Original Paper

Diagnostic Value of Nineteen Different Imaging Methods for Patients with Breast Cancer: a Network Meta-Analysis

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Key Words

Breast cancer • Diagnostic value • Magnetic resonance imaging • Mammography • Ultrasonography • Scintimammography • Sensitivity • Network meta-analysis

Abstract

Background/Aims: We performed a network meta-analysis (NMA) to investigate and compare the diagnostic value of 19 different imaging methods used for breast cancer (BC). **Methods:** Cochrane Library, PubMed and EMBASE were searched to collect the relevant literature from the inception of the study until November 2016. A combination of direct and indirect comparisons was performed using an NMA to evaluate the combined odd ratios (OR) and draw the surface under the cumulative ranking curves (SUCRA) of the diagnostic value of different imaging methods for BC. **Results:** A total of 39 eligible diagnostic tests regarding 19 imaging methods (mammography [MG], breast-specific gamma imaging [BSGI], color Doppler sonography [CD], contrast-enhanced magnetic resonance imaging [CE-MRI], digital breast tomosynthesis [DBT], fluorodeoxyglucose positron-emission tomography/computed tomography [FDG PET/CT], fluorodeoxyglucose positron-emission tomography [FDG-PET], full field digital mammography [FFDM], handheld breast ultrasound [HHUS], magnetic resonance imaging [MRI], automated breast volume scanner [ABUS], magnetic resonance mammography [MRM], scintimammography [SMM], single photon emission computed tomography scintimammography [SPECT SMM], ultrasound elastography [UE], ultrasonography [US], mammography + ultrasonography [MG + US], mammography + scintimammography [MG + SMM], and ultrasound elastography + ultrasonography [UE + US]) were included in the study. According to this network meta-analysis, in comparison to the MG method, the CE-MRI, MRI, MRM, MG + SMM and UE + US methods exhibited relatively higher sensitivity, and the specificity of the FDG PET/CT method was higher, while the BSGI and MRI methods exhibited higher accuracy. **Conclusion:** The results from this NMA indicate that the diagnostic value of the BSGI, MG + SMM, MRI and CE-MRI methods for BC were relatively higher in terms of sensitivity, specificity and accuracy.

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Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women, and approximately 1.7 million new cases of BC and 0.5 million cancer deaths owing to BC were recorded worldwide in 2012 [1]. BC ranks first among the cancers diagnosed in women between 20 and 59 years of age [2]. During the past 30 years, BC mortality in Chinese females has followed a gradual upward trend, making it the fifth most common cause of cancer death in females [1]. BC is also a huge financial burden and source of pain in patients' daily lives [3]. The clinical outcome of BC is immensely variable, ranging from complete curability to a time span of 10 years post-surgical treatment, owing to the heterogeneous group of tumors presented with BC [4, 5]. The complicated scenarios arising in BC can be explained by its complex neoplasm and both genetic and environmental factors [6]. In addition, family history, high breast density, overweight, and environmental factors, such as X- and γ -radiation, hormones and breast-feeding, play a key part in contributing to this complicated scenario [7]. The ultimate outcome of BC relies on its initial stage at diagnosis, with the main prognostic factors being lymph node involvement, tumor size and histological grade [8]. However, the heterogeneous tumors of BC can behave in different manners even at the same stage, and the prognosis varies from individual to individual [9]. BC has been classified into the following five molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor-2 (HER-2) overexpressing, basal-like, and normal-like [10]. Complex tumor therapy development and new opportunities in surgery, which take into account both oncological principles and esthetic aspects, have set the requirements far higher for diagnostic imaging of the breast and for radiologists [11].

Great strides have been achieved in screening for BC over the past decades. The improved awareness and screening have brought about early diagnosis in BC patients, which in turn contributes to higher survival rates in female BC patients [12]. Diagnostic methods for BC are classified as magnetic resonance imaging (MRI), mammography (MG), ultrasonography (US), scintimammography (SMM), and bioluminescence imaging (BLI) [13, 14]. In both in situ and invasive BC, the increasingly used method of diagnosis is the MRI [15]. Nevertheless, the use of breast MRI remains controversial because of the debate regarding the long-term clinical benefits from surgical excision of additional tumor detected by MRI in the ipsilateral breast [16, 17]. Additionally, the randomized trial of preoperative MRI does not effectively affect the frequency of avoidable operations (total initial mastectomies not justified by pathology, and re-excisions and mastectomies within six months after breast-conserving surgery) [18, 19]. Therefore, we require additional imaging examinations to detect the exact location and extension of recurrent lesions [20]. Other imaging methods, such as MG, US, and SMM, as well as combined diagnosis, also present their own set of advantages and disadvantages in sensitivity, specificity and accuracy in the diagnosis of BC [11]. The statistical factors in reviews that compare various interventions and network meta-analysis (NMA), if properly used, can exert decision-making better than the pairwise meta-analysis [21].

The exact pre-therapeutic tumor sizing using imaging methods plays a central role [13], and NMA is a relatively new statistical technique that gives access to compare both direct and indirect evidence [22]. NMA shows further development in evidence synthesis, particularly in the decision-making field, and it not only combines data from random comparisons to offer an internally consistent estimation but also realizes randomization in the evidence [23, 24]. Therefore, we conducted an NMA to analyze the sensitivity, specificity and accuracy of different imaging methods to find the most accurate and efficient method in the diagnosis of BC.

Materials and Methods

Search strategy

The full text is written in accordance with a network meta-analysis of the PRISMA declaration [25]. We accessed the Cochrane Library, PubMed and EMBASE databases to obtain literature relevant to this

study. Relevant articles were also reviewed manually in case of the omission of any potentially relevant literature. The literature search was limited to the English language and ended in November 2016. The search terms included a combination of keywords and free words as follows: breast cancer (BC), magnetic resonance imaging (MRI), mammography (MG), computed tomography (CT), ultrasonography (US), scintimammography (SMM), ultrasound elastography (UE), digital breast tomosynthesis (DBT), color Doppler sonography (CD), breast-specific gamma imaging (BSGI), automated breast volume scanner (ABUS), sensitivity, comparative study, sonography, mammography, elastography and diagnosis. The detailed search strategies are shown (for all online suppl. material, see www.karger.com/10.1159/000489443) in Suppl. material.

Inclusion and exclusion criteria

The inclusion criteria for the study were as follows: (1) the study designs must be diagnostic tests; (2) the imaging methods were limited to MG (used with a mammography system), BSGI (conducted with a high-resolution breast-specific gamma camera), CD, contrast-enhanced magnetic resonance imaging (CE-MRI, using a 3 T MRI scanner in the prone position applying a dedicated four-channel breast coil), DBT (performed with a commercially available device comprising of a custom-designed high-power (mA) tungsten (W) anode X-ray tube and rhodium, silver, and aluminum X-ray filters), fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT, using a combined whole-body PET/CT in-line system with a high-resolution PET scanner and a 64-row detector CT scanner), fluorodeoxyglucose positron-emission tomography (FDG-PET, performed with 3D acquisition on a special partial-ring PET scanner in the prone position on a special device allowing the breast to depend freely), full field digital mammography (FFDM, conducted with a tomosynthesis capable unit), handheld breast ultrasound (HHUS, using a 13.5 MHz transducer), MRI, ABUS (with scanning unit, including a 14 MHz high-frequency linear transducer), magnetic resonance mammography (MRM, regarded as Breast MRI), SMM (with a single-detector gamma camera including a parallel-hole low-energy high-resolution collimator), single photon emission computed tomography scintimammography (SPECT SMM), UE (complementary to and independent from B-mode and Doppler imaging, which offer the acoustic impedance and vascular flow information), US, mammography + ultrasonography (MG + US, mammography in comparison to ultrasonography), mammography + scintimammography (MG + SMM, mammography in comparison to scintimammography), and ultrasound elastography + ultrasonography (UE + US, ultrasound elastography in comparison to ultrasonography); (3) study subjects were consecutive patients aging from 12 to 92 years with a possible breast lesion detected by self-examination, physical examination or screening mammography, and patients underwent examination before final diagnosis and confirmation by histopathologic examination; and (4) the outcome indicators of studies include sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. The exclusion criteria included were as follows: (1) literature lacking data integrity (such as non-pairwise studies); (2) duplicate publications; (3) conference reports, systematic reviews and summary articles; (4) studies unrelated to BC; (5) non-English studies; and (6) non-human studies.

Data extraction and quality assessment

Two researchers independently carried out data extracted on the basis of predefined form. The main data included the primary author, date of publication, country, ethnicity, age, gender, gold standard and diagnostic modalities. Any dispute appearing during data extraction was resolved through discussion with 2 researchers. The quality of all included studies was assessed by researchers, according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [26]. The QUADAS-2 tool included the following 4 key domains: patient selection, index test, reference standard, and flow of patients through the study and timing of the index tests and reference standard (flow and timing). The Review Manager 5 (RevMan 5.2.3, Cochrane Collaboration, Oxford, UK) statistical computing software was used to carry out quality assessment and investigation of publication bias.

Statistical analysis

Firstly, traditional pairwise meta-analyses were performed for studies to compare different diagnostic modalities using the Stata version 13.1 software (StataCorp, College Station, TX, USA). The pooled estimates of odd ratios (ORs) and 95% confidence intervals (CI) for sensitivity, specificity, PPV, NPV and accuracy of BC were shown. Heterogeneity among studies was tested using the I-square and Chi-square tests [27]. Secondly,

the R version 3.2.1 statistical computing software and network package were used to draw the network graphs, with each node representing different interventions, the node size reflecting the number of patients, and the thickness of lines between nodes indicating the number of included studies. Thirdly, Bayesian network meta-analyses were performed to combine the effective sizes of direct and indirect comparisons. Each analysis was based on non-informative priors for precision and effective sizes. Lack of auto-correlation and convergence were checked and confirmed by four chains and a 20,000-simulation burn-in phase; finally, direct probability statements were derived from an additional 50,000-simulation phase [28]. The node-splitting method was adopted to evaluate the consistency between direct and indirect evidence, and the consistency or inconsistency model was selected based on the results of the aforementioned evaluation [29]. To provide assistance in the interpretation of ORs, the surface under the cumulative ranking curve (SUCRA) was used to calculate the probability of each intervention, being the most effective diagnostic method based on a Bayesian approach using probability values, and the larger the SUCRA value is, the better the rank of the intervention [30, 31]. Cluster analyses were conducted to evaluate different imaging methods on the diagnostic value of BC treatment, by grouping different interventions according to similarities of two variables to judge the efficacies by comparing the advantages and disadvantages of different imaging methods [30]. Comparison-adjusted funnel plots were performed to detect the small study effects on data [30, 32]. R (V3.2.1) package gemtc (V0.6), along with the Markov Chain Monte Carlo engine Open BUGS (V3.4.0), was used for all computations in this network meta-analysis.

Results

Baseline characteristics of included studies

A total of 5,446 studies relevant to this study were initially retrieved. After excluding duplicate studies ($n = 46$), letters or reviews ($n = 159$), non-human studies ($n = 156$) and non-English studies ($n = 466$), a total of 4,719 studies were evaluated for eligibility by full-text review. After full-text review, case-control studies ($n = 2717$), studies unrelated to BC ($n = 1318$), studies irrelevant to imaging methods ($n = 642$), and studies lacking data or with incomplete data ($n = 3$) were ruled out. Finally, we identified 39 diagnostic tests that met the inclusion criteria [33-71] (Fig. 1), including a total of 2,890 patients diagnosed with BC using the gold standard and 19 imaging methods, among which MG method was the most widely adopted method of diagnosis. The included studies were published between 1996 and 2015. In addition, 25 of the 39 enrolled studies were two-arm trials, 8 studies were three-arm trials, and 6 studies were four-arm trials. The baseline characteristics of the included studies are shown in Table 1, and the QUADAS-2 for evaluating the risk of bias is shown in Fig. 2. The results indicated that variations in test technology, execution, or interpretation may exert influence on the estimation of the diagnostic accuracy of a test.

Pairwise meta-analysis for the diagnostic value of 19 imaging methods for BC

We conducted a direct-paired comparison of the diagnostic value of 19 different imaging methods for the treatment of BC. The results revealed

Fig. 1. Flow chart showing literature search and study selection with 39 relevant studies ultimately enrolled in our network meta-analysis.

Table 1. Baseline characteristics of included studies. Note: M = method; NR = not reported; A = mammography; B = breast-specific gamma imaging; C = Color Doppler sonography; D = contrast-enhanced magnetic resonance imaging; E = digital breast tomosynthesis; F = fluorodeoxyglucose positron-emission tomography/computed tomography; G = fluorodeoxyglucose positron-emission tomography; H = full field digital mammography; I = handheld breast ultrasound; J = magnetic resonance imaging; K = automated breast volume scanner; L = magnetic resonance mammography; M = scintimammography; N = single photon emission computed tomography scintimammography; O = ultrasound elastography; P = ultrasonography; Q = mammography+ultrasonography; R = mammography + scintimammography; S = ultrasound elastography + ultrasonography; a and b are different articles written by Kim BS in 2012

Author	Year	Country	Standard method	Patient numbers	Age	Diagnostic modalities			
						M1	M2	M3	M4
Palmedo H [71]	1996	Germany	biopsy	56	58(22-81)	M	A	J	-
Bone B [70]	1997	Sweden	biopsy	238	52(23-83)	A	J	-	-
Helbich TH [69]	1997	Austria	biopsy	75	47(19-85)	J	N	-	-
Bloher JU [68]	1999	Germany	biopsy	168	NR	C	A	P	J
Alamo L [67]	2001	Germany	cytology	40	47(32-52)	C	D	-	-
Lumachi F [66]	2001	Italy	biopsy	87	48(26-79)	A	M	R	-
Malich A [65]	2001	Germany	biopsy	100	NR	P	L	-	-
Kolb TM [64]	2002	USA	biopsy	27825	59.6(44-75)	A	P	-	-
Bagni B [63]	2003	Italy	biopsy	45	51(32-85)	M	J	-	-
Bone B [62]	2003	Sweden	histopathology	111	54(33-81)	A	M	D	M
Chen DR [61]	2003	China	biopsy	32	44.6(29-62)	N	P	-	-
Goerres GW [60]	2003	Switzerland	Cytology or histology	40	57.2(32-76)	G	J	-	-
Heinisch M [59]	2003	Australia	histopathology	473	48.4(25-77)	G	D	-	-
Houssami N [58]	2003	Austria	biopsy	258	40(22-55)	P	A	-	-
Berg WA [57]	2004	USA	biopsy	33	48.7(26-81)	A	P	Q	J
Brem RF [56]	2007	USA	biopsy	296	53(33-70)	B	J	-	-
Zhi H [55]	2007	China	biopsy or fine-needle aspiration cytology	97	42(17-87)	A	P	O	S
Pediconi F [54]	2009	Italy	histopathology	78	47.5(16-77)	J	A	P	-
Vassiou K [53]	2009	Greece	biopsy	251	53(39-68)	A	P	L	Q
Benndorf M [52]	2010	Germany	biopsy	97	54.4(42-66)	A	J	-	-
Hatzung G [51]	2010	Germany	biopsy	110	54.8(21-92)	P	A	O	S
Leong LC [50]	2010	Singapore	biopsy	90	46.7(18-74)	P	O	S	-
Moy L [49]	2010	USA	biopsy	242	43(24-65)	J	F	-	-
Liew PL [48]	2011	China	fine-needle aspiration cytology	351	46.2(12-87)	A	P	-	-
Spangler ML [47]	2011	USA	biopsy	299	NR	H	E	-	-
Svane G [46]	2011	Sweden	histopathology	144	56.8(40-85)	A	E	-	-
Kim BS-a [45]	2012	Korea	biopsy	97.059	44.1(36-52)	B	J	-	-
Kim BS-b [44]	2012	Korea	biopsy	228	45.0(37-53)	B	A	P	-
Michell MJ [43]	2012	UK	biopsy	759	NR	H	E	-	-
Svahn TM [42]	2012	USA	biopsy	191	60(42-79)	E	A	-	-
Golatta M [41]	2013	Germany	biopsy	51	51(33-83)	K	I	A	-
Shao H [40]	2013	China	pathological report	90	53.2(26-85)	A	J	P	-
Thibault F [39]	2013	France	biopsy	131	61(40-90)	E	H	-	-
Choi WJ [38]	2014	Korea	biopsy	3700	47(19-82)	K	I	-	-
Grigoryev M [37]	2014	Germany	biopsy	105	51	P	A	-	-
Chou CP [36]	2015	China	biopsy	59	53.3(40-64)	J	F	P	-
Kim SA [35]	2015	Korea	biopsy	118.643	49.6(29-78)	E	P	-	-
Magometschnigg HF [34]	2015	Germany	biopsy	172	57(18-87)	F	D	-	-
Moon HJ [33]	2015	Korea	biopsy	4394	53.8(40-87)	A	P	-	-

that compared with the MG method, the BSGI method exhibited higher sensitivity and NPV, as well as lower accuracy, whereas the MRI method exhibited higher sensitivity, NPV and accuracy; the sensitivity and NPV of the UE + US and MRM methods were relatively higher; the SMM method presented relatively higher specificity, PPV and accuracy; and the US method exhibited lower specificity, PPV and accuracy and higher sensitivity. The results also demonstrated that the MG + US method exhibited higher specificity and PPV and lower sensitivity and NPV, whereas the MG + SMM method exhibited higher sensitivity and NPV (Table 2).

Evidence network of 19 imaging methods for BC

This study includes 19 imaging methods: A = mammography; B = breast-specific gamma imaging; C = color Doppler sonography; D = contrast-enhanced magnetic resonance imaging; E = digital breast tomosynthesis; F = fluorodeoxyglucose positron-emission tomography/computed tomography; G = fluorodeoxyglucose positron-emission tomography; H = full field digital mammography; I = handheld breast ultrasound; J = magnetic resonance

Table 2. Estimated OR and 95% CI of pairwise meta-analysis for sensitivity, specificity, PPV, NPV and accuracy for breast cancer. Note: NA = not available; A = mammography; B = breast-specific gamma imaging; C = Color Doppler sonography; D = contrast-enhanced magnetic resonance imaging; E = digital breast tomosynthesis; F = fluorodeoxyglucose positron-emission tomography/computed tomography; G = fluorodeoxyglucose positron-emission tomography; H = full field digital mammography; I = handheld breast ultrasound; J = magnetic resonance imaging; K = automated breast volume scanner; L = magnetic resonance mammography; M = scintimammography; N = single photon emission computed tomography scintimammography; O = ultrasound elastography; P = ultrasonography; Q = mammography+ultrasonography; R = mammography + scintimammography; S = ultrasound elastography + ultrasonography; OR = Odds ratios; 95% CI = 95% confidence intervals; PPV = positive predictive value; NPV = negative predictive value. The terms with lines represent statistical differences. If 95% confidence interval does not contain 1, there are statistical differences

imaging; K = automated breast volume scanner; L = magnetic resonance mammography; M = scintimammography; N = single photon emission computed tomography scintimammography; O = ultrasound elastography; P = ultrasonography; Q = mammography + ultrasonography; R = mammography + scintimammography; and S = ultrasound elastography + ultrasonography. According to Fig. 3, it is revealed that the MG and US methods diagnosed the highest number of BC patients and have relatively more studies in terms of sensitivity, specificity, PPV, NPV and accuracy.

Inconsistency tests of the sensitivity, specificity, PPV, NPV and accuracy of 19 imaging methods for BC

The sensitivity, specificity, PPV, NPV and accuracy of the included imaging methods were analyzed using inconsistency tests employing the node-splitting method, and the results indicated consistency among the direct and indirect evidence of all outcomes, and therefore, the consistency model was adopted in this study (all $P > 0.05$) (Table 3 and 4).

Main results of network meta-analysis of the diagnostic value of 19 imaging methods for BC

The results of this network meta-analysis revealed that the sensitivity and NPV of the CE-MRI, MRM and MG + SMM methods were relatively higher compared with the MG

Included study	Comparison	Heterogeneity test		Pairwise meta-analysis		
		I ²	P _h	OR (95% CI)	Z	P
Sensitivity						
3 studies	M vs. A	0.0%	0.919	0.89 (0.51, 1.54)	0.42	0.673
7 studies	J vs. A	64.3%	0.01	4.00 (2.72, 5.89)	7.04	0.000
1 study	C vs. A	NA	NA	0.79 (0.33, 1.86)	0.55	0.585
13 studies	P vs. A	75.3%	0.000	1.84 (1.52, 2.23)	6.30	0.000
2 studies	R vs. A	0.00%	0.592	3.28 (1.48, 7.26)	2.93	0.003
1 study	D vs. A	NA	NA	2.65 (0.89, 7.92)	1.75	0.081
2 studies	Q vs. A	69.0%	0.073	3.97 (2.34, 6.74)	5.10	0.000
2 studies	O vs. A	0.0%	0.367	0.77 (0.43, 1.37)	0.88	0.380
2 studies	S vs. A	0.0%	0.371	3.89 (1.76, 8.58)	3.36	0.001
1 study	L vs. A	NA	NA	10.64 (1.30, 87.26)	2.20	0.028
2 studies	E vs. A	70.2%	0.067	1.46 (0.76, 2.78)	1.14	0.255
1 study	B vs. A	NA	NA	10.17 (5.21, 19.87)	6.79	0.000
1 study	K vs. A	NA	NA	0.45 (0.10, 1.98)	1.06	0.289
1 study	I vs. A	NA	NA	7.71 (0.38, 155.64)	1.33	0.183
Specificity						
3 studies	M vs. A	56.6%	0.100	4.72 (2.24, 9.92)	4.09	0.000
7 studies	J vs. A	90.0%	0.000	0.91 (0.67, 1.22)	0.65	0.514
1 study	C vs. A	NA	NA	0.88 (0.43, 1.84)	0.33	0.743
13 studies	P vs. A	85.5%	0.000	0.35 (0.32, 0.39)	22.57	0.000
2 studies	R vs. A	84.0%	0.012	0.84 (0.37, 1.91)	0.42	0.676
1 study	D vs. A	NA	NA	0.60 (0.22, 1.62)	1.00	0.318
2 studies	Q vs. A	92.4%	0.000	0.22 (0.12, 0.38)	5.25	0.000
2 studies	O vs. A	96.7%	0.000	0.76 (0.47, 1.23)	1.10	0.270
2 studies	S vs. A	97.4%	0.000	0.64 (0.40, 1.01)	1.90	0.058
1 study	L vs. A	NA	NA	1.18 (0.38, 3.63)	0.29	0.775
2 studies	E vs. A	0.0%	0.616	0.89 (0.55, 1.43)	0.49	0.624
1 study	B vs. A	NA	NA	0.47 (0.14, 1.64)	1.18	0.237
1 study	K vs. A	NA	NA	2.98 (0.79, 11.25)	1.61	0.107
1 study	I vs. A	NA	NA	0.49 (0.13, 1.93)	1.02	0.308
PPV						
3 studies	M vs. A	0.0%	0.508	2.23 (1.19, 4.16)	2.51	0.012
7 studies	J vs. A	78.1%	0.000	1.17 (0.89, 1.53)	1.09	0.274
1 study	C vs. A	NA	NA	0.77 (0.37, 1.59)	0.71	0.476
13 studies	P vs. A	69.2%	0.000	0.63 (0.53, 0.74)	5.39	0.000
2 studies	R vs. A	74.7%	0.047	1.06 (0.54, 2.08)	0.16	0.874
1 study	D vs. A	NA	NA	0.84 (0.38, 1.87)	0.42	0.677
2 studies	Q vs. A	71.9%	0.059	0.58 (0.37, 0.91)	2.37	0.018
2 studies	O vs. A	94.5%	0.000	0.89 (0.52, 1.54)	0.41	0.684
2 studies	S vs. A	95.1%	0.000	1.05 (0.62, 1.78)	0.16	0.869
1 study	L vs. A	NA	NA	1.27 (0.55, 2.91)	0.56	0.578
2 studies	E vs. A	0.0%	0.824	1.14 (0.73, 1.79)	0.58	0.564
1 study	B vs. A	NA	NA	0.86 (0.25, 2.94)	0.24	0.810
1 study	K vs. A	NA	NA	1.64 (0.53, 5.07)	0.86	0.387
1 study	I vs. A	NA	NA	0.87 (0.34, 2.21)	0.30	0.765
NPV						
3 studies	M vs. A	0.0%	0.530	1.45 (0.73, 2.86)	1.06	0.288
7 studies	J vs. A	54.8%	0.039	2.54 (1.68, 3.86)	4.39	0.000
1 study	C vs. A	NA	NA	0.91 (0.38, 2.15)	0.22	0.826
13 studies	P vs. A	56.8%	0.006	1.13 (0.93, 1.39)	1.22	0.223
2 studies	R vs. A	43.5%	0.183	2.72 (1.08, 6.84)	2.13	0.033
1 study	D vs. A	NA	NA	1.89 (0.55, 6.57)	1.01	0.314
2 studies	Q vs. A	0.0%	0.674	1.28 (0.66, 2.50)	0.74	0.461
2 studies	O vs. A	69.5%	0.070	0.79 (0.47, 1.33)	0.89	0.372
2 studies	S vs. A	0.0%	0.758	3.07 (1.43, 6.58)	2.88	0.004
1 study	L vs. A	NA	NA	9.90 (1.06, 92.66)	2.01	0.045
2 studies	E vs. A	53.9%	0.141	1.35 (0.69, 2.63)	0.88	0.381
1 study	B vs. A	NA	NA	5.58 (2.78, 11.21)	4.84	0.000
1 study	K vs. A	NA	NA	0.81 (0.16, 4.20)	0.25	0.804
1 study	I vs. A	NA	NA	4.53 (0.19, 105.84)	0.94	0.347
Accuracy						
3 studies	M vs. A	39.9%	0.189	1.62 (1.07, 2.45)	2.28	0.022
7 studies	J vs. A	80.8%	0.000	1.64 (1.32, 2.04)	4.42	0.000
1 study	C vs. A	NA	NA	0.83 (0.48, 1.45)	0.65	0.513
13 studies	P vs. A	94.6%	0.000	0.49 (0.46, 0.53)	17.42	0.000
2 studies	R vs. A	85.1%	0.010	1.65 (0.99, 2.75)	1.91	0.056
1 study	D vs. A	NA	NA	1.18 (0.62, 2.24)	0.49	0.622
2 studies	Q vs. A	0.0%	0.531	1.06 (0.76, 1.48)	0.34	0.735
2 studies	O vs. A	95.9%	0.000	0.77 (0.54, 1.11)	1.38	0.167
2 studies	S vs. A	97.2%	0.000	1.08 (0.74, 1.58)	0.39	0.698
1 study	L vs. A	NA	NA	1.87 (0.89, 3.91)	1.65	0.099
2 studies	E vs. A	51.1%	0.153	1.05 (0.73, 1.52)	0.28	0.778
1 study	B vs. A	NA	NA	0.20 (0.11, 0.34)	5.96	0.000
1 study	K vs. A	NA	NA	1.23 (0.50, 3.00)	0.45	0.650
1 study	I vs. A	NA	NA	1.00 (0.42, 2.39)	0.00	1.000

Fig. 2. Evaluation of quality assessment of diagnostic accuracy studies (QUADAS) of included studies. Note: Thirty-nine diagnostic tests were analyzed in this network meta-analysis.

Fig. 3. Evidence network plot of diagnostic value of nineteen imaging methods for BC. Note: A = mammography (MG); B = breast-specific gamma imaging (BSGI); C = color Doppler sonography (CD); D = contrast-enhanced magnetic resonance imaging (CE-MRI); E = digital breast tomosynthesis (DBT); F = fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT); G = fluorodeoxyglucose positron-emission tomography (FDG-PET); H = full field digital mammography (FFDM); I = handheld breast ultrasound (HHUS); J = magnetic resonance imaging (MRI); K = automated breast volume scanner (ABUS); L = magnetic resonance mammography (MRM); M = scintimammography (SMM); N = single photon emission computed tomography scintimammography (SPECT SMM); O = ultrasound elastography (UE); P = ultrasonography (US); Q = mammography + ultrasonography (MG + US); R = mammography + scintimammography (MG + SMM); S = ultrasound elastography + ultrasonography (UE + US); and BC = breast cancer.

Table 3. P values of direct and indirect pairwise comparisons among nineteen diagnostic modalities under five outcome indicators. Note: PPV = positive predictive value; NPV = negative predictive value

Pairwise comparisons	P values														
	B vs. A	C vs. A	D vs. A	E vs. A	J vs. A	L vs. A	M vs. A	O vs. A	P vs. A	S vs. A	J vs. B	P vs. B	D vs. C	J vs. C	F vs. D
Sensitivity	0.16	0.068	0.11	0.71	0.62	0.69	0.46	0.11	0.076	0.12	0.45	0.97	0.082	0.051	0.099
Specificity	0.20	0.35	0.68	0.75	0.32	0.30	0.81	0.85	0.53	0.65	0.34	0.62	0.32	0.48	0.068
PPV	0.15	0.16	0.60	0.82	0.38	0.50	0.95	0.46	0.71	0.54	0.38	0.75	0.14	0.22	0.082
NPV	0.80	0.10	0.08	0.45	0.63	0.87	0.51	0.06	0.77	0.23	0.97	0.70	0.13	0.05	0.079
Accuracy	0.51	0.32	0.93	0.89	0.45	0.93	0.94	0.14	0.78	0.31	0.28	0.18	0.30	0.59	0.76

Table 4. P values of direct and indirect pairwise comparisons among nineteen diagnostic modalities under five outcome indicators. Note: PPV = positive predictive value; NPV = negative predictive value

Pairwise comparisons	P values												
	G vs. D	M vs. D	R vs. D	P vs. E	J vs. F	P vs. F	J vs. G	M vs. J	N vs. J	P vs. J	Q vs. J	Q vs. L	P vs. N
Sensitivity	0.11	0.12	0.14	0.69	0.18	0.16	0.11	0.68	0.65	0.35	0.91	0.99	0.66
Specificity	0.32	0.97	0.50	0.75	0.06	0.068	0.333	0.98	0.46	0.73	0.63	0.68	0.44
PPV	0.42	0.96	0.40	0.81	0.06	0.054	0.42	0.98	0.32	0.76	0.52	0.74	0.33
NPV	0.05	0.06	0.05	0.44	0.13	0.47	0.07	0.37	0.52	0.63	0.60	0.87	0.50
Accuracy	0.51	0.65	0.18	0.88	0.77	0.81	0.51	0.36	0.51	0.61	0.63	0.88	0.53

method. In addition, the sensitivity, NPV and accuracy of the MRI method were relatively higher compared to the MG method. The BSGI method exhibited relatively higher PPV and accuracy, the FDG PET/CT method exhibited higher specificity and PPV, and the sensitivity of UE + US method ranked higher compared to the MG method (Fig. 4 and see online suppl. material, Suppl. Tables 1-5).

SUCRA values of the diagnostic value of 19 imaging methods for BC

As shown in Table 5, the SUCRA values of the diagnostic value of 19 imaging methods for BC indicated that the MRM method ranked the highest in terms of sensitivity and NPV

Table 5. SUCRA values of nineteen diagnostic modalities under five outcome indicators. Note: SUCRA = surface under the cumulative ranking curves; A = mammography; B = breast-specific gamma imaging; C = Color Doppler sonography; D = contrast-enhanced magnetic resonance imaging; E = digital breast tomosynthesis; F = fluorodeoxyglucose positron-emission tomography/computed tomography; G = fluorodeoxyglucose positron-emission tomography; H = full field digital mammography; I = handheld breast ultrasound; J = magnetic resonance imaging; K = automated breast volume scanner; L = magnetic resonance mammography; M = scintimammography; N = single photon emission computed tomography scintimammography; O = ultrasound elastography; P = ultrasonography; Q = mammography + ultrasonography; R = mammography + scintimammography; S = ultrasound elastography + ultrasonography; PPV = positive predictive value; NPV = negative predictive value. The Figures with underlines represent the largest SUCRA values.

Treatment	SUCRA value				
	Sensitivity	Specificity	PPV	NPV	Accuracy
A	0.3030	0.5132	0.4153	0.2726	0.3705
B	0.6620	0.7763	0.8379	0.6937	<u>0.9742</u>
C	0.2670	0.6153	0.5268	0.2716	0.4721
D	0.8830	0.5842	0.5789	0.8721	0.5479
E	0.3670	0.4847	0.4642	0.4837	0.4463
F	0.1160	<u>0.9437</u>	<u>0.9495</u>	0.1911	0.4600
G	0.7800	0.3584	0.3158	0.7758	0.3463
H	0.3160	0.4432	0.4211	0.3832	0.3858
I	0.5560	0.4821	0.3805	0.5216	0.4063
J	0.7470	0.4742	0.5753	0.7632	0.7084
K	0.3180	0.5958	0.6221	0.3947	0.5432
L	<u>0.9520</u>	0.2095	0.2800	<u>0.9011</u>	0.6179
M	0.3950	0.8326	0.8079	0.5811	0.6726
N	0.3680	0.6384	0.6242	0.4368	0.6132
O	0.3390	0.4458	0.4553	0.2816	0.3800
P	0.4710	0.2868	0.3026	0.3537	0.3158
Q	0.6370	0.2511	0.2784	0.4284	0.4426
R	0.7580	0.6353	0.6295	0.7505	0.7658
S	0.7040	0.4221	0.5142	0.6200	0.5126

Fig. 4. Forest plots of diagnostic value of nineteen imaging methods for BC. Note: A = mammography (MG); B = breast-specific gamma imaging (BSGI); C = color Doppler sonography (CD); D = contrast-enhanced magnetic resonance imaging (CE-MRI); E = digital breast tomosynthesis (DBT); F = fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT); G = fluorodeoxyglucose positron-emission tomography (FDG-PET); H = full field digital mammography (FFDM); I = handheld breast ultrasound (HHUS); J = magnetic resonance imaging (MRI); K = automated breast volume scanner (ABUS); L = magnetic resonance mammography (MRM); M = scintimammography (SMM); N = single photon emission computed tomography scintimammography (SPECT SMM); O = ultrasound elastography (UE); P = ultrasonography (US); Q = mammography + ultrasonography (MG + US); R = mammography + scintimammography (MG + SMM); S = ultrasound elastography + ultrasonography (UE + US); and BC = breast cancer.

(sensitivity: 95.2%; NPV: 90.1%), while the FDG PET/CT method exhibited the highest sensitivity and PPV (specificity: 94.37%; PPV: 94.95%), and the BSGI method exhibited the highest accuracy among all 19 imaging methods (97.42%).

Fig. 5. Cluster ranking plots based on SUCRA values of sensitivity, specificity and accuracy of nineteen imaging methods for BC. Note: A = mammography (MG); B = breast-specific gamma imaging (BSGI); C = Color Doppler sonography (CD); D = contrast-enhanced magnetic resonance imaging (CE-MRI); E = digital breast tomosynthesis (DBT); F = fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT); G = fluorodeoxyglucose positron-emission tomography (FDG-PET); H = full field digital mammography (FFDM); I = handheld breast ultrasound (HHUS); J = magnetic resonance imaging (MRI); K = automated breast volume scanner (ABUS); L = magnetic resonance mammography (MRM); M = scintimammography (SMM); N = single photon emission computed tomography scintimammography (SPECT SMM); O = ultrasound elastography (UE); P = ultrasonography (US); Q = mammography + ultrasonography (MG + US); R = mammography + scintimammography (MG + SMM); S = ultrasound elastography + ultrasonography (UE + US); BC = breast cancer; and SUCRA = surface under the cumulative ranking.

Fig. 6. Comparison-adjusted funnel plot for diagnostic value of nineteen imaging methods for BC. Note: the red line shows the null hypothesis that the study-specific effect sizes are not distinct from the respective comparison-specific pooled effect estimates; distinct colors suggest distinct comparisons; net funnel adds linear regression line including the study effect sizes centered at the comparison-specific summary effect ($y_{IXY} - \mu_{XY}$); y_{IXY} means effect value of a single study, and μ_{XY} means mean effect value of all studies relative to the control group; A = mammography (MG); B = breast-specific gamma imaging (BSGI); C = Color Doppler sonography (CD); D = contrast-enhanced magnetic resonance imaging (CE-MRI); E = digital breast tomosynthesis (DBT); F = fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT); G = fluorodeoxyglucose positron-emission tomography (FDG-PET); H = full field digital mammography (FFDM); I = handheld breast ultrasound (HHUS); J = magnetic resonance imaging (MRI); K = automated breast volume scanner (ABUS); L = magnetic resonance mammography (MRM); M = scintimammography (SMM); N = single photon emission computed tomography scintimammography (SPECT SMM); O = ultrasound elastography (UE); P = ultrasonography (US); Q = mammography + ultrasonography (MG + US); R = mammography + scintimammography (MG + SMM); S = ultrasound elastography + ultrasonography (UE + US); BC = breast cancer.

Cluster analysis of the diagnostic value of 19 imaging methods for BC

The cluster analysis based on SUCRA values revealed that the BSGI, MG + SMM, MRI and CE-MRI methods showed the greatest diagnostic value in BC detection, with reference to sensitivity, specificity and accuracy (Fig. 5).

Assessment of publication bias of the diagnostic value of 19 imaging methods for BC

The results of assessment of publication bias showed symmetrical distribution, indicating no small sample effect or publication bias in this network meta-analysis (Fig. 6).

Discussion

BC is the leading cancer among women worldwide. Early detection of BC plays a critical role in improving the quality of life and survival of patients suffering from BC [72]. Women presenting with symptoms or palpable findings during clinical examinations are usually investigated with breast imaging, which generally consists of the MG method, breast sonography, or both [56]. A study found that consecutive patients could reduce the selection bias [73]. This study performed an NMA with consecutive patients and found that the diagnostic value of the BSGI, MG + SMM, MRI and CE-MRI methods for BC was relatively higher in terms of sensitivity, specificity and accuracy.

This NMA showed that compared with the MG method, the CE-MRI, MRI, MRM, MG + SMM and UE + US methods were relatively more sensitive; the FDG PET/CT method exhibited higher specificity; and the BSGI and MRI methods were more accurate. A meta-analysis of diagnostic tests serves as a useful way to summarize findings by analyzing different studies, and a previously conducted meta-analysis comparing the diagnostic value of FDG-PET, MRI, and bone scintigraphy (BS) in the detection of bone metastases of BC found that MRI was a superior imaging method in comparison to FDG-PET and BS [74]. Biopsy is a common method in diagnosis of BC [75-77], which is consistent with our findings (Table 1). In addition, another study found that vacuum-assisted breast biopsy had high levels of diagnostic accuracy and sensitivity when evaluating mammographically detected breast by performing a meta-analysis [78]. A screening MG was used to examine the breasts of an asymptomatic woman, while a diagnostic MG was performed in a patient presenting with signs or symptoms of breast disease: a possible abnormality detected on screening MG or other imaging, or prior MG findings requiring imaging follow up [79]. The factors implicated in missing identification of cancers include technique sensitivity, distracting lesions, tumor growth rate, tumor growth pattern and the background upon which the tumor is displayed. The background in the MG method consists of normal dense breast structures superimposed onto a two-dimensional (2D) plane, comprising a so-called "anatomic background", which plays a larger role than quantum noise in the non-detection of certain lesion types and sizes [80]. The sensitivity of the MG method is limited in dense breast tissue, due to the presence of overlapping fibroglandular tissue, which reduces the conspicuousness of abnormalities [81]. Tumor growth pattern is an additional factor influencing cancer visibility in breast tissues. Tumors that do not produce a mass are often difficult to detect using the MG method [80].

The results of cluster analysis indicated that the BSGI, MG + SMM, MRI and CE-MRI methods showed the greatest diagnostic value in BC detection, in terms of sensitivity, specificity and accuracy. Compared with MG method, the BSGI method was comparatively more sensitive but at the cost of accuracy; the MRI method exhibited higher sensitivity and accuracy; the UE + US and MRM methods were more sensitive; the SMM method exhibited relatively higher specificity and accuracy; the US method exhibited lower specificity and accuracy but higher sensitivity; the MG + US method exhibited higher specificity and lower sensitivity; and the NPVMG + SMM method had higher sensitivity. Although, the combination of MG, clinical examination, and MRI methods was more sensitive than any other individual or combination tests, the sensitivity of the MG method ranges from 30% to 98% and has been reported to be as low as 30%-48% in the cases of dense breasts [57]. Along with

MG and ultrasound, MRI is the gold standard in diagnosing breast imaging; however, it is a complicated and expensive procedure with relatively low specificity, which leads to high false-positive rates [82]. The BSGI method has an equally high sensitivity, but it is more specific and much easier to interpret, therefore exhibiting great potential to indicate or exclude the extent of BC [83]. Moreover, according to a recent meta-analysis, MRI significantly boosted mastectomy rates and was suggested to play an unfavorable harm-benefit ratio for routine use of MRI preoperation in BC patients [84]. When comparing SMM and MG, the SMM method exhibited better diagnostic accuracy in the detection of recurrence of BC [85]. SMM is often considered to be a supplementary tool in the preoperative work of BC patients, and the high negative predictive value of SMM adds to its ability in the aspect of decreasing the amount of unnecessary surgical interventions or negative breast biopsies [86]. The CE-MRI method is conducive to predicting the efficiency of neoadjuvant chemotherapy in BC and was, therefore, endowed with the potential to supply functional parameters that can be integrated to optimize the strategies for neoadjuvant chemotherapy [87]. Comparing the results of the SMM, MG and MRI methods, all three methods exhibited high sensitivity for the detection of palpable BC, but the SMM method presented with a significantly higher specificity in comparison to the MG and MRI methods [71].

This study could not offer enough direct comparisons of individual imaging method due to limited references and data, and the vast majority of the studies were of low quality, but we comprehensively compared the different diagnostic value and limitations of 19 imaging methods for BC. Additionally, the Chinese literature was not retrieved because of failure to conform to the QUADAS-2 quality standard, which might affect the final results of this network meta-analysis to some extent. In conclusion, the BSGI, MG + SMM, MRI and CE-MRI methods exhibited a higher diagnostic value for BC, which provides evidence toward the further development of the diagnosis of BC to improve the survival of patients suffering from BC.

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