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FULL PAPER

Evaluation of background parenchymal enhancement on breast MRI: a systematic review

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Objective: To perform a systematic review of the methods used for background parenchymal enhancement (BPE) evaluation on breast MRI.
Methods: Studies dealing with BPE assessment on breast MRI were retrieved from major medical libraries independently by four reviewers up to 6 October 2015. The keywords used for database searching are "background parenchymal enhancement", "parenchymal enhancement", "MRI" and "breast". The studies were included if qualitative and/or quantitative methods for BPE assessment were described.
Results: Of the 420 studies identified, a total of 52 articles were included in the systematic review. 28 studies performed only a qualitative assessment of BPE, 13 studies performed only a quantitative assessment and 11 studies performed both qualitative and quantitative assessments. A wide heterogeneity was found in the MRI sequences and in the quantitative methods used for BPE assessment.
Conclusion: A wide variability exists in the quantitative evaluation of BPE on breast MRI. More studies focused on a reliable and comparable method for quantitative BPE assessment are needed.
Advances in knowledge: More studies focused on a quantitative BPE assessment are needed.

INTRODUCTION

As stated by the research committee of the European Society of Radiology, the future of medicine lies in the so-called "personalized medicine" (PM).[1,2] The concept of PM could be reassumed in delivering the right treatment to the right patient at the right time. The concept of PM is strictly linked to "precision medicine", which has been defined in 2011 by the National Research Council of the National Academies white paper entitled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a new Taxonomy of Disease".[3] In light of these new goals of modern medicine, biomedical imaging requires a correct and rational use of quantitative imaging biomarkers (QIBs).[4]

In addition, implementation of quantitative imaging on a large scale will be critical to meet the demands of PM.[4] Indeed, PM presents new challenges to the radiologists with the need for validation and assessment of QIBs for diagnosis and treatment response assessment.[1–6] One primary metrology area of interest in the assessment of performance of a QIB is the ability of the QIB to consistently reproduce equivalent results when conditions change, as would be expected in any clinical trial.[6] In this perspective, background parenchymal enhancement (BPE), the term used to describe the enhancement of the normal breast tissue, is emerging as an imaging biomarker.[7]

The "degree" of BPE is linked to the risk of developing breast cancer, may affect the reading of breast MRI, the staging and the risk of cancer and even the long-term outcome, particularly in patients with certain subtypes at immunohistochemistry.[8–15] BPE can be visually assessed qualitatively using the Breast Imaging-Reporting and Data System (BI-RADS) scores or quantitatively using software.[7,16] However, radiologist agreement for BPE qualitative evaluation is fair[17] and, to the best of our knowledge, there is a lack of uniformity on quantitative

measurements of BPE on breast MRI. Indeed, an absolute categorizing method based on percentage is not supported by the American College of Radiology (ACR), suggesting the need for further research in this topic.[16] It is crucial that in the era of PM, the methods used for the evaluation of BPE, as for other imaging biomarkers, are reliable and comparable among different imaging sites.[5] Therefore, the purpose of this study was to perform a systematic review of the methods currently adopted to assess BPE on breast MRI and to drive future research on this QIB.

METHODS AND MATERIALS

We followed the guidelines defined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses.[18] The protocol of this study was published on the International Prospective Register of Systematic Reviews (protocol number: CRD42015026904) on 8 October 2015 (http://www.crd.york.ac.uk/PROSPERO/).

Search strategy

We identified all relevant studies that assessed the evaluation of BPE on breast MRI. A literature search using PubMed (http://www.pubmed.org), Embase (http://www.embase.com.proxy.medlib.iupui.edu/search), ISI Web of Science (http://apps.webofknowledge.com), SpringerLink, ScienceDirect and Cochrane library (http://www.thecochranelibrary.com) was performed independently by four reviewers (AT, BB, FV and FR) up to 6 October 2015. A manual revision of the reference lists was also performed to integrate the initial search with additional studies, if necessary. We did not directly contact the authors for additional data.

The search strategy included the following terms related to studies on humans: "background parenchymal enhancement" or "parenchymal enhancement", in combination with "magnetic resonance imaging", "evaluation" or "assessment", "breast".

The detailed search strategy in PubMed is presented in the Supplementary Material.

Inclusion criteria

Studies were included if they met all the following criteria:

(1) females older than 18 years who underwent breast MRI
(2) BPE assessed on MRI.
(3) The method used for BPE assessment clearly stated: qualitative with BI-RADS, qualitative without BI-RADS, automated quantitative on two-dimensional MRI slices, automated quantitative on three-dimensional MRI volumes, semi-automated quantitative on two-dimensional MRI slices and semi-automated quantitative on three-dimensional MRI volumes.
(4) Only publications in English language were included.

Exclusion criteria: (1) case reports or case series, review articles, letters and comments; (2) duplicate publication; (3) BPE not assessed; (4) MRI examinations below 1.5 T.

No publication date restriction was used.

Study selection

Two authors (AT and BB) independently and manually reviewed article titles and abstracts for study selection, based on the predefined criteria. Then, the same authors independently read the methods in the full text of those studies to confirm fulfilment of the inclusion criteria. Disagreements arising during each phase of the study selection were resolved in consensus. If consensus could not be reached, a clinical expert (MC) was asked to resolve any disagreements.

Data extraction and analysis

Two authors (AT and BB) independently extracted the data from each eligible study. A duplicate data extraction was performed and discrepancies were resolved by consensus. The following data were extracted from each study: first author, journal and publication year, country of the study, study designation (retrospective or prospective), study population, magnetic field of the MRI scanner (1.5 T or 3.0 T), menstrual period of patients undergoing MRI, the type of contrast media used (high-relaxivity contrast media and no high-relaxivity contrast media), the type of BPE assessment (qualitative method, quantitative method, including automated software), the sequences in which BPE was qualitatively and quantitatively assessed and the method used for the quantitative evaluation of BPE. In particular, we recorded studies assessing BPE quantitatively using a region of interest (ROI), fibroglandular tissue segmentation, automatic method or other methods. To assess studies using ROI, we considered studies in which BPE was assessed by using an ROI traced to include a normal fibroglandular tissue, or the most enhanced part of the normal fibroglandular tissue, or the normal tissue extending from the tumour, e.g. excluding breast lesion enhancement. To assess studies using fibroglandular tissue segmentation, we considered studies in which BPE was calculated by enhancements of every pixel/voxel contained within a previously segmented fibroglandular tissue. To assess studies using an automatic method, we considered studies in which the use of fully automatic software that gives the value of BPE without the need for further control by a radiologist was specified. We also recorded studies using other methods, different from the ROI, fibroglandular or automatic ones.

Among the studies assessing BPE qualitatively, we recorded each study with intrareader and interreader agreement assessments for all readings by using the kappa statistics. We recorded kappa values for both ordinal (minimal, mild, moderate or marked BPE) and dichotomized variables (low and high BPE), when assessed. The strength of kappa agreement was defined as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.81, substantial; 0.81–1.00, almost perfect.

We divided articles published in 2015 from those published before 2015 to evaluate the increased interest on this topic in the past year. We performed a narrative synthesis of the qualitative and quantitative methods reported.

Risk of bias

The quality assessments of the eligible study were evaluated independently by two authors (Blind, Blind) using a modified Quality Assessment of Studies of Diagnostic Accuracy Studies (QUADAS-2) checklist, which comprised four domains: patient selection, index test and reference standard, and flow and timing. For the purpose of this study, the domains "index test"

and "reference standard" were considered together: in addition to the standard questions of these domains, we included the quality of the description of BPE assessment and the quality of MR images where the BPE assessment was performed, when available. Each domain is assessed in terms of risk of bias and the first three in terms of concerns regarding applicability. The answers "yes" (+), "no" (−) or "unclear" (?) to the standard questions of each domain represent the judgment regarding bias and applicability: low risk of bias, high risk of bias and insufficient data to permit a judgement, respectively. The two authors then discussed the results of their quality assessments. Disagreements were resolved by consensus.

RESULTS

The initial database search identified 420 articles. A total of 63 full-text articles were assessed after removal of duplicates and reading abstracts because they did not meet the selection criteria. From the 63 full-text articles, 11 studies were excluded because they did not meet the screening criteria and a total of 52 articles were included in the systematic review (Figure 1). Tables 1 and 2 show the characteristics of the included studies that assessed BPE with a qualitative and quantitative method, respectively. Among these 52 studies, 28 (54%) studies performed only a qualitative assessment, 13 (25%) studies performed only a quantitative assessment and 11 (21%) studies performed both qualitative and quantitative assessments of BPE and were included in both tables. Among these 52 studies, 20 (38%) studies were published in 2015.

Qualitative background parenchymal enhancement assessment

Among the 39 (28+11) studies that assessed BPE qualitatively,[7,8,10–13,15,17,19–49] 38% (15/39) studies were published in 2015 (January–October 2015) and 62% (24/39) studies were published during 2010–2014. Most of the studies were performed in the USA (17/39 studies), the Korea (10/39 studies) and Japan (6/39 studies). Only one study[47] had a prospective study design. The patient population of the included studies ranged from 18 to 1275 patients. 20 studies performed breast MRI using a 1.5-T scanner, 9 studies performed breast MRI using a 3.0-T scanner and 9 studies used both 1.5-T and 3.0-T scanners. In one study,[11] the MRI scanner was not clearly stated but it was above 1.5 T. Most of the studies (59%; 23/39 studies) used gadopentetate dimeglumine as contrast agent. Only 3/39 (8%) studies used a high-relaxivity contrast agent.[7,35,42] All the studies graded BPE on a four-point scale as minimal, mild, moderate or marked in accordance with the BI-RADS categories.[16] Iacconi et al[28] classified BPE according to the BI-RADS lexicon but for statistical purpose, clumped the studies into two groups (low and high BPE). 16 studies qualitatively assessed BPE using a combination of unenhanced and contrast-enhanced fat-suppressed T_1 weighted and subtracted images, and 5 studies added maximum intensity projection images also; 14 studies qualitatively assessed BPE using a combination of post-contrast fat-suppressed T_1 weighted and/or subtraction images; 1 study[33] used only maximum intensity projection images; in 3 studies, the sequences used for qualitative BPE assessment were not clearly stated (Table 1).

A total of nine studies evaluated the intrareader and/or interreader agreement of qualitative evaluation of BPE.[7,8,17,25,39,44–46,49] In particular, four studies[7,8,17,49] evaluated both intrareader and interreader agreements and the other five studies evaluated only interreader agreement. Kappa values for intrareader agreement were moderate to almost perfect, while more variability was

Figure 1. A flowchart of the selection of studies. BPE, background parenchymal enhancement.

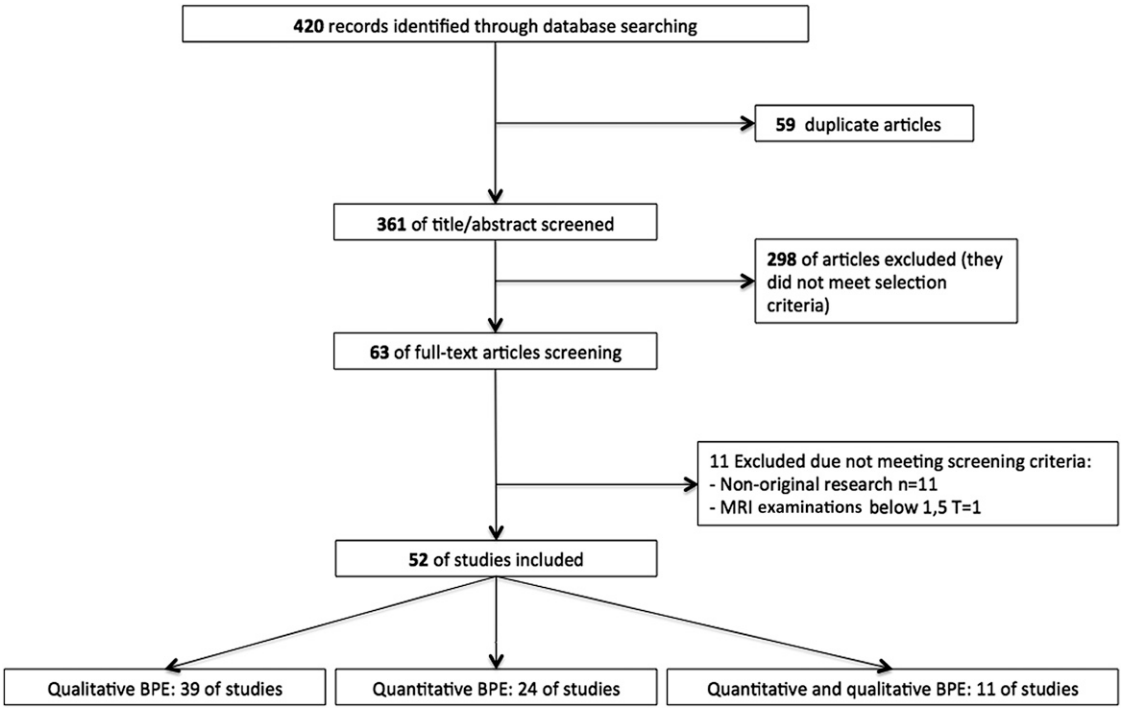

Table 1. Characteristic of the 39 studies that assess background parenchymal enhancement (BPE) qualitatively included in the systematic review

Study	Year	Journal	Country	Design	Study population	Magnetic field (T)	Contrast media (commercial names)	Sequences used for qualitative assessment of BPE				
								Combination of unenhanced and contrast-enhanced fat-suppressed T_1 weighted and subtracted images	Combination of the unenhanced, initial contrast-enhanced subtraction and MIP images	MIP	Post-contrast series and/or subtracted images	Not clear
Albert et al[19]	2015	*Clin Imaging*	USA	R	475	3.0 and 1.5	Magnevist® (Bayer Schering Pharma AG, Berlin, Germany)	x[a]				
Amarosa et al[b 20]	2013	*Radiology*	USA	R	58	3.0	Magnevist	x				
Baek et al[21]	2014	*Eur J Radiol*	Korea	R	322	3.0 and 1.5	Magnevist		x[c]			
Cho et al[b 22]	2015	*Eur J Radiol*	USA	R	77	3.0	Magnevist	x				
Choi and Kim[23]	2015	*Acta Radiol*	Korea	R	98	1.5	Magnevist	x[a]				
Cubuk et al[b 24]	2010	*Rad Med*	Turkey	R	26	1.5	Magnevist				x	
DeMartini et al[11]	2012	*AJR Am J Roentgenol*	USA	R	736	Not clear	not clear		x			
DeLeo et al[25]	2015	*AJR Am J Roentgenol*	USA	R	55	3.0 and 1.5	not clear	x				
Dontchos et al[10]	2015	*Radiology*	USA	R	487	1.5	Omniscan (gadodiamide)		x			
Grimm et al[26]	2015	*AJR Am J Roentgenol*	USA	R	222	3.0 and 1.5	Magnevist					x
Hambly et al[12]	2011	*AJR Am J Roentgenol*	USA	R	250	1.5	Magnevist	x				
Hansen et al[27]	2014	*J Magn Reson Imaging*	Germany	R	468	1.5	Gadovist® (gadobutrol, Bayer Inc., ON)				x[a]	
Iacconi et al[28]	2014	*Eur J Radiol*	USA	R	96	3.0 and 1.5	Magnevist					x
Jansen et al[b 29]	2011	*Eur Radiol*	USA	R	229	1.5	Omniscan				x	
Kajihara et al[b 30]	2013	*Magn Reson Med Sci*	Japan	R	165	1.5	Magnevist				x	

(Continued)

Table 1. (Continued)

Study	Year	Journal	Country	Design	Study population	Magnetic field (T)	Contrast media (commercial names)	Sequences used for qualitative assessment of BPE				
								Combination of unenhanced and contrast-enhanced fat-suppressed T_1 weighted and subtracted images	Combination of the unenhanced, initial contrast-enhanced subtraction and MIP images	MIP	Post-contrast series and/or subtracted images	Not clear
Kawamura et al[31]	2015	*Nagoya J Med Sci*	Japan	R	160	3.0	Magnevist	x[a]				
Kim JY et al[b 32]	2015	*Magn Reson Imaging*	Korea	R	81	3.0	Gadovist				x[a]	
Kim MY et al[33]	2015	*Clin Radiol*	Korea	R	178	3.0	Dotarem®			x		
Kim MY, et al[b 34]	2013	*Acta Radiol*	Korea	R	133	1.5	Gadovist	x[a]				
Kim SA et al[b 35]	2014	*Radiology*	Korea	R	215	1.5	MultiHance® (Bracco Imaging, Milan, Italy)	x[a]				
Kim YJ et al[36]	2014	*Asian Pac j Cancer Prev*	Korea	R	62	3.0	Gadovist				x[a]	
King et al[8]	2012	*Radiology*	USA	R	149	3.0 and 1.5	Magnevist	x				
King et al[37]	2012	*Breast J*	USA	R	88	1.5	Magnevist	x				
King et al[38]	2012	*Eur Radiol*	USA	R	330	3.0 and 1.5	Magnevist	x				
King et al[39]	2011	*Radiology*	USA	R	1275	1.5	Magnevist	x				
Kohara et al[40]	2015	*Nagoya*	Japan	R	91	3.0	Magnevist				x[a]	
Koo et al[41]	2013	*Eur J Radiol*	Korea	R	52	1.5	Gadovist	x[a]				
Melsaether et al[17]	2014	*AJR Am J Roentgenol*	USA	R	119	3.0 and 1.5	Magnevist	x[a]				
Myers et al[42]	2015	*Clin Breast Cancer*	USA	R	168	1.5	MultiHance					x
Park et al[43]	2015	*BrJ Radiol*	Korea	R	314	3.0 and 1.5	Magnevist		x			
Preibsch et al[44]	2015	*Eur Radiol*	Germany	R	73	1.5	Gadovist				x[d]	
Price et al[45]	2014	*Eur Radiol*	USA	R	18	1.5	Magnevist				x[a]	

(Continued)

Table 1. (Continued)

Study	Year	Journal	Country	Design	Study population	Magnetic field (T)	Contrast media (commercial names)	Sequences used for qualitative assessment of BPE				
								Combination of unenhanced and contrast-enhanced fat-suppressed T_1 weighted and subtracted images	Combination of the unenhanced, initial contrast-enhanced subtraction and MIP images	MIP	Post-contrast series and/or subtracted images	Not clear
Scaranelo et al[b] [46]	2013	*Radiology*	Canada	R	147	1.5	Gadovist				x[a]	
Schrading et al[b] [47]	2014	*Radiology*	Germany	P	40	1.5	Magnevist	x[a]				
Tagliafico et al[b] [7]	2015	*Br J Radiol*	Italy	R	48	3.0	MultiHance				x[a]	
Uematsu et al[15]	2012	*Breast Cancer*	Japan	R	70	1.5	Magnevist				x[a]	
Uematsu et al[13]	2011	*Eur Radiol*	Japan	R	146	1.5	Magnevist				x[a]	
Uematsu et al[48]	2012	*Eur J Radiol*	Japan	R	146	1.5	Magnevist				x[a]	
Yoon et al[49]	2015	*Eur Radiol*	Korea	R	145	3.0	Magnevist		x			

MIP, maximum intensity projection; P, prospective study; R, retrospective study.
[a]Early post-contrast images were used.
[b]Articles with both qualitative and quantitative assessments of BPE.
[c]The unenhanced images were not used.
[d]Only subtracted images were used.

Table 2. Characteristic of the 24 studies that assess background parenchymal enhancement (BPE) quantitatively included in the systematic review

Study	Year	Journal	Country	Design	Study population	Magnetic field (T)	Contrast media	Method used for quantitative assessment of BPE			Software used
								ROI	Fibroglandular tissue segmentation	Other	
Amarosa et al[a] [20]	2013	*Radiology*	USA	R	58	3.0	Magnevist® (Bayer Schering Pharma AG, Berlin, Germany)			x	Interactive Data Language (Exelis, Boulder, CO)
Chen et al[50]	2015	*Translational Oncology*	USA	R	46	1.5	Omniscan		x		
Chen et al[51]	2013	*Magn Reson Imaging*	USA	R	45	1.5	Omniscan		x		
Cho et al[a] [22]	2015	*Eur J Radiol*	USA	R	77	3.0	Magnevist	x			MATLAB®, (MathWorks®, Natick, MA)
Cubuk et al[a] [24]	2010	*Rad Med*	Turkey	R	26	1.5	Magnevist	x			
Hattangadi et al[52]	2008	*Am J Roentgenol*	USA	P	42	1.5	Magnevist	x			
Hegenscheid et al[53]	2012	*Eur Radiol*	Germany	P	651	1.5	Gadovist® (gadobutrol, Bayer Inc., ON)	x			Syngo 2008A MultiModality Workplace (Siemens Medical Solutions, Erlangen, Germany)
Hegenscheid et al[54]	2013	*Radiology*	Germany	P	651	1.5	Gadovist	x			Syngo 2008A MultiModality Workplace
Jansen et al[a] [29]	2011	*Eur Radiol*	USA	R	101	1.5	Omniscan	x			CADstream research v. 5.0 (Confirma, CA)
Kajihara et al[a] [30]	2013	*Magn Reson Med Sci*	Japan	R	165	1.5	Magnevist	x			Aquarius (TeraRecon

(Continued)

Table 2. (Continued)

Study	Year	Journal	Country	Design	Study population	Magnetic field (T)	Contrast media	Method used for quantitative assessment of BPE			Software used
								ROI	Fibroglandular tissue segmentation	Other	
											Inc., San Mateo, CA)
Kang et al[55]	2014	*J Magn Reson Imaging*	Korea	P	272	3.0	Magnevist	x			Extended MR Work Space (Philips Medical Systems)
Kim JY et al[a] [32]	2015	*Magn Reson Imaging*	Korea	R	81	3.0	Gadovist	x			
Kim MY et al[a] [34]	2013	*Acta Radiol*	Korea	R	133	1.5	Gadovist	x			
Kim SA et al[a] [35]	2014	*Radiology*	Korea	R	215	1.5	MultiHance® (Bracco Imaging, Milan, Italy)	x			
Klifa et al[56]	2011	*J Magn Reson Imaging*	USA	R	16	1.5	Magnevist		x		
Mazurowski et al[57]	2014	*Radiology*	USA	R	48	1.5	not clear			x[b]	
Mousa et al[58]	2012	*Menopause*	Canada	P	14	1.5	Gadovist/ Omniscan	x			
Scaranelo et al[a] [46]	2013	*Radiology*	Canada	R	147	1.5	Gadovist	x			
Schrading et al[a] [47]	2014	*Radiology*	Germany	P	40	1.5	Magnevist	x			View Forum (Philips, Best, Netherlands)
Schrading and Kuhl[59]	2015	*Radiology*	Germany	P	62	1.5	Magnevist	x			DynaCAD software package, v. 3.0 (Invivo, Philips Healthcare, Best, Netherlands)

(Continued)

Table 2. (Continued)

Study	Year	Journal	Country	Design	Study population	Magnetic field (T)	Contrast media	Method used for quantitative assessment of BPE			Software used
								ROI	Fibroglandular tissue segmentation	Other	
Tagliafico et al[a] [7]	2015	*Br J Radiol*	Italy	R	48	3.0	MultiHance			x[b]	MedDensity© (Genova, Italy)
Van der Velden et al[14]	2015	*Radiology*	Netherlands	R	531	1.5	ProHance® (gadoteridol, Bracco Diagnostics, Inc., Singen Germany)		x		Insight Segmentation and Registration Toolkit and Visualization Toolkit (Kitware, Clifton Park, NY) and MeVisLab software (MeVis Medical Solutions, Bremen, Germany)
Wu et al[60]	2015	*Breast Cancer Res*	USA	R	55	1.5	Omniscan		x[b]		
Yang et al[61]	2015	*Med Phys*	China	R	115[c]	1.5	Magnevist			x	

P, prospective study; R, retrospective study; ROI, region of interest.
In the last column, there is the name of the software used, when retrievable.
[a]Articles with both qualitative and quantitative assessments of BPE.
[b]Automatic method.
[c]MR images.

found for kappa values for interreader agreement, which was demonstrated to be fair to almost perfect (Table 3).

In the majority of studies (seven of nine studies), the agreement was assessed for ordinal variables. In the studies by King et al[8] and Melsaether et al,[17] the authors assessed intrareader and interreader agreements for both ordinal and dichotomized variables, but the strength of kappa agreement was not changed.

Quantitative background parenchymal enhancement assessment

Among the 24 (13 + 11) studies that assessed BPE quantitatively,[7,14,20,22,24,29,30,32,34,35,46,47,50–61] 33% (8/24) studies were published in 2015 (January–October 2015) and 67% (16/24) studies were published during 2008–2014. Most of the studies were performed in the USA (9/24 studies), the Korea (4/24 studies) and Germany (4/24 studies). A total of 7 studies were prospective, and 17 studies were retrospective. The patient population of the included studies ranged from 16 to 651 patients. 18 studies performed breast MRI using a 1.5-T scanner and 5 studies performed breast MRI using a 3.0-T scanner. Most of the studies (42%; 10/24 studies) used gadopentetate dimeglumine (Magnevist®; Bayer Schering Pharma AG, Berlin, Germany) as contrast agent. Only 2/24 (8%) studies[7,35] used a high-relaxivity contrast agent (gadobenate dimeglumine, MultiHance®; Bracco Imaging, Milan, Italy). 15 (62%) studies performed a quantitative evaluation of parenchymal enhancement from an ROI. Among these studies, BPE was described as a signal enhancement ratio in four studies.[29,34,35,52] The signal enhancement ratio was based on the comparison of signal intensity in an early contrast-enhanced image with signal intensity in a delayed contrast-enhanced image relative to a pre-contrast image.

BPE was described as percentage enhancement rates or a relative percentage enhancement in 11 studies,[22,24,30,32,46,47,53–55,58,59] with the use of both pre- and post-contrast images. There was a wide heterogeneity in the time selection of images obtained after contrast agent injection for relative percentage enhancement or percentage enhancement rate calculation.

Three studies performed a quantitative evaluation of BPE using an automatic method.[7,57,60] Tagliafico et al[7] assessed BPE using fully automated software that performed an objective and reproducible voxel-by-voxel analysis. This software used an algorithm based on the maximum entropy method and a threshold value.[7] Mazurowski et al[57] used computer vision algorithms that extracted all the features automatically, including a dynamic feature of the background parenchyma.[57] Wu et al[60] used a validated fully automated method that allowed segmentation and quantitative measure of fibroglandular tissues and BPE.[60]

Qualitative and quantitative background parenchymal enhancement assessment

Among the 11 studies that assessed BPE in both qualitative and quantitative methods,[7,20,22,24,29,30,32,34,35,46,47] 27% (3/11) studies were published in 2015 (January–October 2015) and 73% (8/11) studies were published during 2010–2014. Most of the studies were performed in the USA (3/11 studies) and the Korea (3/11 studies). The majority of the studies (10/11 studies) were prospective. The patient population of the included studies ranged from 26 to 229 patients. Seven studies performed breast MRI using a 1.5-T scanner and four studies performed breast

Table 3. Intrareader and interreader agreement for all readings for qualitative background parenchymal enhancement (BPE) evaluation among the nine studies that assessed agreement by using kappa statistics

Study	Year	Journal	Number of readers	Agreement	
				Intrareader (for dichotomized variables)	Interreader (for dichotomized variables)
DeLeo et al[25]	2015	*AJR Am J Roentgenol*	2	n.a.	0.49
King et al[39]	2012	*Eur Radiol*	2	n.a.	0.95
King et al[8]	2011	*Radiology*	2	0.62(0.69)	0.47(0.57)
Melsaether et al[a] [17]	2014	*AJR Am J Roentgenol*	4	0.79(0.80)	0.45(0.47)
Preibsch et al[b] [44]	2015	*Eur Radiol*	2	n.a.	Right breast:0.73 Left breast:0.77
Price et al[45]	2014	*Eur Radiol*	3	n.a.	0.3–0.6
Scaranelo et al[46]	2013	*Radiology*	2	n.a.	0.37
Tagliafico et al[7]	2015	*Br J Radiol*	2	0.69	0.70
Yoon et al[49]	2015	*Eur Radiol*	2	0.82	0.85

n.a., not available.
In two studies (King et al[8] and Melsaether et al[17]), the authors assessed the agreement for dichotomized variables also (low or high BPE).
[a]Pooled over all four readers; values after training at the end of the third lecture.
[b]Kappa values before neoadjuvant chemotherapy.

MRI using a 3.0-T scanner. Most of the studies (45%; 5/11 studies) used gadopentetate dimeglumine (Magnevist) as contrast agent. Among these 11 studies that assessed BPE in both qualitative and quantitative methods, only the study of Kim et al[34] found a statistical difference between qualitative and quantitative data.

Considering the menstrual period of patients who were pre-menopausal who underwent MRI, in the majority of studies (30 of 52 studies), the patient menstrual cycle was unknown or not available.[8,10,12–15,21,23,26,28,32–36,38,40–43,48–54,57,59,61] In five studies,[11,17,19,29,44] the authors acknowledged that owing to the retrospective nature of the study, it was not possible to analyze the point of menstrual cycle, although, following institutional protocol, screening breast MRI of patients who were pre-menopausal was performed during the second week of the menstrual cycle. In a total of 14 studies, the authors stated the menstrual period.[7,20,22,24,25,27,30,31,39,45,46,55,56,60] In 8 of these 14 studies, breast MRI were performed ideally in the second week of the menstrual cycle.[7,22,24,25,27,45,56,60] In three studies,[37,47,58] the patients were post-menopausal females.

Risk of bias

Assessment of the methodological quality of the included studies by the modified QUADAS-2 tool is depicted in Tables 4 and 5.

The domain of "patient selection" for the qualitative and quantitative BPE evaluation was unclear in the studies of DeMartini et al,[11] Choi and Kim,[23] Jansen et al,[29] Kajihara et al,[30] Kang et al,[55] Kim JY et al[32] and Park et al.[43] The domain "index test and reference standard" was described in detail in most of the studies that assessed BPE qualitatively and quantitatively. A risk of bias and concerns regarding applicability were judged in the study of Chen et al[50] and in the studies of Grimm et al[26] and Myers et al,[42] specifically for the low quality of MRI examinations where the BPE assessment was performed and a low detail of the qualitative assessment of BPE, respectively. The domain of "flow and timing" was the only domain to potentially contribute a high risk of bias in the studies evaluated. However, we believe that this domain could be less relevant because we focused only on the methods of assessment of BPE which, in most instances, are performed with a retrospective review of a data set of breast MRI.

DISCUSSION

We performed a systematic review of the literature currently available on qualitative and quantitative assessments of BPE in breast MRI. We divided the 52 articles included in the systematic review into those that performed a qualitative evaluation of BPE and those that performed a quantitative evaluation of BPE. Most of the studies found (28/52 studies) performed only a qualitative evaluation of BPE, 13 studies performed only a quantitative evaluation and 11 studies performed both qualitative and quantitative evaluations of BPE. Therefore, a total of 24 studies performed a quantitative assessment of BPE. Among these 24 studies, one of the most difficult issues was the analysis of the quantitative method used, owing to the lack of standardization of the BPE quantitative assessment. Indeed, the studies used different methods and software to evaluate BPE, although the majority of these studies performed a quantitative evaluation of parenchymal enhancement from an ROI. However, the use of ROI usually needs radiologist involvement, and this issue should be faced in the perspective of a standardized quantitative imaging evaluation of BPE. In addition, only three studies used an automatic method, and in all these studies, different software were used. We can state that in the "era" of PM and emerging QIBs, BPE quantitative assessment is still far from standardized. The ACR distances itself from prescribing an absolute quantification method for BPE assessment[16] and this is probably the source of heterogeneity that we found in our study. Indeed, our study found extensive heterogeneity in the methods used for BPE quantitative assessments and encourages further studies assessing comparable methods for quantitative BPE evaluation.

Among the 11 studies that performed a BPE assessment with both qualitative and quantitative methods, only 1 study[34] reported a statistical difference between the qualitative and quantitative methods used. Noteworthy, the study by Kim et al[32] was able to associate high values of BPE around the tumours on pre-operative MRI with an increased risk of ipsilateral breast tumour recurrence. Without the use a quantitative approach, this information would have been missed. Indeed, with a study design similar to that of Kim et al,[34] a huge number of breast MRI examinations were necessary to obtain the same information.

Our systematic review found that the majority of studies published had a retrospective design, and only few studies were prospective. A retrospective study design reduces the possibility of associating BPE with other factors relevant to tumour biology. In addition, in the majority of the studies, the menstrual period of pre-menopausal females who underwent MRI was unknown or not available.

Regarding the contrast media used, we found that only few studies used high-relaxivity contrast media. The use of high-relaxivity contrast media such as gadobenate dimeglumine is reported to offer advantages of lesion conspicuity, detection rate and sensitivity for malignant breast lesions.[62] Besides, a higher enhancement of benign lesions and breast parenchyma is possible with high-relaxivity contrast media;[62] therefore, we cannot confirm that the amount of BPE assessed with the same method, but different contrast media, is comparable.

Regarding the quality assessment, we used a modified QUADAS-2 checklist, since our systematic review did not focus on diagnostic accuracy studies; indeed, we merged the domains "index test" and "reference standard". In addition to the standard questions of these domains,[63] we also considered the quality of the description of BPE assessment and the quality of MR images in which the BPE assessment was performed. In spite of the modified method of quality assessment, the domain of "flow and timing" was the only domain to potentially contribute a high risk of bias in the included studies. However, this review focused on the methods used on BPE evaluation, and the majority of the studies performed the assessment with a retrospective review of the breast MRI data set; therefore, we believe that this domain could be less relevant and the overall risk of bias in these studies could be considered low.

Table 4. Risk of bias table demonstrating the overall risk of bias for each of the domains of patient selection, index test and reference standard, and flow and timing

Study	Patient selection	Index test and reference standard	Flow and timing
Albert et al[19]	+	+	+
Amarosa et al[a] [20]	+	+	?
Baek et al[21]	+	+	+
Cho et al[a] [22]	+	+	+
Choi and Kim[23]	?	+	?
Cubuk R et al[a] [24]	+	?	?
DeMartini et al[11]	?	+	+
DeLeo et al[25]	+	+	+
Dontchos et al[10]	+	+	+
Grimm et al[26]	+	−	?
Hambly et al[12]	+	+	−
Hansen et al[27]	+	+	+
Iacconi et al[28]	+	+	?
Jansen et al[a] [29]	?	+	?
Kajihara et al[a] [30]	?	+	?
Kawamura et al[31]	+	+	+
Kim JY et al[a] [32]	?	+	+
Kim MY et al[33]	+	?	+
Kim MY[a] [34]	+	+	+
Kim SA et al[a] [35]	+	+	+
Kim YJ et al[36]	+	?	−
King et al[8]	+	+	+
King et al[37]	+	+	+
King et al[38]	+	+	+
King et al[39]	+	+	+
Kohara et al[40]	+	+	?
Koo et al[41]	+	+	+
Melsaether et al[17]	+	+	+
Myers et al[42]	+	−	?
Park et al[43]	?	+	?
Preibsch et al[44]	+	+	?
Price et al[45]	+	+	+
Scaranelo et al[a] [46]	+	+	+
Schrading et al[a] [47]	+	+	+
Tagliafico et al[a] [7]	+	+	+
Uematsu et al[15]	+	+	?
Uematsu et al[13]	+	+	?
Uematsu et al[48]	+	+	?
Yoon et al[49]	+	+	?

+, low risk of bias; −, high risk of bias; ?, unclear.
[a]Studies that assessed background parenchymal enhancement with both qualitative and quantitative methods.

Table 5. Risk of bias table demonstrating the overall risk of bias for each of the domains of patient selection, index test and reference standard, and flow and timing

Study	Patient selection	Index test and reference standard	Flow and timing
Amarosa et al[a] [20]	+	+	?
Chen et al[50]	+	−	?
Chen et al[51]	+	+	?
Cho et al[a] [22]	+	+	+
Cubuk R et al[a] [24]	+	?	−
Hattangadi et al[52]	+	?	?
Hegenscheid et al[53]	+	+	+
Hegenscheid et al[54]	+	+	+
Jansen et al[a] [29]	+	+	?
Kajihara et al[a] [30]	?	+	?
Kang et al[55]	?	+	+
Kim JY et al[a] [32]	?	+	+
Kim MY et al[a] [34]	+	?	?
Kim SA et al[a] [35]	+	+	+
Klifa et al[56]	+	+	+
Mazurowski et al[57]	+	?	?
Mousa et al[58]	+	+	−
Scaranelo et al[a] [46]	+	+	+
Schrading et al[a] [47]	+	+	+
Schrading and Kuhl[59]	+	?	+
Tagliafico et al[a] [7]	+	+	+
Van der Velden et al[14]	+	+	+
Wu et al[60]	+	+	+
Yang et al[61]	+	+	?

+, low risk of bias; −, high risk of bias; ?, unclear.
[a]Studies that assessed background parenchymal enhancement with both qualitative and quantitative methods.

Considering qualitative evaluation, BPE was always graded on a four-point scale by the BI-RADS categories representing the main standardized area in BPE assessment, as recommended by the ACR BI-RADS fifth edition itself.[16] However, a huge variability in the MRI sequences adopted to assess BPE was noted, although the main principle was to find the sequences in which the amount of BPE was most evident. It is clear that there is no consensus on what MRI sequences the BPE should be assessed even with the relatively simple suggested BI-RADS grading system. In addition, a wide variability was found among kappa values for the interreader agreement, from fair to almost perfect agreement. Considering intrareader agreement, kappa values were moderate to almost perfect. However, only 9 of 39 studies assessed intrareader and/or interreader agreement for the qualitative evaluation of BPE, and further studies could be useful on this topic.

Considering quantitative evaluation, we acknowledge that our study did not include a detailed description of the methods used for the quantitative assessment of BPE. However, we performed the division of these studies among four main different methods (ROI, fibroglandular tissue segmentation, automatic methods or other methods) to allow a more uniform analysis. Further systematic reviews that focus on this topic could be useful to provide future directions for a standardization of quantitative methods used to assess BPE.

Finally, the first study on BPE assessment was published in 2008[52] and 38% (20/52) of all the studies included were published in 2015, reflecting the growing interest in this topic. The relatively recent interest in BPE assessment could be another possible explanation for the wide variability found in the sequences used for the qualitative assessment and in the methods used for the quantitative assessment.

In conclusion, since BPE is considered an emerging imaging biomarker, new methods to assess BPE quantitatively are being developed. However, a wide variability exists in the methods

used to perform a quantitative evaluation of BPE on breast MRI. In addition, no consensus exists on the sequences to be used to visually assess BPE. Therefore, more studies on quantitative BPE assessment are needed.

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