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Should MRI replace mammography as the initial screening modality for asymptomatic women aged 18 – 45 years at high risk of developing breast cancer? A systematic review

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ABSTRACT

Background: Breast cancer occurs in both men and women, although it is more prevalent among women. Mammography is generally the diagnostic imaging modality of choice, but it is limited in the detection of breast cancer in young women, aged 18-45 years due to the dense nature of their breast tissue. **Aims and Objectives:** This review explores whether MRI should replace mammography as the initial screening modality for asymptomatic women, aged 18-45 years at high risk of developing breast cancer. **Materials and Methods:** A systematic review of the literature was undertaken. A search of Medline, Pubmed central, Cinahl and Google scholar for English language literature from 2004 to 2015 was undertaken. Also a review of reference lists, author searching and review of NICE evidence base for exiting guidelines was done. Included studies were assessed for bias using STARD quality assessment tool and data were extracted systematically using a purposefully designed data extraction form. **Result:** From the seven included studies, 179 participants of the total population had breast cancer and a total of 199 breast cancer was detected by both modality used. MRI detected a total 148 breast cancers compared to 78 detected by mammography, and 10 interval cancer was reported. Sensitivity estimate from the included studies ranged from 25% to 100% while specificity ranged from 79% to 99%. MRI detected more breast cancer but had a moderate specificity compared to mammography as reported in the literature. **Conclusion:** In the absence of contraindication and accessibility, MRI should be used as the initial screening modality for asymptomatic women aged 18 – 45 years, at high risk of developing breast cancer.

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INTRODUCTION

Breast cancer in asymptomatic women aged 18 to 45 years who are predisposed to the gene mutation (Breast cancer 1(BRCA1) and Breast cancer 2 (BRCA2)) or with a strong family history of breast cancer are often given less attention.[1] In 2012, out of the 14.1 million new cases of cancer diagnosed in the world, 1.7 million were due to breast cancer in women, which represent an incidence rate of 25% of all cancers in women.[2] It is however noted that breast cancer susceptibility gene (BRCA1 and BRCA2) may be responsible for 5 - 10% of all breast cancer cases in the general population.[3] And the carriers of this susceptibility gene, faces a lifetime risk of 60% to 80% of developing the disease.[4,5]

In asymptomatic women aged 18 to 45 years at high risk of developing breast cancer, mutational test is

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usually recommended for them. The test is performed by mutation screening to identify the gene (BRCA1 and BRCA2). The mutational screening processes involve a combination of proteins-truncation test and heteroduplex analysis, supplemented with linkage analysis of BRCA1 and BRCA2 alleles.[6] BRCA1 and BRCA2 mutation accounts for 20% to 25% of hereditary breast cancer[7] and in young asymptomatic women aged 18 to 45 years at high risk, BRCA1 and BRCA2 are held responsible for the development of the breast cancer and often both breasts are affected by the disease.[8] Breast cancer at advanced stage in asymptomatic women aged 18 to 45 years are usually of the aggressive subtype with adverse pathological factors, which may include high grade tumours, lymphovascular invasion, hormone receptor negativity, and HER2 overexpression.[9,10] These are usually classified as HER2-positive breast cancer (those that test positive to the protein - Human Epidermal growth factor Receptor 2 (HER2)). It becomes imperative to detect this cancer at an early age in these women and also in older women for effective management of the disease. Over the years Mammography has been used in the screening of breast cancer and in the reduction of breast cancer mortality in postmenopausal women by about 20% to 35%.[11] It was reported to have a sensitivity of about 36% - 46% and specificity of 93% - 99.8%.[12-16] But has a known limitation in the detection of breast cancer in younger women aged 18 to 45 years, due to the dense nature of their breast tissues, leading to increased mammographic densities which obscure radiologic features of early breast cancer.[17] More so germ line mutation gene (BRCA1 and BRCA2) which are associated with breast cancer in young high risk women have benign appearance on mammography, especially BRCA1.[17] In this group of women, mammography is reported to have a sensitivity of about 25% and specificity of 96.8%.[15] However, approximately 6.6% of all breast cancer cases are diagnosed in women younger than 40 years, while 2.4% of these are diagnosed in women less than 35 years and 0.65% in women less than 30 years.[10]

The impact of this limitation was reduced by the introduction of adjunct screening modalities such as high-frequency breast Ultrasound, Clinical breast examination (CBE), and Magnetic resonance imaging (MRI). Currently, annual clinical breast examination, Surgery, Radiation therapy and mammography (beginning at age 40), are used in the management of women at high risk of developing breast cancer.

This review is set to explore whether Magnetic Resonance Imaging (MRI) should replace mammography as the initial screening modality for asymptomatic women, aged 18-45 years at high risk of developing breast cancer.

MATERIALS AND METHODS

A search of Medline, PubMed Central (PMC), and Cinahl databases and Google scholar was undertaken supplemented by hand searching of some imaging journals (Synergy and British journal of Radiology; Radiography), review of the National Institute for Health & Care Excellence (NICE) evidence base for existing guidelines. Also review of reference lists, author searching was undertaken. Citations were identified using the Medical Subject Heading terms (MeSH) and key search terms and their alternatives: Breast cancer (Asymptomatic; BRCA1; BRCA2), Magnetic Resonance Imaging (MRI; MR; Nuclear Magnetic Resonance (NMR)); Mammography (Mammo). The search was limited to primary research studies published in English from 2004 to July 2015, in order to take advantage of recent technological advancement in MRI. After the identification of potential relevant research studies, the title, abstracts and when necessary the full text of the yielded search result, were screened to determine whether they met the inclusion/exclusion, which was derived from the primary research question "Should MRI replace mammography as the initial screening modality for asymptomatic women aged 18-45 years at high risk of developing breast cancer?" and are listed in Table 1. The rule out principle was employed in the selection of included primary research papers and where the reviewer was certain that a paper lack the necessary information, they were rejected. However at each stage where the reviewer was uncertain, whether a paper should be included, the paper was retained. All retained paper was re-examined to make final decision on inclusion/exclusion.

The included papers were assessed for quality using the Standards for Reporting of Diagnostic Accuracy (STARD),[18,26] by at least 2 authors and data were extracted into Microsoft Excel[27] spread sheet for consistency using a purposefully designed data extraction form. However paper's with uncertainty in quality was resolved through discussion and consensus was reached. The STARD[26] assessment checklist was used to document the paper quality (Table 2). Each article were then rated to determine the overall quality, using Good, Fair or Poor rating scale. From the summary, each study had a Yes (Y) to No (N) score of 19/25, 23/25, 24/25, 19/25, 22/25 + 1 unclear, 21/25, 19/25 + 2 unclear, respectively. Four studies had an overall quality rating of 'Good' and three had a 'Fair' overall rating. This implies that a thorough methodology was used and common bias of diagnostic accuracy studies was low. However none of the included studies was ratted poor. A final value of award was given to each paper, where 'High' was given to a study with low risk of bias, 'Average' was given to studies with an unclear risk of bias and 'low'

Table 1: Inclusion/exclusion criteria

Question component	Inclusion criteria	Exclusion criteria
Population	• Asymptomatic women 18-45 years at high risk of developing breast cancer	• Studies involving symptomatic women and studies involving young women where data could not be clearly evaluated
Index test	• MRI	• Studies not involving MRI or where MRI data cannot be evaluated independently
Comparator test	• Mammography	• Other imaging modality
Outcome measures	• Sensitivity and Specificity • Diagnostic accuracy • Type of cancer detected.	• -
Study design	• Prospective studies	• Studies without comparison between Mammography and MRI • Retrospective studies
Reference Standard	• Histopathology • Biopsy	• -

was given to studies with a high risk of bias in the final evaluation (Table 3).

The data extracted was compared and data analysis was done by descriptive synthesis.[24] A Meta-analysis was inappropriate due to the variations in the extracted data, technical parameters, methods of determining diagnostic accuracy and clinical characteristic.

RESULTS

Figure 1 shows a flow chart diagram, detailing the review process. The detail of the included studies and quality assessment awarded are summarized in Table 3. Tables 4 and 5 holds the details of the index test characteristics and extracted outcome measures.

Sensitivity estimates

All the included studies, used biopsy and positive test (Histopathology) as the reference standard. Sensitivity across the included studies ranged from 71% to 100%. In two studies (Leach et al.[14] (2005) and Hagen et al.[19] (2007)), different volume of Gadolinium contrast was administered. Leach et al.[14] (2005) administered intravenously 0.1 mmol/kg and 0.2 mmol/kg bodyweight while Hagen et al.[19] (2007) administered intravenously 0.1 mmol/kg and 20ml. They reported a sensitivity of 77% and 86% respectively, which was lower than that reported by Lehman et al.[22] (2005) and Kuhl et al.[15] (2005) who administered consistently 0.1 mmol/kg bodyweight.

Specificity estimates

Specificity across the included studies ranged from 79% to 97%. The study by (Leach et al.[14] (2005)) reported a specificity of 81% but there was no record of specificity reported by Hagen et al.[19] (2007). The study by Weinstein et al.[21] (2009) reported the lowest specificity at 79% with all other studies reporting a sensitivity of 90% and higher.

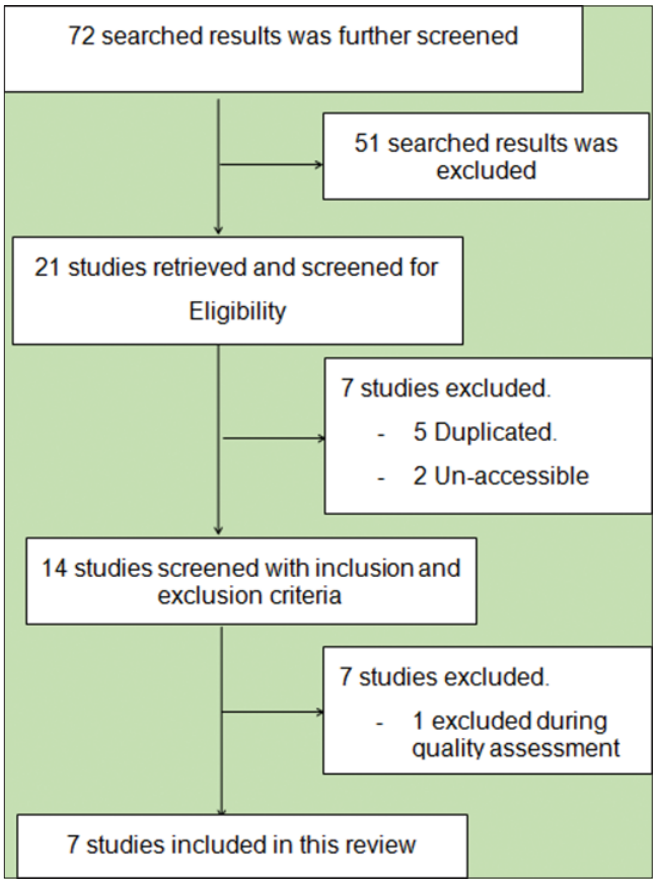

Figure 1: Flow diagram outline the screening process

Variations in diagnostic pulse sequence, scan time, and slice thickness

There was a significant variation in the scan time among the included studies, which depends on the magnetic field strength, pulse sequence used and RF coil type. Three studies, Weinstein et al., Leach et al., and Hagen et al., used a dedicated breast coil, while three other studies did not report the coil type used (Lehman et al., Kriege et al., and Kuhl et al.,). Only one study by Warner et al. made used of a phase array coil. All study employed the use of 1.5T magnet, which is the most common magnet field strength in the UK. However Weinstein et al. and Leach et al. also

Table 2: STARD appraisal of included studies

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Total	Overall rating
Weinstein et al.[21]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	19	Fair
Lehman et al.[22]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	23	Good
Leach et al.[14]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	24	Good
Warner et al.[12]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	19	Fair
Kriege et al.[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	22+1 UC	Good
Kuhl et al.[15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	21	Good
Hagen et al.[19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	UC	Y	Y	Y	N	UC	Y	N	UC	19+1 UC	Fair

Abbreviations: Q=Question, Y=Yes, N=No, UC=Unclear

combined a 3T and 1T magnet in their study. There was no report of the magnetic field strength used by Lehman et al., and Kriege et al. With regard to the pulse sequence used, there is a significant variation between the studies. Three studies, Weinstein et al., Lehman et al., and Warner et al. included T2 sequences. Only the study of Leach et al. included a T1 sequence. Spoiled Gradient Recalled Acquisition in Steady State (SPGR) was employed in one study (Warner et al.) and a Dynamic contrast enhanced 3D (DCE 3D) was employed by Hagen et al., Fat saturation was used by all studies except Hagen et al. and two other studies that did not give a report of the sequence used (Kriege et al., and Kuhl et al.)

Scan time depend largely on the MRI field strength and sequence used, as a result of this, there were variation in the scan time among the included studies. Three studies (Weinstein et al., Warner et al., Hagen et al.) recorded a scan time less than 1.50 sec per sequence. However, Weinstein et al. recorded 6 min in the post contrast series, and Hagen et al. reported a record of 7min. There was no record from four studies (Lehman et al., Leach et al., Kriege et al., and Kuhl et al.)

Diagnostic accuracy analysis

A total of 199 cancer was diagnosed, of which 148 was detected by MRI and 78 by Mammography. Among this detected cancers, it was observed that some type of cancers was detected more on one modality than on the other, this is summarise in Table 5. Three studies reported 10 interval cancer,[12,13,19] while four studies did not.[14,15,20,21] Mammography had the lowest sensitivity between 25% to 50% and a high specificity between 93% and 99%, while MRI had the highest sensitivity between 71% to 100% and a low specificity of 79% to 97%. The diagnostic yields are summarized in Table 6. Similarly, a plot of sensitivity and specificity for each modality is graphically demonstrated on Figure 2. It was observed that the sensitivity of all the included studies for MRI, showed a slight difference in the sensitivity values, while that for Mammography shows a cluster of similar sensitivity values when plotted against specificity. From the graph, the area of the circle illustrate the sample size, a larger circle area represents a larger sample size. The results consistently show's that the specificities of MRI and mammography are similar but that the sensitivity of mammography is consistently lower than that of MRI.

DISCUSSION

In these review, from the seven included studies, a pool of 4,793 asymptomatic women at high-risk of developing breast cancer were screened, most of whom were BRCA1

Table 3: Characteristic and quality assessment (QA) of included studies

Study author/ year	Title	Objective	Location	Study type	No. of patient (n)	Number of withdrawal/ exclusion	Mean age	Ethnicity	QA
Weinstein et al.[21] (2009)	Multimodality screening of high-risk women: A prospective cohort2 study	To prospectively compare cancer detection of digital mammography, whole-breast ultrasound and contrast-enhanced MRI in a high-risk screening population previously screened negative by film screen mammogram	Philadelphia	Prospective	612	3	49 years	-	Average
Lehman et al.[22] (2005)	Screening women at high risk for breast cancer with mammography and magnetic resonance imaging	To determine the feasibility of using MRI to screen high risk patients for breast cancer, including determining whether imaging and biopsy procedures are reliableand ensuring that the proposed interpretation criteria do not result in excessive false-positive examination	United States and Canada	Prospective	367	23	45 years	-	Average
Leach et al.[14] (2005)	Screening with Magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective cohort study	To compare the diagnostic accuracy of yearly contrast enhanced MRI with X-ray mammography in women aged 35-49 years	United Kingdom	Prospective	649	189	40 years	-	Average
Warner et al.[12] (2004)	Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination	To compare the sensitivity and specificity of 4 methods of breast cancer surveillance (Mammography, ultrasound, MRI, CBE) in women hereditary susceptibility to breast cancer due to a BRCA1 or BRCA2 mutation	Canada	Prospective	236	62	47 years	Ashkenazi Jewish	Average
Kriege et al.[23] (2004)	Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition	To determine whether screening with MRI facilitated the early diagnosis of hereditary cancer	Netherlands	Prospective	1909	43	40 years	Dutch	Low
Kuhl et al.[15] (2005)	Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer	To compare individually the respective diagnostic accuracies achieved with mammography, breast ultrasound and MRI	Germany	Prospective	529	61	42 years	Germans	Average

(Contd...)

Table 3: *Continued*

Study author/ year	Title	Objective	Location	Study type	No. of patient (n)	Number of withdrawal/ exclusion	Mean age	Ethnicity	QA
Hagen et al.[19] (2007)	Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series	To compare the sensitivities of breast MRI and X-ray mammography in the diagnosis of cancer	Norway	Prospective	491	63	41 years	Norwegian	Average

Table 4: Index test characteristics extracted from included studies

Studies	Field strength	Pulse sequence	Parameter	Scan time	Slice thickness	Coil type	Gadolinium agent per bodyweight
Weinstein *et al*.[21] (2009)	1.5 T or 3T	Pre-contrast: FAT-SAT T2 Sagittal. Post-contrast: FAT-SAT GE Sagittal	TR/TE - (4000/85) Matrix size - 512×256 Slab Interleaved - 13	1 Min 6 Min	2 – 3.5 mm	Dedicated surface breast coil array	0.1mmol/kg (Ominiscan)
Lehman *et al*.[22] (2005)	No record	Pre-contrast: FSE T1, T2 Sagittal. FAT-SAT T2 Sagittal. Post-contrast: FAT-SAT GE Sagittal	Pre-contrast: TR/TE - (4000/80) Matrix size - 256×256. Sat T1 (TR≤50/TE≤4.5) Post-contrast: Sat T1 (TR≤50/TE≤4.5) Matrix size - 256×128×32-60 (3D) Flip angle – 60° (Gradient echo)	No record	≤ 3 mm	No record	No record
Leach *et al*.[14] (2005)	1.0T 1.5T	FAT-SAT TI Coronal		No record	No record	Dedicated breast coil	0.1 mmol per kg. 0.2 mmol per kg. (Gadopentetatedimeglumine)
Warner *et al*.[12] (2004)	1.5T	SPGR – Coronal. SPGR – Sagittal, FAT-SAT T2 - Sagittal FSE T2 - Sagittal	TR/TE - 12.9 ms/43 ms matrix =256×256. TR/TE - 18.4 ms/4.3 ms Flip angle – 40° TR/TE - 4000 ms/102 ms Flip angle – 40	1 min 30s	4 -5 mm	Phase array coil	0.1 mmol/kg (Ominiscan)
Kriege *et al*.[23] (2004)	No record	No record	No record	No record	No record	No record	No record
Kuhl *et al*.[15] (2005)	1.5T	No record	No record	No record	No record	No record	0.1 mmol/kg
Hagen *et al*.[19] (2007)	1.5T	DCE 3D – T1 Coronal. DCE 3D – T1 Coronal	No record	1.01-1.30 min. 7 min	2.5-2.67 mm 2 mm	Dedicated breast coil	0.1 mmol/kg. 20 ml

FSE: Fast Spin Echo, DCE: Dynamic contrast enhanced, FAT-SAT: Fat suppresion, SPGR: Spoiled Gradient Recalled Acquisition in Steady State

and BRCA2 mutation carrier and women with a strong family history of breast cancer. Of which 199 breast cancers was detected in 179 participants. A total of 444 participants were either withdrawn or excluded from the studies.

A high sensitivity of 71% to 100% and a low specificity of 79% to 97% were reported for MRI, and a low sensitivity of 25% to 50% and a high specificity of 93% and 99% were also reported for Mammography. MRI was found in all the included studies to be more sensitive in the screening of asymptomatic women (18-45 years) at high-risk of developing breast cancer compare to Mammography. The highest sensitivity in this review for MRI was reported by Lehman et al.[22] with a sensitivity of 100% and the lowest was reported by Weinstein et al.[21] with a sensitivity of 71%. Hagen et al.[19] reported the highest sensitivity for Mammography to be 50% and Lehman et al.[22] reported the lowest with a sensitivity of 25%. The huge difference in the sensitivity between MRI and mammography reported could be as a result of the comparative nature or biological factor of the breast of the screened population (18-45 years) in

the study, since the sensitivity of mammography is inversely related to the density of the breast.

However, comparing the specificity of the two modalities, mammography was found to have a high specificity than MRI in five of the included studies with the highest specificity of 99.9%,[12] and the lowest with 93%,[14] while that reported for MRI was 97%[15] and 79%.[21] From this finding, there is only a slight difference in the specificity between both modality, which may be statistically significant in clinical practice.

However the true negative for MRI compared to Mammography was also slightly lower with a difference of 8 (Table 7), this slight difference could be attributed to the fact that only two studies[12,15] actually gave a report for true negative (TN) values.

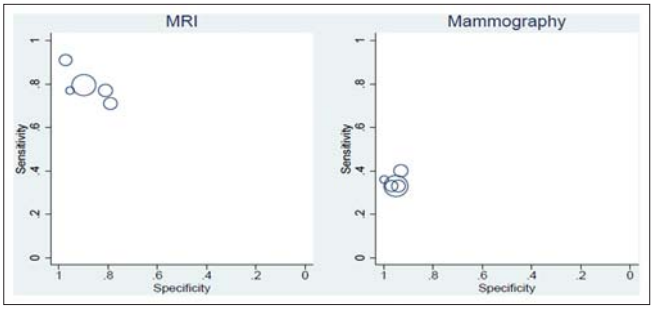

Figure 2: A graph of sensitivity and specificity for MRI and Mammography of the included studies

Similarly, false positive (FP) outcome was found to be higher screening with MRI than with Mammography (Table 7), which lead to increase number of participant who were sent for biopsy, compared to those sent from Mammography. The biopsy recommendation rate for MRI in three studies report[15,21,22] was 25%, 8.5%, 78% and for Mammography, 29%, 2.2%, 59% respectively. Four of the other included studies did not give values for the biopsy recommendation rates for both modalities. This indicate that the biopsy recommendation rate was higher in MRI, exception of the 29% reported by Weinstein et al.[21] for mammography, which was higher than the 25% reported for MRI.

The positive predictive values (PPV) for both of the modality also shows some significant difference, two of the included studies[15,22] reported higher PPV for MRI (12.9%, 50%) than Mammography (12.5%, 23.7%) respectively. While in two other studies,[12,14] Mammography had a higher PPV than MRI, (10%, 80% Vs 7.3%, 42%) respectively. There was no report on PPV in the other three studies.[19,21,23]

A total of 111 Invasive cancer (IC) (56% of total cancer detected) and 40 Ductal carcinoma in situ (DCIS) (20% of total cancer detected) was detected in the course of the screening among the seven studies. It was observed from most of the included studies that Mammography was better

Table 5: Cancer types detected by MRI and mammography, extracted from the seven studies

Cancer types	Weinstein et al.[21]			Lehman et al.[22]			Leach et al.[14]			Warner et al.[12]			Kriege et al.[23]			Kuhl et al.[15]			Hagen et al.[19]		
	Td	MRI	MAM	Td	MRI	MAM	Td	MRI	MAM	Td	MRI	MAM	Td	MRI	MAM	Td	MRI	MAM	Td	MRI	MAM
IC	11	n/s	n/s	3	+ve	+ve	27	n/s	n/s	16	n/s	n/s	4	-	4	34	34	+ve	16	n/s	n/s
DCIS	9	n/s	n/s	1	-	+ve	6	n/s	n/s	6	n/s	n/s	6	1	5	9	-	9	3	n/s	n/s
Follow up	2 years			None			5 years			1 years			2.7 years			5.3 years			0.5 years		
Reference standard	Biopsy			Positive test: Histopathology			Positive test: Histopathology			Positive test: Histopathology and Biopsy			Biopsy			Positive test: Histopathology			Histopathology and Biopsy		

Abbreviation: n/s: Not specified, +ve: Detected on, Td: Total detected, MRI: Magnetic resonance imaging, Mam: Mammography, IC: Invasive cancer, DCIS: Ductal carcinoma in situ

Table 6: Summary of the study outcome for breast cancer in asymptomatic women at high risk and parameter for diagnostic accuracy between MRI and mammography

S/N	Studies	Study design	No. of participant	Cancer yield			Participant with cancer	Diagnosed cancer		Interval cancer yield	Normal participant	Image test (%)			
												MRI		Mam	
				MRI	Mam	Total		IC	DCIS			Sn	Sp	Sn	Sp
1	Weinstein et al.[21]	Prospective	612	12	13	25	18	11	9	-	594	71	79	33	94
2	Lehman et al.[22]	Prospective	367	3	1	4	4	3	1	-	363	100	-	25	-
3	Leach et al.[14]	Prospective	649	27	14	35	20	27	6	-	629	77	81	40	93
4	Warner et al.[12]	Prospective	236	17	8	22	21	16	6	1	215	85	93	38	99.6
5	Kriege et al.[23]	Prospective	1909	32	18	45	50	4	6	4	1859	79.5	90	33	95
6	Kuhl et al.[15]	Prospective	529	39	14	43	41	34	9	-	488	91	97	33	97
7	Hagen et al.[19]	Prospective	491	18	10	25	25	16	3	5	466	86	-	50	-

Abbreviation: MRI: Magnetic resonance imaging, Mam: Mammography, IC: Invasive cancer, DCIS: Ductal carcinoma in situ, Sn: Sensitivity, Sp: Specificity

Table 7: Summary of the included study TP, FN, TP, TN, PPV, NPV, BRR, DY for MRI and Mammography

S/N	Studies	MRI								Mammography							
		FP	FN	TP	TN	PPV (%)	NPV (%)	BRR (%)	DY (%)	FP	FN	TP	TN	PPV (%)	NPV (%)	BRR (%)	DY (%)
1	Weinstein et al., (2009)	-	-	-	-	-	-	25	1.1	-	-	-	-	-	-	29	2.1
2	Lehman et al., (2005)	20	-	-	-	12.9	-	8.5	0.8	3	-	-	-	12.5	-	2.2	0.3
3	Leach et al., (2005)	-	-	-	-	7.3	99	-	-	-	-	-	-	10	99	-	-
4	Warner et al., (2004)	15	2	11	208	42	99	-	-	1	8	5	222	83	97	-	-
5	Kriege et al., (2004)	-	-	167	-	-	-	-	-	-	-	112	-	-	-	-	-
6	Kuhl et al., (2005)	39	4	39	1,370	50	-	78	16	45	29	14	1,364	23.7	-	59	40
7	Hagen et al., (2007)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviation: FP: False Positive, FN: False Negative, TP: True Positive, TN: True Negative, PPV: Positive Predictive Value, NPV: Negative Predictive Value, BRR: Biopsy Recommendation Rate, DY: Diagnostic Yield, - : No record

in detecting DCIS compared to MRI. The reason for this could be as a result of the presence of micro-calcifications that is associated with DCIS, which can easily be detected by mammography. However four of these studies did not specify the actual number of DCIS detected by each of the various modalities as seen in the data extracted on Table 5. Only three of the studies gave values for the number of DCIS detected.[15,22,23] Base on the few available data, the finding cannot be a conclusively one, which gives more room for further confirmation.

Furthermore, the diagnostic yield found for MRI and mammography was reported by three studies[15,21,22] In these reports, it was noted that the diagnostic yield of mammography, was higher than that of MRI in two of the studies,[15,21] where the percentages of the diagnostic yield for mammography was 40% and 2.1% Vs 16% and 1.1% for MRI, respectively. On the other hand, MRI was higher in Lehman et al.[22] report and was reported to be 0.8% vs 0.3% for mammography. There was no report in four of the other studies.[12,14,19,23]

Also, due to the rapidly progressive nature of some breast cancer associated with high risk population, some of the studies performed annual primary examination and also a follow up examinations on the study population. Table 5 holds a summary of the given follow up periods of each of the included studies, although no follow up report was given in Lehman et al.[22] and a median follow up period of 0.5 years and 5.3 years was reported by Kuhl et al.[15] and Hagen et al.[19] From the results of the follow ups, it was observed that MRI was still significantly more sensitive compared to mammography in the screening of asymptomatic women at high risk in the review population.

CONCLUSION

The evidence from this review demonstrate that MRI has a high sensitivity, and detected more breast cancer compared to that reported for mammography, in spite of its low specificity. Base on this evidence and in line with NICE guideline[25], we suggests in our conclusion that, MRI should be used as the initial screening modality for asymptomatic women aged 18 – 45 years at high risk of developing breast cancer in the absence of any contraindication and accessibility.

LIMITATIONS STRENGTH

This systematic review was undertaken as part of a Master of Science award at the University of Bradford. The review was initially done by AG under the supervision of BS. For publication purpose, the review process was repeated with independent evaluation by DM to ensure rigour of systematic review process.

One of the major limitations in this systematic review was observed during the data synthesis process. As a result of insufficient reports of some parameters required for a meta-analysis, only a descriptive synthesis was done for the review. Thus the review lacks homogeneity verification using statistical test of meta-analysis which could lead to some limitation in drawing the conclusion of the findings.

Also the review could suffer from publication bias, due to the fact that non-English language studies were excluded.

In the course of the review, it was however noted that some of the studies reviewed did not provide sufficient reports on some of the data's need to be extracted.

More so, most of the studies had a wide variation in the age range for their study population and some did not confine the study within the age range for this review, which could also be a possible source of bias.

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Authors Contribution:
AGM - Concept and design of the studies, Reviewed of literature, Data extraction, Manuscript preparation, Editing and critical revision of the manuscript; **BS -** Supervision of the studies, Critical review of the studies and Editing; **DM -** Data extraction, Critical review of the manuscript, Editing and Proof reading of the manuscript; **CNI -** Editing and Proof reading of the manuscript; **UA -** Editing and Proof reading of the manuscript.

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