BMI* body mass index, *NR* not reported

[a]This study included two groups (screen detected) and (Interval), and assessed odds per one SD of MD increase (OPERA)

between four category BIRADS and volumetric method [23]. Similarly, a previous study comparing 992 digital films reported "very good" agreement ($K=0.82$) between volumetric density distribution and BIRADS [26]. Such imperfect agreement between automated and visual methods may contribute to contradictory results. For example, the Ji et al. study of 688 BCs found significant association of MD and receptors when MD was visually assessed, but not when MD was measured by Quantra (Table 2) [27].

Assessment subjectivity

A substantial number of identified studies relied on "visual" assessment of MD which is a subjective method of measurement. Many studies investigated intra- and inter-observer variability, particularly with BIRADS classification; this being the most commonly used visual assessment, and reported highly variable results. Masroor et al. reported poor intra-reader agreement of ($K=0.17$) among readings made 3 months apart, and similar poor inter-reader agreement of ($K=0.13$) between two readers assessing 254 mammograms [28]. On the other hand, in a BIRADS assessment of 992 mammograms, van der Waal et al. reported a very good intra- and inter-observer agreement ($K=0.87$ and 0.84, respectively) [26]. Such good agreement may be attributed, at least partially, to a pre-study pilot followed by a meeting in which reporting guidelines were reviewed and discrepancies were resolved. Similarly, Ang et al. reported excellent agreement (ICC > 0.80), both within and among eleven readers, assessing 120 mammograms, twice, 3 years apart, using visual analogue scales [29].

Important biological confounders

Increasing MD correlates directly and incrementally with BC risk. Paradoxically, however, MD correlates inversely with age and BMI [30, 31], which are also known to increase BC risk. Therefore, studies investigating the relation between BC and MD need to be adjusted for the confounding effect of these two factors. Such adjustment has been made in some but not all studies.

Timing and laterality of the mammogram

Studies evaluating the association between MD and BC pathology looked at mammograms at widely variable intervals from time of BC diagnosis. In some studies, time from the index mammogram to cancer diagnosis was 17.6 years [32]. During these years, MD will most likely have been affected by other factors including age, menopausal transition, body weight change and childbearing, with consequent impact on subsequent BC risk. Hence, the former MD may not be accurately representative of the actual MD that

Table 2 Association between high MD and molecular markers of BC, age and menopausal status of the patient

Study			Subjects		Methods			Molecular features					Demographic Features	
References	Design		Age	Number	Image acquisition	MD measure	Adjustment	Oestrogen receptor	Progesterone receptor	HER2	Ki 67	Subtype	Age	Menopausal state
Hinton et al. [80]	R	Case only	NR	337	SFM	Wolfe's grades, V (4 categories)	None	ER +ve $P=0.01$	–	–	–	–		
Ciatto et al. [134]	R	CCS	<40–>69	365 cases 365 controls	SFM	Wolfe's grades, V (4 categories)	Age	No association P NR						
Nielsen et al. [84]	NM	Case only	<50–≥70	92	SFM	Wolfe's grades, V (4 categories)	None	ER −ve (P 0.039)						
Ferranti et al. [135]	R	Case only	26–86	982	nr	Visual (3 categories: dense/heterogenous/fatty)	None	–	–	–	–	–	Younger $P<0.0001$ Log linear mod	–
Ziv et al. [136]	R	NCC	Mean: 55.7	701 cases 44,110 controls	NR	BI-RADS, V (4 categories)	Age, BMI	No association $P=0.73$	–	–	–	–		
Roubidoux et al. [83]	R	Case only	34–86	121	SFM	BI-RADS, V (4 categories)	Age only	ER −ve $P<0.05$	–	–	–		Younger $P<0.001$	Pre-men $P<0.001$
Aiello et al. [49]	Cross sectional		12.5%≤, rest>50	546	SFM	BI-RADS, V (dichotomised:1&2 vs 3&4)	Age, BMI	No association P NR	No association $P=0.1$	No association P NR	No association P NR			
Morishita et al. [128]	R	Case only	28–86	163	NR	BI-RADS, V (4 categories)	None	No association P NR					Younger $P<0.05$	
Fasching et al. [44]	P	Case only	Mean: 60.2	434	NR	BI-RADS, V (4 categories)	None	No association $P=0.938$	No association $P=0.995$	No association $P=0.825$	No association $P=0.635$		Younger $P<0.001$	–
Ghosh et al. [51]	R	Case only	≥40	286	Digitised	CAM (continuous)	Age, BMI	No association $P=0.11$	No association $P=0.37$	–	–			
Yang et al. [137]	R	Case only	23–46	198	NR	BI-RADS, V (4 categories)	None	–				No association (L vs. H2P vs. TN) $P=0.3$		
Kavanagh et al. [138]	R	CCS	40–79	1394 cases 5316 controls	Digitised	CAM, (6 categories: 4 lowest quintiles, 2 upper deciles)	Age only	–					Younger $P<0.001$	
Ma et al. [139]	R	NCC	35–64	479 cases 376 controls	Digitised	CAM (4 categories: <10, 10–29, 30–59, >60%)	Age, BMI	No association $P>0.30$		No association $P>0.30$	–	No Association (LA vs. TN) P trend=0.44		
Olsen et al. [24]	R	NCC	50–69	694 cases 47,358 controls	SFM	BIRADS, V dichotomised (4, 3 and part of 2 vs part of 2 &1	Age only	No association P NR	–	–	–	–		
Cil et al. [33]	R	Case only	33–87	335	NR	Wolfe's grades, V (3 categories)	None	No association $P=0.84$	–	–	–		Younger $P<0.01$	Pre-men $P<0.01$

Table 2 (continued)

Study			Subjects		Methods			Molecular features					Demographic Features	
References	Design		Age	Number	Image acquisition	MD measure	Adjustment	Oestrogen receptor	Progesterone receptor	HER2	Ki 67	Subtype	Age	Menopausal state
Ding et al. [79]	R	CCS	50–75	370 cases 1904 controls	Digitised	Cumulus, (4 categories: < 10, 10–24, 25–49, ≥ 50%)	Age only	ER +ve $P = 0.048$	–	–	–	–		
Arora et al. [45]	R	Case only	27–91	1323	DM and SFM	BI-RADS, V (4 categories)	Age only		–	–	–	No association (L vs H2P vs TN) $P = 0.26$ Sig Association (LA vs others) $P = 0.05$	Younger $P < 0.0001$	–
Yaghjyan et al. [38]	P	NCC	Mean: 60.2	1042 cases 1794 controls	Digitised	Cumulus, (4 categories: < 10, 10–24, 25–49, ≥ 50%)	Age, BMI	ER –ve $P = 0.04$	No association $P = 0.87$	No association $P = 0.40$	–			
Conroy et al. [78]	P	NCC	Mean: 62	667 cases 607 controls	Digitised	Cumulus, (4 categories: < 10, 10–24, 25–49, ≥ 50%)	None	SR +ve $P = 0.01$		–	–	–		
Jiang et al. [140]	R	Case only	27–79	108	DM	BI-RADS, V (4 categories)	None	No association $P > 0.05$	No association $P > 0.05$	–	No Association $P > 0.05$	–	Younger $P < 0.01$	Pre-men $P < 0.01$
Eriksson et al. [50]	R	Case only	50–74	1747	Digitised	Cumulus, (continuous)	Age, BMI	No association $P = 0.733$	No association $P = 0.779$	–	–		–	–
Eriksson et al. [132]	R	Case only	32–86	110	Digitised	Cumulus, (continuous)	None	No association $P = 0.065$	No association $P = 0.099$	No Association $P = 0.973$	–	No association $P = 0.249$	Younger $P < 0.001$	Pre-men $P < 0.001$
Phipps et al. [141]	R	Case only	40–84	13,797	NR	BI-RADS, V (4 categories)	None		–	–	–	No association P NR	–	–
Heusinger et al. [82]	R	Case only	< 45–70	2410 cases	Digitised	CAM (3 categories: tertiles over 10%)	Age, BMI	ER –ve $P < 0.00001$	No association $P = 0.06$	No association $P = 0.29$	–	–	Younger $P < 0.00001$	Pre-men $P < 0.00001$
Bertrand et al. [82]	R	NCC	Mean: 57	3414 cases 7199 controls	Digitised	CAM (4 categories: ≤ 10, 10–25, 26–50, > 50%)	Age, BMI	No association $P = 0.66$	No association $P = 0.10$	No association $P = 0.69$	–	–	–	–
Pollán et al. [40]	P	NCC	45–65	1172 cases 1831 controls	SFM	Boyd's 6 categories (V)	Age only		–	–	–	No association $P = 0.380$	–	–
Razzaghi et al. [142]	P	NCC	20–74	491 cases 528 controls	NR	BI-RADS, V (4 categories)	Age, BMI		–	–	–	No association (LA vs. TN) P trend = 0.74	–	–
Kim et al. [143]	R	Case only	25–84	281	DM	BI-RADS, V (dichotomised:1&2 vs 3&4)	None					No association $P = 0.524$		

Table 2 (continued)

Study			Subjects		Methods			Molecular features					Demographic Features	
References	Design		Age	Number	Image acquisition	MD measure	Adjustment	Oestrogen receptor	Progesterone receptor	HER2	Ki 67	Subtype	Age	Menopausal state
Rauch et al. [144]	R	Case only	Mean 56	1187 DCIS	NM	BI-RADS, V (4 categories)	None	No association $P=0.054$						
Gao et al. [145]	R	Case only	29–88	426	DM	BI-RADS, V (4 categories)	None		–	–	–	No association (non-TN vs. TN) $P=0.8590$	–	–
Elsamany et al. [121]	R	Case only	NR	60 MBC	NR	Wolfe's, V High MD (> 50%) vs Low MD (≤ 25%)	Age, BMI	No association $P=0.06$		No association $P=0.180$			Younger $P=0.010$	Pre-men $P=0.001$
Masarwah et al. [52]	R	Case only	32–86	270	DM, digitised	Visual (2 categories: > 25 vs. < 25, Or 6 categories: Percentiles)	Age, BMI	No association P NR	No association P NR	No association P NR		No association $P<0.05$	Younger $P<0.001$	Pre-men $P<0.001$
Yaghjyan et al. [146]	P	NCC	Mean 59.2	1010 2077	digitised	CAM (4 categories: < 10, 10–24, 25–49, ≥ 50%)	Age, BMI	No association $P=0.08$	No association 0.63	No association 0.43	No association 0.47			
Sartor et al. [147], Olsson et al. [95]	R	Case only	50–74	670	DM and SFM	BI-RADS, V (3 categories: 1, 2&3, 4)	Age, BMI	No association $P=0.47$	No association $P=0.88$	No association $P=0.41$	No association $P=0.39$	No association (L vs. H2P vs. TN) $P=0.17$	Younger $P<0.0001$	Pre-men $P=0.001$
Kim et al. [81]	R	Case only	NM	178	DM	BI-RADS, V (4 categories)	Age only	ER +ve $P=0.045$	PR +ve $P=0.002$	No association P 0.084	–	Sig association (non-TN vs. TN) $P=0.02$	Younger $P<0.0001$	Pre-men $P<0.0001$
Kim et al. [148]	R	Case only	Means 51.9, 52.9, 53.8	94 DCIS	DM	BI-RADS, V (4 categories)	None					No association $P=0.444$		
Jung et al. [149]	R	Case only	29–78	344	DM	BI-RADS, V (4 categories)	None					No association $P=0.093$ (TN vs. NTN) $P=0.188$(LA vs LB vs H2P)		
Edwards et al. [89]	R	Case only	> 18	457	DM	BI-RADS, V (4 categories) Volpara (continuous)	Age					No association $P=0.183$ H2P $P=0.002$		
Maskarinecet al. [48]	P	NCC	40–65	820 820	Digitised	Cumulus (4 categories: < 10, 10–19, 2–49, ≥ 50%)	Age, BMI	No association $P=0.33$	No association $P=0.21$	No association $P=0.17$				
Krishnan et al. [46][a]	R	NCC	Mean 65 & 62	392 cases 1146 controls	Digitised	Cumulus, (continuous)	Age, BMI	No association $P=0.23$	No association $P=0.64$	No association $P=0.69$				
Shin et al. [150]	P&R	CCS	NR	642 cases 1241 controls	DM	CAM (continuous)	Age, BMI	No association $P=0.795$	No association $P=0.653$	No association $P=0.689$		No Association $P>0.10$		

Table 2 (continued)

Study			Subjects		Methods			Molecular features					Demographic Features	
References	Design		Age	Number	Image acquisition	MD measure	Adjustment	Oestrogen receptor	Progesterone receptor	HER2	Ki 67	Subtype	Age	Menopausal state
Shaikh et al. [47]	Cross Sectional		Mean 54	123	DM	Cumulus, (continuous)	Age, BMI	ER +ve $P=0.02$	No association $P=0.38$	No association $P=0.32$		Sig association (non-TN vs TN) $P=0.01$	Younger $P<0.01$	No Association $P=0.96$
Ji et al. [27]	R	Case only	35–76	688	DM	BI-RADS, V (4 categories)	None	ER +ve $P=0.026$	PR +ve $P=0.030$	HER2 +ve 0.024	No association $P=0.787$	No association $P>0.05$		
						Quantra (4 categories)		No association $P=0.757$	No association $P=0.433$	No association $P=0.288$	No association $P=0.470$	No association $P>0.05$		
Hwang et al. [88]	R	Case only	Mean 54.3	969	SFM, DM	BI-RADS, V (4 categories)	None	No association $P=0.067$	PR +ve $P=0.003$	No association $P=0.280$			Younger $P<0.001$	

Study design—P prospective, R retrospective, NR not reported

Image acquisition—SFM screen film mammography, DM digital mammography

MD Measure—MD mammographic density, BIRADS breast imaging reporting and data systems, CAM computer-assisted method

BMI body mass index

HER2 human epidermal growth factor receptor two

Subtype—LA Luminal A, TN triple negative

Age: younger designates significantly higher association between MD and BC in younger versus older women

Menopausal status: pre-men designates significantly higher association between MD and BC in pre-menopausal versus post-menopausal women

[a]This study included two groups (screen detected) and (Interval), and assessed odds per one SD of MD increase (OPERA)

Table 3 Association between MD and Mode of detection

Study			Subjects				Methods				Results			
References	Design		Source	Age[a]	SBC	IBC	Image	Side	Adjustment	MD Measure	Measure	SBC	IBC	Significance
Van Giles et al. [151]	R	Case only	Nijmegan BCSP	NR	1684	669	SFM	NR	None	4 categories, V (<5, 5–25, 26–75, > 75%)	Frequency of SBC and IBC cancer in women with HMD (> 75%)	2.8%	9.9%	NR
Mandelson et al. [152]	R	Case only	BCSP for Group Health Cooperative of Puget Sound	NR	388	149	SFM	CL	None	BIRADS, V	Frequency of SBC and IBC cancer in women with HMD (≥ 75%)	1.8%	10.7%	NR
Crane et al. [153]	R	Case only	BreastScreen South Australia	50–73	246	233	NM	CL	Age	BIRADS (V)	Relative odds of IBC as opposed to SBC in women with HMD (≥ 75%) compared to LMD	2.62		$P < 0.001$
Ciatto et al. [154]	R	CCS	Florence City BCSP, 96–99	50–69	346	90	SFM	NR	None	4 categories (V) Wolfe's (V)	Frequency of SBC and IBC cancer in women with HMD (≥ 75% or P2DY)	7.2% 62.5%	27.8% 62.6%	$P < 0.01$ $P = 0.96$
Chiarelli et al. [155]	R	Case only	Ontario BCSP, 94–02	NR	450	87 (M), 288 (T)	SFM Digitised	CL	BMI	Boyd's 6 categories (V) 6 categories (CAM)	Relative odds of IBC as opposed to SBC in women with HMD (≥ 75%) compared to LMD	4.06, 7.76 1.35, 4.17		NR
Porter et al. [118]	R	Case only	Nottingham Breast Institute- NHS BCSP, 87–97	NR	455	304	NM	CL	None	BIRADS (V)	Frequency of SBC and IBC cancer in women with HMD (≥ 75%)	6.2	15.1	$P < 0.0001$

Table 3 (continued)

Study			Subjects				Methods				Results			
References	Design		Source	Age[a]	SBC	IBC	Image	Side	Adjustment	MD Measure	Measure	SBC	IBC	Significance
Boyd et al. [4]	R	NCC	NBSS, 81–90 OBSP, 93–98 SMPBC, 93–99	40–70	717	124 (< 12 m) 262 (≥ 12 m)	SFM Digitised	NR	Age, BMI	Boyd's 6 categories (V, CAM)	Odds ratio of IBC and SBC in women with HMD (≥ 75%) compared to LMD	3.5	17.3 5.7	NR
Kavanagh et al. [138]	R	CCS	BreastScreen Victoria, 94–96	40–79	683 (S) 351 (L)	370	NM	IL	Age	CAM	Odds ratio of IBC and SBC in women with HMD (D10) compared to LMD (Q1)	0.98 3.72	4.65	NR
Nickson et al. [130]	R	Case only	BreastScreen Victoria, 94–96	NR	1007	341	Digitised	IL	Age	Thresholding technique	Frequency of SBC and IBC cancer in women with HMD (D10, ≥ 39.1%)	6.4	20.5	NR
Pollan et al. [40]	R	CCS	Navarre BCSP, 96–98, 02–04	Mean 53	870	240	SFM	L	Age	Boyd 6 categories (V)	Odds ratio of IBC and SBC in women with HMD (≥ 75%) compared to LMD	2.17	7.72	NR
Nickson et al. [94]	R	CCS	BreastScreen Victoria, 94–96	NR	653 (small BC) 332 (Large BC)	367	Digitised	IL	Age	Cumulus, Auto density	Odds ratio of IBC and SBC in women with HMD (D10) compared to LMD (Q1)	1.3, 2.2 6.6, 6.4	4.1, 4.7	NR
Domingo et al. [156]	R	NCC	Spanish BCSP, 00–06	57.6 (S), 57.4 (M), 56.4 (T)	1297	224 (M) 455 (T)	SFM DM	NR	Age	BIRADS (V)	Frequency of SBC and IBC cancer in women with HMD (≥ 75%)	11.6%	16.5% 17%	$P < 0.001$
Chiarelli et al. [157]	R	Case only	Ontario BCSP, 08–09	NR	669 429	178 145	SFM DM	CL	Age, BMI	BIRADS (V)	Relative odds of IBC as opposed to SBC in women with HMD (≥ 75%) compared to LMD (< 25%)	6.4 2.41		NR

Table 3 (continued)

Study			Subjects				Methods				Results			
References	Design		Source	Age[a]	SBC	IBC	Image	Side	Adjustment	MD Measure	Measure	SBC	IBC	Significance
Sartor et al. [147] and Olsson et al. [95]	P	Case only	Malmo Diet and Cancer Study	Med 63.9	364	304	SFM DM	Both	Age, BMI	Three categories (fatty, medium, dense)	Frequency of SBC and IBC cancer in women with HMD (≥75%)	32.7%	33.6%	NR
Strand et al. [93, 158]	R	Case only	Libro-1 (01–08), Cahres	Mean 60, 61	1009 1029	394 385	Digitised	CL	Age, BMI	Thresholding technique	Median PMD Mean PMD (SD)	17.6 20 (13)	23.5 26 (16)	$P<0.001$ $P<0.0001$
Krishnan et al. [46]	R	NCC	BreastScreen Victoria	Mean 62, 65	244	148	Digitised	CL	Age, BMI	Cumulus	Mean PMD (SD)	15.5 (15.7)	25.2 (17.9)	$P<0.01$
Timmermans et al. [159]	R	Case only	Flemish BCSP	NR	1963	692	SFM DM	NR	None	BIRADS (V)	Frequency of SBC and IBC cancer in women with HMD (≥75%)	7.2%	23.8%	NR
Strand et al. [74]	R	Case only	Libro-1	Mean 60.3	1466	546	Digitised	CL	Age, BMI	Thresholding technique	Frequency of SBC and IBC cancer in women with HMD (PD≥20%)	39%	59%	NR
Nguyen et al. [160]	R	NCC	BreastScreen Victoria	NR	422	168	Digitised	CL	Age, BMI	Cumulus	Odds ratio of IBC and SBC in women with HMD (Q4) compared to LMD (Q1)	1.95	10.4	NR
Van der Wall et al. [96]	R	Case only	Nijmegen BCSP	38–97	1100	490 (≤24 m) 423 (>24 m)	SFM	NR	Age	>25 vs. <25 (V)	Frequency of SBC and IBC cancer in women with HMD (PD≥25%)	31%	52% 31.4%	NR

[a]Age at cancer diagnosis, BCSP Breast Cancer Screening Program, NHS National Health Service, NBSS National Breast screening Study, OBSP Ontario Breast Screening Program, SMPBC Screening Mammography Program of British Columbia, IBC Interval BC, SBC screen-detected BC, M Missed (i.e. IBC missed at screening but seen on retrospective review of the screening mammogram, T True IBC with no visible signs on the previous screening mammogram), BIRADS Breast Imaging Reporting and Data Systems, CAM computer-assisted method, V Visual, HMD High Mammographic Density, LMD Low Mammographic Density, BMI Body Mass Index, CCS Case–Control Study, NR not reported, CL Contralateral, IL Ipsilateral, SFM Screen Film Mammography, DM Digital Mammography

Table 4 Association between MD and BC survival

Study			Subjects			Methods					Results						Conclusion
Ref	Design		*N*	Type	Age	Image	MD measure	Side	Time	Adjust	FU	N of BC adverse events		Survival measure	HMD	LMD	Sig	
												HMD	LMD					
Hinton et al. [80]	R	Case only	141	Post-menopausal, with min FU 5 y after mastectomy	NR	SFM	Wolfe's, V (dichotomised: DY vs P/N patters)	Both	D	None	5 y	41		N of deaths with (DY) pattern vs those with (P or N) patterns	16/41 vs. 25/41		0.001	Better survival probability in HMD
Porter et al. [118]	R	Case only	759	Invasive BC	50–64	NR	BI-RADS, V (4 categories)	CL	BD (within 3 y, SBC), D (IBC)	None	Med 9 y	NR	NR	BC-specific survival across BIRADS MD patterns	NR	NR	0.12	No ass Bw MD and survival
Olsen et al. [24]	R	Case only	1009	All BC cases	50–69	NR	BIRADS, V (dichotomise: 4, 3 and part of 2 vs part of 2 &1)	NR	BD	Age	About 4 y	86/694	60/315	BC fatality rate ratio in (M/D) vs (F) pattern	0.60 (0.43–0.84)		NR	Better survival in HMD
												53/694	37/315	BC mortality rate ratio in (M/D) vs (F) pattern	1.78 (1.17–2.72)			
Chiu et al. [119]	R	Case only	873	All BC cases	45–59	SFM	Tabar, V (dichotomise: 5&4 vs 1-3)	IL	NR	Age, BMI	Mean 25 y	28/149	99/724	RR of BC death in HMD vs LMD	1.91 (1.26–2.91)		NR	No ass Bw MD and survival
Gierach et al. [117]	R	Case only	9232	Invasive BC	≥30	SFM, DM	BIRADS, V (dichotomised: 4 vs 2)	NR	BD (within 5 y)	Age, BMI	Mean 6.6 y	84/918	346/3735	HR of BC death in HMD vs LMD	0.92 (0.71–1.19)		NR	No ass Bw MD and survival
												126/918	806/3735	HR of all cause death in HMD vs LMD	0.83 (0.68–1.02)			
Zhang et al. [120]	R	Case only	15243	All BC cases	<40-> 80	NR	BIRADS, V (dichotomised: 3&4 vs 1&2)	NR	NR	Age	NR	NR	NR	HR of BC death in HMD vs LMD	0.893		0.0717	No ass Bw MD and survival
Maskarinec et al. [112]	P	Case only	607	All BC cases	63.3	digitised	Cumulus (high vs low, using median of 35%)	Both	BD (mean 6.3)	Age, BMI	Mean 12.9 y	15/303	12/304	HR of BC death in HMD vs LMD	0.83		0.67	No ass Bw MD and survival
												45/303	55/304	HR of all cause death in HMD vs LMD	1.37		0.16	
												39/303	32/304	HR second BC in HMD vs LMD	1.72		0.15	

Table 4 (continued)

Study			Subjects			Methods					Results							Conclusion
Ref	Design		*N*	Type	Age	Image	MD measure	Side	Time	Adjust	FU	N of BC adverse events		Survival measure	HMD	LMD	Sig	
												HMD	LMD					
Elsamany et al. [121]	R	Case only	60	Metastatic BC	NR	NR	Wolfe's, V (High MD; > 50% vs. Low MD; ≤ 25%)	IL	D	Age, BMI	Med 18 m	23/30	13/30	Progression-free survival in HMD vs LMD	23.3%	56.7%	0.017	Better survival in LMD
Olsson et al. [95]	P	Case only	619	invasive BC	Mean 64	SFM, DM	3 categories (fatty, medium, dense)	CL	D	Age, BMI	Mean 7.8	32/214	7/93	HR of BC death in (dense) vs (fatty)	2.56 (1.07–6.11)		0.039	Better survival in LMD
Masarwah et al. [52]	R	Case only	270	135 H2P BC, and age matched 135 H2 N invasive BC	32–86	DM, digitised	Boyd 6 categories, V (dichotomised: LOD; > 25%, vs. MID; < 25%)	IL	D	Age, BMI	Mean 6.4	17/112	40/158	Disease-free survival in MID vs LOD	84.8% vs. 74.7%		0.048	Better survival in HMD
												11/112	39/158	Overall survival in MID vs LOD	90.2% vs. 75.3%		0.003	
Andersson et al. [116]	R	Case only	1740	Post-menopausal women with BC	50–74	digitised	Cumulus (highest 3 vs. lowest quartiles)	CL	1 y BD to 1 m after D	Age, BMI	13–15 y	269		BC-specific death in relation to baseline MD	NR		0.648	No ass Bw MD and survival
Hwang et al. [88]	R	Case only	967	Operable invasive BC	25–87	SFM, DM	BIRADS, V (dichotomised: 3 and 4 vs. 1 and 2)	NR	D	Age, BMI	Mean 70.8 m	94		Overall survival in HMD vs LMD	NR	NR	< 0.001	Better survival in HMD
												101		Disease-free survival in HMD vs LMD	NR	NR	No Dif	
Strand et al. [74]	R	Case only	1925	invasive BC	Mean 60.3	digitised	Automated (> 20% vs < 20%)	CL	BD (within 3 y)	Age, BMI	14 y	153		HR of BC adverse events in HMD vs LMD (regional or distant recurrence or BC death)	1.11 (0.79–1.55)		NR	No ass Bw MD and survival
Van der Wall et al. [96]	R	Case only	2233	Invasive BC	38–97	SFM	Wolfe's, V (dichotomised: > 25% vs. < 25%)		BD and D	Age	NR[a]	173/777	306/1456	HR of BC death in HMD vs. LMD	0.94 (0.77–1.15)		0.58	No ass Bw MD and survival

HMD high mammographic density, *LMD*, LOD low mammographic density, *MID* mixed density, *M/D* mixed/dense, *F* fatty, *BMI* body mass index, *CCS* case–control study, *NR* not reported, *CL* contralateral, *IL* ipsilateral, *RR* relative risk, *HR* hazard ratio, Interval BC, *SBC* screen-detected BC, *m* month, *y* year, *SFM* screen film mammography, *DM* digital mammography, *BIRADS* breast imaging reporting and data systems, *CAM* computer-assisted method, *V* visual, *BD* before diagnosis, D at time of "Diagnosis"

[a]This study followed patients to death, or moving out of the area or end of the study

predisposed to that cancer. On the other hand, other studies used the diagnostic mammogram as the index mammogram and correlated its MD to the characteristics of the already-existing BC, which should remove such confounders [33].

Laterality of the used mammogram is another point of heterogeneity among studies. In studies employing the ipsilateral mammogram, the cancer field effect could potentially have impacted the MD. However, a substantial impact on correlative analyses with subsequent BC features beyond this effect appears unlikely since excellent correlation between MD of both breasts has been demonstrated [34]. Therefore, the optimal mammogram to be used depends on the context of the research question; mammograms taken many years before diagnosis may provide aetiologic insights, while those closer to diagnosis may provide a better baseline for subsequent longitudinal follow-up of MD in studying changes in response to treatment.

Correlation of MD with pathologic features

Histopathology

Invasive versus in situ BC Numerous studies have demonstrated the increased risk of invasive BC (IBC) with HMD. In particular, Boyd et al. demonstrated that women in the highest MD category (i.e. upper quartile or 75% density) had a 4- to 6-fold higher relative risk of IBC compared to those in the lowest MD category (i.e. lower quartile or 25%) [35]. The association between HMD and BC risk is not confined to invasive malignancy, but extends to carcinoma in situ (CIS, both lobular and ductal), as also demonstrated by Boyd et al, who found a 9.7-fold higher risk of developing CIS or atypical hyperplasia in women with HMD compared to those with LMD [36, 37]. Six studies compared the risk of association of HMD with IBC vs. CIS. Yaghjyan et al. confirmed the increased risk of both IBC and CIS in higher MD categories [38]. In addition, as also suggested by indirect comparison of the results of Boyd, Yaghjyan found that the positive association between HMD and CIS was significantly stronger than the association with invasive disease (OR 6.58 and 3, respectively, $P<0.01$) [38]. An additional five studies found a similar magnitude of association between MD and both ductal carcinoma in situ (DCIS) and IBC [32, 39–42]. In the aforementioned six studies, only Sala et al. included an additional analysis accounting also for the mode of detection, in which they reported that the ORs of screen-detected BC were similar to those of BC detected in any mode, for both CIS and IBC [39]. Bertand et al. found that the HMD-conferred risk for CIS was significantly stronger among younger women, while the predisposition to invasive BC remained consistent across age groups [32]. Taken together, these results suggest that the biological effectors underlying HMD may act at an early stage in BC pathogenesis, and that both CIS and IBC have a common pathobiological driver in MD.

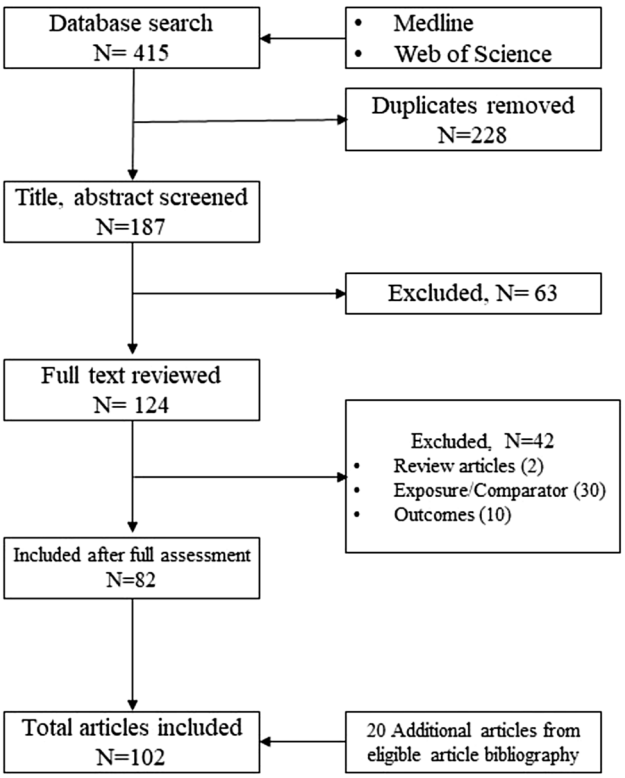

Fig. 1 Methods: Article identification, screening and selection

Histopathological type Although HMD has been reported to be associated with ductal epithelial hyperplasia [43], no study has demonstrated a differing risk of invasive or in situ ductal carcinoma relative to lobular pathology in HMD tissue. Twelve studies have investigated the association between MD and type of invasive BC pathology (Table 1). Ten studies, of which six were adjusted for age and BMI, found no association. In the other two studies, invasive lobular pathology was reported to be significantly more likely among cancer patients with HMD compared to those with LMD [44, 45]; none of these, however, adjusted for BMI.

Grading and lymphovascular invasion To date, 21 studies have investigated the relationship between MD and tumour grade with mixed results (Table 1). Out of the nine studies which adjusted their analyses for age and BMI, six did not find an association between MD and grade [32, 46–50]. Only Yaghjyan et al. [38] reported a significantly positive association between higher MD and higher tumour grade. On the contrary, Ghosh et al. [51] observed a trend towards a stronger association of HMD with lower tumour grade, and Masarwah et al. [52] reported a significant inverse relationship between percentile MD categories and tumour grade,

although no relation existed when MD was dichotomised into < 25% and > 25%. The latter two studies [51, 52], however, had the lowest number of cases among the nine, and hence were least powered. Out of seven studies reporting on lymphovascular invasion (LVI) (Table 1), only Arora et al. [45] and Aiello et al. [49] demonstrated LVI presence to be positively associated with MD. Taken together, these studies suggest little or no impact of MD on invasive tumour grade or LVI.

Gross pathology

Location It is not clear whether the link between HMD and BC risk is a direct effect of local tissue conditions or whether HMD represents a more general reaction to factors that also drive BC risk. Compared to LMD tissue, HMD tissue has increased proportions of epithelial and stromal tissue [16, 53], greater stromal fibrosis and epithelial hyperplasia [35] and higher insulin-like growth factor-1 (IGF-1) levels [54]. These observations have led to the hypothesis that MD-mediated BC risk is secondary to increased local cell division, although we and others have not detected increased Ki-67 in HMD versus LMD regions of the same breasts [55, 56].

Four studies investigated whether BC location may relate to HMD. Both Ursin et al. and Pereira et al. [57, 58] showed that more tumours arise within dense areas compared to regions of fatty breast tissue, supporting a direct local effect of HMD. Ursin et al. assessed the mammograms of 28 patients with DCIS and found that 21 lesions arose from areas of HMD. It is worth noting that the mammograms used in this study were taken immediately before or at the time of cancer diagnosis, hence a potential cancer field effect cannot be eliminated [58]. Supporting these findings, Pereira et al. obtained similar results in their study of 231 women when assessing mammograms taken, on average, 5 years prior to BC diagnosis [57]. In contrast, Vachon and colleagues assessed mammograms from 372 BC cases and 713 matched controls taken at an average of 7 years before the detection of invasive BC within the Mayo Clinic mammography screening program. They confirmed that although HMD was a marker for BC risk, it did not relate to tumour site; suggesting that MD was acting as a general risk factor for future BC, rather than being location-specific [59]. Finally, in a retrospective cross-sectional study of the quadrant MD of the normal breast of 110 women who had BC, Chan et al. reported that although BC was most frequent in the Upper Outer Quadrant (UOQ) (60.9%), which showed the highest DA in 77.3% of cases, quadrant MD was not the highest in women having BC in other quadrants, refuting therefore the association between quadrant MD and BC location [60]. In the latter two studies, however, mammograms were assessed in quadrants for MD, which may not accurately reflect variations in MD that can be either focal or diffuse.

Additional imaging modalities, especially MD measurements that can address the volume of the breast in a 3-D manner, may add precision to future research findings, which are needed to resolve this important issue. However, it is important to note that the Mayo study was well powered and was unable to detect a difference, suggesting that the risk relating to HMD may be mediated to a greater degree via genetic predisposition or by general environmental conditions rather than local tissue effects. Such a genetic predisposition is further supported by published data that suggest that over 60% of variations in MD are accounted for by genetic variations [61], some of which overlap with BC risk [62], while only 20–30% of the variations are contributed by age, BMI and hormonal influences [63, 64].

Size Twenty-five studies have examined whether MD is positively associated with tumour size (TS) at diagnosis. Of these, only 10 adjusted MD for age and BMI. As summarised in Table 1, several studies reported that MD was either significantly (11 studies) or non-significantly (2 studies) associated with larger TS. Out of these 13 studies, seven studies adjusted for age and BMI. Eleven studies found that MD was not associated with TS, while only one study observed a smaller TS in dense breasts, although in this study MD in the pre-operative mammogram of the cancerous breast was used, such that a confounding field effect of the existing tumour on MD cannot be excluded [44]. Of the twelve studies which did not demonstrate a positive association between MD and TS, only three studies [47, 48, 52] were adjusted for age and BMI. In the study of Masarwah et al., comparing the mean TS between LMD and Mixed (PMD > 25%) rather than HMD may at least partially explain the non-significant association of MD and TS [52]. Additionally, most of the studies demonstrating a positive MD–tumour size association were better powered compared to those that found no or an inverse association. Overall, it appears likely that HMD, when adjusted for age and BMI, is associated with increased tumour size at diagnosis.

Metastatic potential

Twenty-one studies looked at the possible association between lymph node status and MD. Of these, 16 studies found no association, of which the studies by Eriksson et al., Maskarinec et al. and Yaghjyan et al. were well powered and adjusted for potential confounders [38, 48, 50]. By comparison, of the remaining five studies that reported a positive association between MD and lymph node involvement, three [32, 46, 49] had large numbers of participants and adjusted MD for age and BMI, as summarised in Table 1. Overall,

current evidence is non-conclusive, and additional studies are needed.

Less than 5% of breast cancer patients have distant metastasis at presentation [65]. To our knowledge, no clinical study has specifically investigated whether there is an association between MD and distant metastasis at presentation, hence strong data regarding any association between MD and risk of de novo metastasis are lacking. As larger tumour diameter is associated with a higher risk of lymph node and distant metastasis [66, 67], one could hypothesise that HMD is associated with an increased risk of both; at least partially through the predisposition arising from larger tumours. In support of this, we have recently shown that HMD, as opposed to LMD, can lead to increased metastasis of a human BC cell line grown in mice [68].

Local and distant recurrence

To date, seven studies have looked for associations between HMD and risk of local (LR) or distant recurrence (DR) from a previously diagnosed tumour. Five of these studies demonstrated a positive association between HMD and higher risk of LR [33, 69–72], whereas two studies did not find any association with LR risk [73, 74]. No study identified a link with DR. Of note, in the study of Cil et al., this positive association was only significant in women not treated by post-operative radiotherapy [33]. It was unclear why some women in the study did not receive adjuvant radiotherapy despite this generally being the standard of care after breast-conserving surgery (BCS), and so unforeseen confounders for this association cannot be excluded. This observation suggests that women with LMD might safely avoid radiation post-operatively. It is also important to note that, while Cil et al. demonstrated this association in women treated by BCS [33], both Huang et al. and Eriksson et al. [69, 70] have also reproduced the same association between HMD and LR in women treated by mastectomy, which indicates that the positive association is not merely due to a masking effect resulting in unresected residual disease in dense breast tissue for women having BCS. Considering mechanisms of LR, expression of ROCK1, a protein kinase that aids in cell migration was found to be induced in BC cells grown in dense collagen matrix and confirmed in solitary tumour-derived cells surrounding human BC tumours. The presence of such cells again associated with LR but not DR, implicating induction of migration in the association between higher LR rate and HMD [75].

Molecular markers and subtypes

The influence of the hormonal milieu on MD [76, 77] has prompted many authors to explore whether MD has a relationship with either hormone receptor status or molecular subtype of BC. Forty-two studies, summarised in Table 2, have investigated these possible associations. HER-2 receptor status and Ki-67 expression were also reported in some of these studies. Twenty-two studies reported no significant association between MD and hormonal receptor status, which did not differ by menopausal status.

Nine studies, however, have detected a significant association between MD and ER status with contradicting results. Out of the five studies which reported an increased association of HMD with ER+ status, only Shaikh et al. adjusted for age and BMI [47, 78–81]. Similarly, four studies reported an increased association of HMD with ER— status, of which Yaghjyan et al. and Heusinger et al. were both better powered and adjusted MD for key confounders [38, 82–84].

Given the close associations between MD and oestrogen, the reason for these findings is yet to be understood; nevertheless, taken together the results suggest that HMD-conferred BC risk is not directly mediated through parenchymal ER-alpha, the ER routinely measured, within the developing tumour cells. Interestingly, women with breast cancers that were positive for ER-beta staining had high PMD [85]. Paradoxically, however, declining ER-beta has been reported to define the malignant progression of breast neoplasia [86]. Therefore, the role of ER-beta in MD-associated BC pathogenesis remains unclear and warrants further investigations. In this regard, it is worth noting that specificity of antibodies for ER-beta has been a longstanding and continuing issue [87].

A significant association between MD and PR positivity has only been reported in three studies [78, 81, 88] of the 23 examining the association. In the study of Conroy et al. [78], PR status assessment may have been affected by ER status, since they were assessed as one variable. The latter two studies [81, 88] did not adjust for potential confounders. Therefore, MD and PR status appear unlikely to be linked, based on the current evidence. None of the 18 studies reporting HER2 or seven studies reporting Ki-67 observed any significant association with MD.

Regarding association with BC subtype, out of 18 studies exploring a link, four demonstrated significant associations. Arora et al. [45] found that women in the highest MD category had a significantly higher frequency of Luminal A cancers, although distribution of the various subtypes (Luminal A, Luminal B, HER2 enriched and triple negative (TN)) was similar across BIRADS categories. Shaikh et al. noted that TN BC patients had significantly lower PMD compared to non-TN BC [47]. This is in agreement with Kim et al. who found that women with HMD were less likely to have TN BC [81]. Edwards et al. reported significantly higher-volumetric PMD in HER2-positive vs. HER2-negative phenotypes [89]. However, it is important to note that the latter two studies were adjusted only for age, and

therefore, possibly confounded by other factors which affect both MD and subtype such as BMI and menopausal status. Additionally, although adjusted for age and BMI, the study of Shaikh et al. was small [47].

Overall, currently available evidence suggests that MD increases BC risk irrespective of hormonal receptor status or molecular subtype of BC.

Clinical features

Age and menopausal status

It has been demonstrated that MD decreases with advancing age; this decrease paralleling the reduction in endogenous oestrogen levels after menopause [90]. Nineteen studies have investigated the association between MD and the age of the BC patient and ten have looked at the same association with menopausal status. BCs occurring in HMD breasts have been observed to be significantly associated with younger age (all 16 studies), and pre-menopausal status (9 of 10 studies; Table 2). Whether age may modify the MD–BC risk association has been investigated in three studies. Brisson et al. and Pollan et al. reported that younger age significantly increased the magnitude of this association [40, 91]; however, Bertrand et al. demonstrated this positive effect modification of younger age only among women with in situ as opposed to invasive disease, and node positive as opposed to node-negative BC [32]. Additionally, one study reported that age may impact the MD–BC mortality association, with nine-year mortality being 3.1 times higher in women with mammographically dense compared to those with fatty breast among patients in the 35–49 age group, while the corresponding relative mortality was 1.2 in the 50–74 age group.

In view of these findings, the factors driving HMD appear more influential on BC risk and outcome in younger or pre-menopausal women. The relationship between HMD-associated risk of BC and oestrogen exposure remains unclear.

Method of detection

Screen-detected BCs (SBC), by definition, are cancers detected by mammographic screening, while interval BCs (IBC) refer to tumours that are diagnosed in the intervening periods between successive screening mammograms, usually within the first 12 months. Interval tumours are characterised by a higher histologic grade and proliferation index and more rapid tumour growth [92].

Frequency of SBC versus IBC based on MD Twenty studies (Table 3) examined the association of BC risk, by mode of detection, and MD. Seventeen studies found that more IBCs, as compared to SBCs, were classified in HMD category. Two studies reported significantly higher mean/median PMD among IBC as compared to SBC [46, 93]. In one study however, the OR of large size SBC detected in HMD breasts (6.6) exceeded that of IBC (4.1), although the latter exceeded the OR of small SBCs in HMD patients (1.3) [94].

Boyd et al. [4] examined data from three nested case–control studies that were carried out in screening populations (total 1112 case-control pairs) to see if MD was associated with BC risk. Using logistic regression and results adjusted for age, BMI, parity and other key risk factors, HMD ($\geq 75\%$) was found to confer an elevated risk of both screen-detected and interval BCs (both < 12 and > 12 months after last screening) with ORs of 3.5, 17.8 and 5.7, respectively. Similarly, in a large case–control study (1172 cases: 4688 matched controls), Pollan et al. showed that IBCs were seven times more frequent among women with $> 75\%$ dense breasts than among those with $< 10\%$ PMD, while SBCs were only twice as frequent [40]. Boyd et al. suggested that the increase in BC risk within 12 months post screening could be due to a masking effect of HMD on small tumours [4, 35]. While the findings of Pollan et al. partially agree with this proposal, they argue that the substantially increased risk of interval tumours could not be fully explained by the masking effect of HMD, and that HMD may itself also reflect biological changes that increase the risk of interval BC [40].

Taken together, MD associates with increased BC risk irrespective of means of cancer detection; however, the magnitude of risk is larger for IBCs than for SBCs. Future studies are needed to explore possible biological mechanisms behind HMD-associated IBCs, and to confirm whether a stronger pathobiology of interval cancers is driven by HMD, or whether masking by HMD indeed fully explains such increased risk.

Biological behaviour of SBC versus IBC based on MD Although IBCs are known to have more aggressive features than SBC overall, their biological behaviour compared to SBC in HMD breasts is more controversial. Five studies have compared the biological behaviour of IBC and SBC based on MD; one report found significantly higher HR of IBC death among women with dense breasts, while the HR was not significant for SBC (HRs 3.40 and 2.04, respectively) [95]. Two reports did not find HMD to be significantly associated with more adverse events in IBCs (HR 1.03 for LR, DR or death [74], HR 1.07 for death [96]) compared to LMD. Furthermore, in a fourth report that looked at their biological behaviour, IBCs in HMD breasts were less aggressive than those in LMD breasts in terms of a significantly lower frequency of LN involvement and HER2-positivity ($P = 0.03$ and 0.03, respectively) [97]. The latter analysis, however, did not adjust for BMI, a factor associated with both increased tumour proliferation and

LMD [98]. Adjusting only for age and BMI, Eriksson et al. reported a HR of >3 for IBC compared to SDC, in both non-dense and dense breasts. Although this HR was attenuated after adjusting for tumour size and LN metastasis, it remained significant in women with non-dense breasts (HR 1.76, $P=0.047$), but lost significance in the dense breast category (HR 1.41, $P=0.649$) [99].

These findings suggest that the less favourable prognosis of IBC may be attributed more to late detection being initially masked by dense breast tissue and more aggressive biology overall allowing tumourigenesis to occur in the between-screen interval rather than to a more aggressive behaviour driven by HMD biological correlates.

Treatment

Recently, Elsamany et al. documented a significantly better pathological complete response rate to neo-adjuvant chemotherapy in women who had lower as opposed to higher MD in mammograms performed at diagnosis [100], suggesting that a degree of chemoresistance associates with HMD, at least in the primary tumour. However, no relapse or survival results were reported.

The higher local recurrence event rate demonstrated in non-irradiated HMD breasts suggests a larger protective effect of *post-operative radiotherapy* in HMD, as previously discussed. The absence of this excess risk in irradiated patients suggests that BCs evolving in a HMD environment are relatively radiosensitive.

Three studies have looked at whether mastectomy—as opposed to BCS—was more likely to be chosen based on MD category. In their retrospective review of 1323 BC patients, Arora and colleagues demonstrated that women with extremely dense breasts were significantly more likely to undergo *mastectomy*, compared to those with lower MD [45]. The authors attributed the latter finding to higher rates of multicentricity, multifocality and infiltrating lobular cancers in dense breasts, which contraindicate BCS. However, mastectomy rate did not differ by MD category in two further studies [69, 88].

In the *adjuvant setting,* six studies have found that MD reduction in response to endocrine therapy (ET) was associated with significantly improved BC outcomes in terms of lower BC-specific mortality [101, 102], reduced recurrence [103–105] and reduced second contralateral primary BC [106]. It is important to note that these studies included both pre- and post-menopausal women mostly treated with tamoxifen (tam), hence raising the potential use of MD change as a predictive biomarker for tam efficacy, which has been proposed.

Second primary breast cancer

To date, eight studies have found an association between HMD and increased risk of developing a second BC; five of which identified increased risk only in the contralateral breast (CBC) [34, 107–111]. One study found that HMD increased the risk of subsequent BC only in the ipsilateral breast [112]. The National Surgical Breast and Bowel Project B-17 trial showed that women with breasts having >75% dense tissue had a threefold increased risk of a second cancer for either breast [113]. Higher second primary BC rates were reported by Buist et al. in their cohort of 17,286 cases, in extremely dense vs. fatty breast (7.7 vs. 1.3/1000), although it was not clear whether this higher second primary rate was limited to one side or both [73]. Of interest in this context, the study of Sandberg et al. demonstrated 55% lower odds of CBC in tam-treated women who had ≥10% PMD decrease relative to those with lesser or no reduction [106].

Overall, HMD appears to be associated with a higher risk of second primary BC. Data are somewhat conflicting as to whether the increased risk of a second BC is limited to one breast or affects both; however, summating the evidence, risk appears potentially higher in the contralateral breast. In terms of the local effect of HMD on the ipsilateral breast, the effect could represent an altered stromal environment that remains permissive for cancer initiation and re-growth [114]. Alternatively, residual DCIS (for which HMD also confers risk as discussed above) in the ipsilateral breast distant from the initial surgical site could increase ipsilateral risk relative to contralateral. In contrast, ipsilateral radiotherapy could substantially reduce ipsilateral risk while leaving contralateral risk elevated, potentially explaining higher contralateral cancers. The higher MD reported in association with a family history of BC suggests that genetic factors that modulate MD may also influence BC risk in both breasts [115]. In support of this, some of BC-associated single-nucleotide polymorphisms (SNPs) have been recently identified as "novel MD loci" [62]. MD of both breasts from the same woman is similar [34], also explaining why MD estimated in one breast could be a strong risk factor for BC of both sides, simply representing the higher risk of de novo breast cancer associated with higher MD.

Survival

Association between single point MD and BC survival Fourteen studies (summarised in Table 4) looked at the possible associations between MD at a single-time point and BC survival. Eight studies found that MD was not associated with BC-specific survival [74, 96, 112, 116–120]; four studies demonstrated better survival in BC patients with denser breasts [24, 52, 80, 88] and two studies demonstrated better survival with LMD [95, 121].

Several factors might explain these conflicting findings. First is the treatment protocol applied to the study cohort, particularly the employment of radiotherapy and chemotherapy. Maskarinec et al. [112] found that women with BC and dense breasts who did not receive radiotherapy had an elevated risk of death (HR = 1.46; $P = 0.05$), compared to women with fatty breasts. In contrast, in women who received radiation, high PMD was associated with a reduced risk of dying from BC (HR = 0.77; $P = 0.04$). A protective effect of HMD with adjuvant radiotherapy on BC survival may indicate that the stroma associated with HMD potentiates the therapeutic effects of radiotherapy, in keeping with the previously discussed removal of LR risk by radiotherapy in women with HMD. Radenkovic et al. have recently shown that higher STAT3 expression was associated with both better survival and with HMD as opposed to LMD [122]. In contrast, the previously cited study of Elsamany et al. showed inferior chemotherapy responses in breast cancers arising in breasts with HMD [100]. Supporting this, Raviraj et al. showed evidence of epithelial–mesenchymal transition in the tumour cells cultured in high-density collagen matrix, a surrogate for HMD, changes which rendered cells resistant to chemotherapy treatment in culture [123, 124]. Taken together, the treatments applied to studied cohorts could, at least in part, explain the discrepancies in outcomes associated with HMD between cohorts and should be accounted for in future studies.

Second, the studies of Hinton et al. [80] and Olsen et al. [24] did not compensate for BMI and hence the inferior survival in women with fatty breasts could relate to a higher BMI in this group, an established adverse prognostic factor. This is also in keeping with the previously cited study of Gierach et al., in which BMI was found to significantly modify the relationship between MD and BC death such that the adverse relationship between low MD and risk of BC death was most apparent among obese women (HR 2.02, P 0.003) [117].

Third, the method of categorising MD may also affect the results; Masarwah et al. [52] categorised MD into < 25 and > 25%, hence survival in the HMD category may have been affected by those in the middle categories of density.

At present, no solid conclusions can be reached due to lack of well-powered studies to examine the relation between MD and BC-specific survival.

Association between longitudinal MD changes and BC survival Seven studies investigated BC survival in relation to longitudinal changes in MD. Li et al. studied 974 post-menopausal women with BC, finding tam-treated women who experienced a relative reduction in MD by > 20% between baseline and follow-up mammograms had a reduced BC-specific death risk of 50%, as compared with women who experienced minimal change in their MD. In the no-tam group, changes in MD were not associated with any BC-specific survival advantage [101]. Similarly, in a study of 349 tam-treated pre- and post-menopausal women, Nyante et al. found a lower risk of BC death in those with greater MD reduction [102]. In 1740 post-menopausal BC patients, Andersson et al. found no association between baseline MD and survival but reported a better survival among women with greater MD reduction, although in contrast to the work of Li et al. this survival advantage did not differ in tam-treated vs. non-treated women [116]. Further, the additional four studies cited earlier have demonstrated a better disease-free survival in both pre- and post-menopausal women, in terms of lower recurrences and CBC primary, in women having MD reduction within the adjuvant ET setting [41, 104–106]. It is worth noting that a tam-induced MD reduction has also been associated with significant BC risk reduction in the primary prevention setting [17, 18]. The strength and homogeneity of these predictive results suggest that MD might have a role in predicting the response of subsequent BC to ET although predictive effects appear to only apply consistently for patients receiving SERMs rather than AIs [125].

Summary and conclusions

Although the association between HMD and higher BC risk is beyond doubt, associations with BC clinicopathological features are less certain. Current evidence suggests that HMD predisposes to larger tumours, which are known to be associated with higher risk of lymph node and distant metastasis, but does not correlate with an increase in regional or distant metastasis. A consistent adverse impact of HMD on local relapse is apparent, which looks to be well addressed by breast radiotherapy. In general, the data also support an increased risk of second primary breast cancers, with likely higher risk on the contralateral side. The substantially higher risk of interval BC, as opposed to screen-detected BC, among women with dense breasts adds to the existing evidence for the biological relation between MD and BC, rather than carrying a masking effect alone. The fact that HMD confers a higher BC risk in younger and pre-menopausal women, which is inhibited by tam, but does not demonstrate significant differential association to positive steroid hormone receptor status, suggests that HMD-conferred risk is partially but not entirely through oestrogen effects on ER-alpha, and that this relationship is complex. Other conflicting associations of HMD with pathologic and clinical BC features (e.g. location, grading and survival) need further confirmatory studies that take account of treatment regimens, eliminate potential confounders and use optimally timed mammograms.

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Compliance with ethical standards

Conflict of interest Author Redfern is on Advisory Boards for Novartis, Roche, Eisai and Pfizer, but has no shares or other investments. Author Thompson has received consultancy fees from Eisai for a different topic but has no shares or other investments. None of these companies stand to benefit directly or indirectly from this paper. All authors declare that they have no conflict of interest.

Ethical approval/informed consent This is a review article that does not contain any studies with human participants or animals performed by any of the authors.

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