Systematic Review and Meta-Analysis

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Magnetic resonance imaging in screening women at high risk of breast cancer

A meta-analysis

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Abstract

Background: Magnetic resonance imaging (MRI) is more accurate than mammography in screening for breast cancer. Exposure to ionizing radiation from repeated diagnostic X-rays may be a cause of breast cancer.

Methods: We conducted systematic searches on PubMed, Cochrane and Embase to identify studies on women who underwent mammography or MRI screening. A meta-analysis was performed to compare the detection rate of breast cancer by mammography, MRI or both.

Results: A total of 18 diagnostic publications were identified and included in the meta-analysis. Among the 1000 screened women, MRI alone increased the detection rate of breast cancer by 8 compared with mammography alone (RR 0.48, 95% CI 0.42–0.54), and MRI plus mammography increased the detection rate of breast cancer by 1 compared with MRI alone (RR 0.86, 95% CI 0.78–0.96). Subgroup analysis demonstrated that the diagnostic efficacy of MRI plus mammography in breast was obviously better than that of MRI alone or mammography alone.

Conclusions: Screening with MRI alone might be the best choice for women at high risk of breast cancer.

Abbreviations: BRCA1/2 = breast cancer susceptibility gene 1/2, CDR = cancer detection rate, DCIS = ductal carcinoma in situ, MG = mammography, MRI = magnetic resonance imaging, RR = risk ratio.

Keywords: breast cancer, mammography, magnetic resonance imaging, meta-analysis

1. Introduction

Breast cancer is the most common cancer among women all over the world, and it is also the leading cause of cancer death among women in over 100 countries.[1] Women with a known family history of breast or mutations in breast cancer susceptibility gene 1/2 (BRCA1 and BRCA2) genes have higher lifetime risk of breast cancer than the general population.[2] Early diagnosis and correct treatment are the key to improve the prognosis of patients. Mammography is a common screening tool for breast cancer, which has been used in clinic for a long time. However, screening mammography associated with low-dose radiation to the breast may increase the incidence of breast cancer, especially in high-risk women.[3–5]

In addition, some studies have shown that the screening effect of mammography alone is not enough, especially in high-risk women, because the sensitivity of screening is relatively low and the incidence of interval cancers is relatively high in this population.[6–8] In contrast, magnetic resonance imaging (MRI) has no radiation risk and is sensitive enough to detect breast cancer at an early stage. Some experts insist that MRI can replace mammography as a routine screening tool for patients with high-risk breast cancer.[9–11] In the past decade, MRI has become a potential research tool for the detection and diagnosis of breast cancer. Several studies have demonstrated that in addition to mammography, high-risk women with breast cancer can also benefit from breast MRI.[12,13]

Several previous studies have compared the diagnostic performance of MRI with mammography in breast cancer screening. However, due to their small sample size and different research designs, the conclusions are not the same. To further evaluate the role of mammography, MRI, or both in the diagnosis of breast cancer, we conducted this meta-analysis to provide strong evidence to guide future decisions.

WD, ZF, YX, and CW contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of meta-analysis, formal consent is not required.

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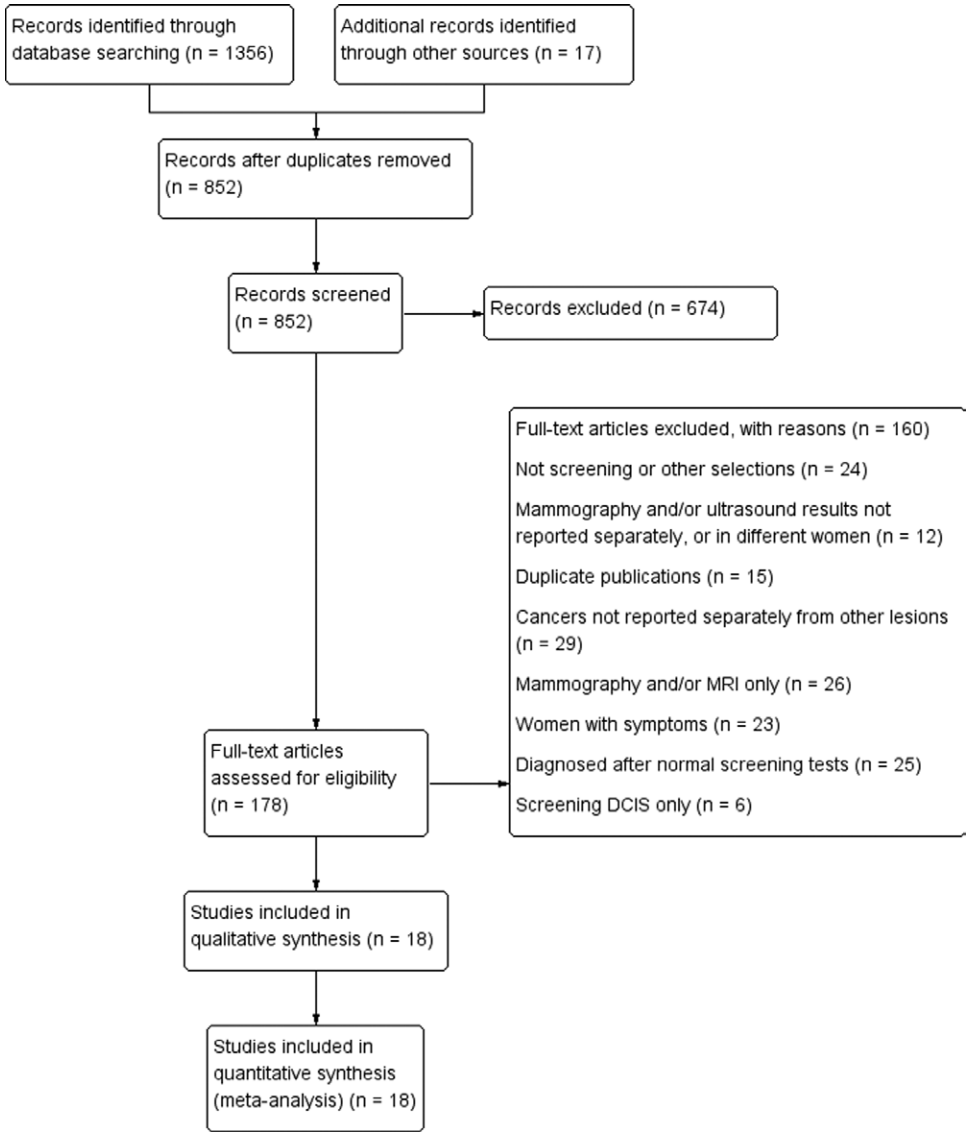

Figure 1. Flow of selection of articles for the systematic review. DCIS = ductal carcinoma in situ, MRI = magnetic resonance imaging.

2. Methods

We conducted a systematic literature review and meta-analysis of publications on mammography and MRI diagnosis of breast cancer. This meta-analysis did not require any program or registration review.

2.1. Data sources and search strategy

The search was developed by W.D., Z.F., and Y.X. PubMed, Embase and Cochrane Library was used to identify all eligible trials between January 2000 and March 2021. Keywords used were: "breast cancer" or "breast carcinoma" or "breast mass"; "mammography" or "MG" or "MRI" or "Magnetic Resonance Imaging"; "high risk" or "high-risk" or "risk"; "screening." Furthermore, all cross-referenced manuscripts and all review articles from retrieved articles were screened for related studies.

2.2. Inclusion and exclusion criteria

After screening the related studies in the databases, all included diagnostic trials needed to meet the following inclusion and exclusion criteria. Inclusion criteria were as follows: the study population were cases with a confirmed diagnosis of breast cancer; diagnostic methods used were mammography or MRI; the gold standard for diagnosis of breast cancer was pathological examination; Include high-risk factors: BRCA1 or BRCA2 mutation carriers, personal or family history of breast or ovarian cancer, history of prior chest radiation. Exclusion criteria were as follows: case report or review study type; patients had obvious symptoms of breast cancer during screening; and duplicated publication or data.

2.3. Data extraction

We used the keywords mentioned to retrieve qualified articles from the database. We selected the included articles in three steps. We used Endnote X7 Resources Management Software to organize, study titles and abstracts, and identify duplicates. After deleting duplicate articles, the titles of all articles would be reviewed and articles that did not match the inclusion criteria would be deleted. Next, the abstract and full text of the article were reviewed according to the inclusion criteria and research objectives. Two researchers independently completed the selection and quality evaluation of the study (Z.F. and Y.X.), and in case of disagreement, the study was submitted to a third person (C.W.). The information extracted from articles was summarized in a form of excerpt.

Table 1

General description and outcomes of the studies included in the meta-analysis.

Authors, publication year	No of participants (studies)	Risk factors	Diagnostic criteria	Mammography				MRI				Mammography + MRI			
						Detected cancers				Detected cancers				Detected cancers	
				N screens	Positive outcomes	N	Per 1000	N screens	Positive outcomes	N	Per 1000	N screens	Positive outcomes	N	Per 1000
Berg et al 2012[14]	7473 (Prospective cohort)	BRCA mutation; personal history of breast cancer; history of prior chest irradiation	BI–RADS (3–5) + Biopsy	7473	759	33	4.4	612	159	9	14.7	612	191	16	26.1
Bigenwald et al 2008[15]	505 (Prospective cohort)	BRCA mutation; family history of breast or ovarian cancer	Biopsy	505	NR	11	21.8	505	NR	41	81.2	NR	NR	NR	NR
Chiarelli et al 2020[12]	20,053 (Prospective cohort)	BRCA mutation; family history of breast cancer; history of prior chest irradiation	Biopsy	20,053	2003	109	5.4	20,053	3121	263	13.1	2,0053	4472	280	14.0
Cho et al 2017[16]	2065 (Prospective cohort)	Personal history of breast cancer	BI–RADS (3–5) + Biopsy	2065	91	9	4.4	2065	221	15	7.3	2065	284	17	8.2
Lehman et al 2007[17]	171 (Prospective cohort)	BRCA mutation; family history of breast or ovarian cancer	BI–RADS (3–5) + Biopsy	171	17	2	11.7	171	41	6	35.1	171	51	6	35.1
Guindalini et al 2019[18]	1223 (Prospective cohort)	BRCA mutation; personal history of breast cancer at age < 35 yr or family history of breast cancer; history of prior chest irradiation at age < 30 yr	Biopsy	1223	34	7	5.7	2111	87	15	7.1	2209	106	16	7.2
Kriege et al 2006[19]	4134 (Prospective cohort)	Familial or genetic predisposition, cumulative lifetime risk of breast cancer > 15%	BI–RADS (3–5) + Biopsy	4134	225	18	4.4	4134	452	32	7.7	4134	448	40	9.7
Kuhl et al 2010[20]	1679 (Prospective cohort)	BRCA mutation; familial and personal history of breast cancer	BI–RADS (4–5) + Biopsy	1679	23	9	5.4	1679	52	25	14.9	1679	67	27	16.1
Leach et al 2005[21]	1881 (Prospective cohort)	BRCA or TP53 mutation; family history of breast or ovarian cancer; family history of classic Li-Fraumeni syndrome	BI–RADS (3–5)	1881	135	14	7.4	1881	371	27	14.4	1881	371	33	17.5
Lehman et al 2005[22]	367 (Prospective cohort)	BRCA mutation; family history of breast cancer	BI–RADS (4–5) + Biopsy	367	8	1	2.7	367	31	4	10.9	367	38	4	10.9
Ng et al 2013[23]	338 (Prospective cohort)	Chest irradiation at age ≤ 35 yr	BI–RADS (3–5) + Biopsy	338	NR	13	38.5	338	NR	12	35.5	338	NR	18	53.3

(*Continued*)

Table 1

(*Continued*)

Authors, publication year	No of participants (studies)	Risk factors	Diagnostic criteria	Mammography				MRI				Mammography + MRI			
				N screens	Positive outcomes	Detected cancers		N screens	Positive outcomes	Detected cancers		N screens	Positive outcomes	Detected cancers	
						N	Per 1000			N	Per 1000			N	Per 1000
Podo et al 2002[24]	781 (Prospective cohort)	BRCA mutation; family history of breast cancer	BI–RADS (4–5) + Biopsy	781	NR	13	16.6	781	NR	24	30.7	781	NR	40	51.2
Riedl et al 2015[25]	1365 (Prospective cohort)	BRCA mutation; family history of breast cancer	BI–RADS (4–5) + Biopsy	1365	53	15	11.0	1365	183	36	26.4	1365	204	38	27.8
Sardanelli et al 2011[26]	1095 (Prospective cohort)	BRCA mutation; family and personal history of breast or ovarian cancer	BI–RADS (4–5) + Biopsy	1095	35	25	22.8	1045	75	42	40.2	1024	77	41	40.0
Stoutjesdijk, et al 2001[27]	262 (retrospective cohort)	BRCA mutation; family and personal history of breast or ovarian cancer	BI–RADS (3–5) + Biopsy	262	15	5	19.1	258	30	13	50.4	75	21	12	160.0
Vreemann et al 2018[28]	6553 (retrospective cohort)	BRCA mutation	BI–RADS (4–5) + Biopsy	6553	215	66	10.1	6553	399	112	17.1	6553	502	125	19.1
Weinstein et al 2009[29]	569 (Prospective cohort)	BRCA mutation; personal history of breast cancer, LCIS or atypical hyperplasia; history of prior chest irradiation	Biopsy	569	72	7	12.3	571	129	12		571	NR	19	33.3
Weinstock et al 2015[30]	571 (Prospective cohort)	Personal history of breast cancer	BI–RADS (4–5) + Biopsy	571	NR	3	5.3	571	NR	8	NR	571	NR	11	19.3

BI–RADS = breast imaging reporting and data system, BRCA = breast cancer susceptibility gene, LCIS = lobular carcinoma in situ, NR = not report.

2.4. Quality assessment

We used the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) to evaluate the methodological quality of the included studies. QUADAS-2 mainly focuses on patient selection, index test reference standard, and flow and timing, which reflects the main quality of the diagnostic study. If the study meets the above criteria, the study belongs to the risk of low bias; otherwise it belongs to the risk of high bias.

2.5. Statistical analysis

The differences between the two groups were estimated by the pooled risk ratio (RR) along with 95% CIs. The summary RR estimates were estimated using a fixed-effect or random-effect model. Subgroup analyses were performed to detect the effects of stratification factors and other baseline characteristics. According to I^2 statistics, statistical heterogeneity was estimated as follows: I^2 < 30% meant "low heterogeneity"; I^2 between 30% and 50% represented "moderate heterogeneity"; I^2 > 50% represented "substantial heterogeneity." if the heterogeneity was low or moderate, a fixed-effect model was used. Otherwise, the random-effect model was used after exploring the cause of heterogeneity. A 2-sided P value of < .05 indicated a significant difference. All calculations were performed, and figures were generated, using Review Manager Version 5.3 software (The Cochrane Collaboration, Oxford, UK).

3. Results

According to our search strategy, a total of 1373 records were retrieved from PubMed, Embase, and Cochrane Library. After removing the duplicate and irrelevant records, 178 full-text articles were available for the meta-analysis. However, after the full-text article evaluation, 160 studies were excluded. Finally, a total of 18 studies examined the benefits of screening with mammography and MRI in the same women at high risk of breast cancer (Fig. 1).

Among those included, 2 were retrospective studies and the other 16 were prospective work. A total of 21,157 women underwent 51,085 mammogram screenings, 45,060 MRI screenings, and 44,449 combined mammogram and MRI screenings. A total of 1799 cases of breast cancer were screened: 360 cases were detected by mammography only, 696 cases were detected by MRI only, 743 were detected by both. The general characteristics of the 18 studies included in the meta-analysis were demonstrated in Table 1.

3.1. Meta-analysis mammography alone versus MRI alone

The mean cancer detection rate (CDR) of mammography was 7.0‰ (360/51,085), and the mean CDR of MRI was 15.4‰ (696/45,060). The fixed-effects model was used because there were no heterogeneities (I^2 = 0%, P = .48) between these data. Among the 1000 screened women, MRI alone increased the detection rate of breast cancer by 8 compared with

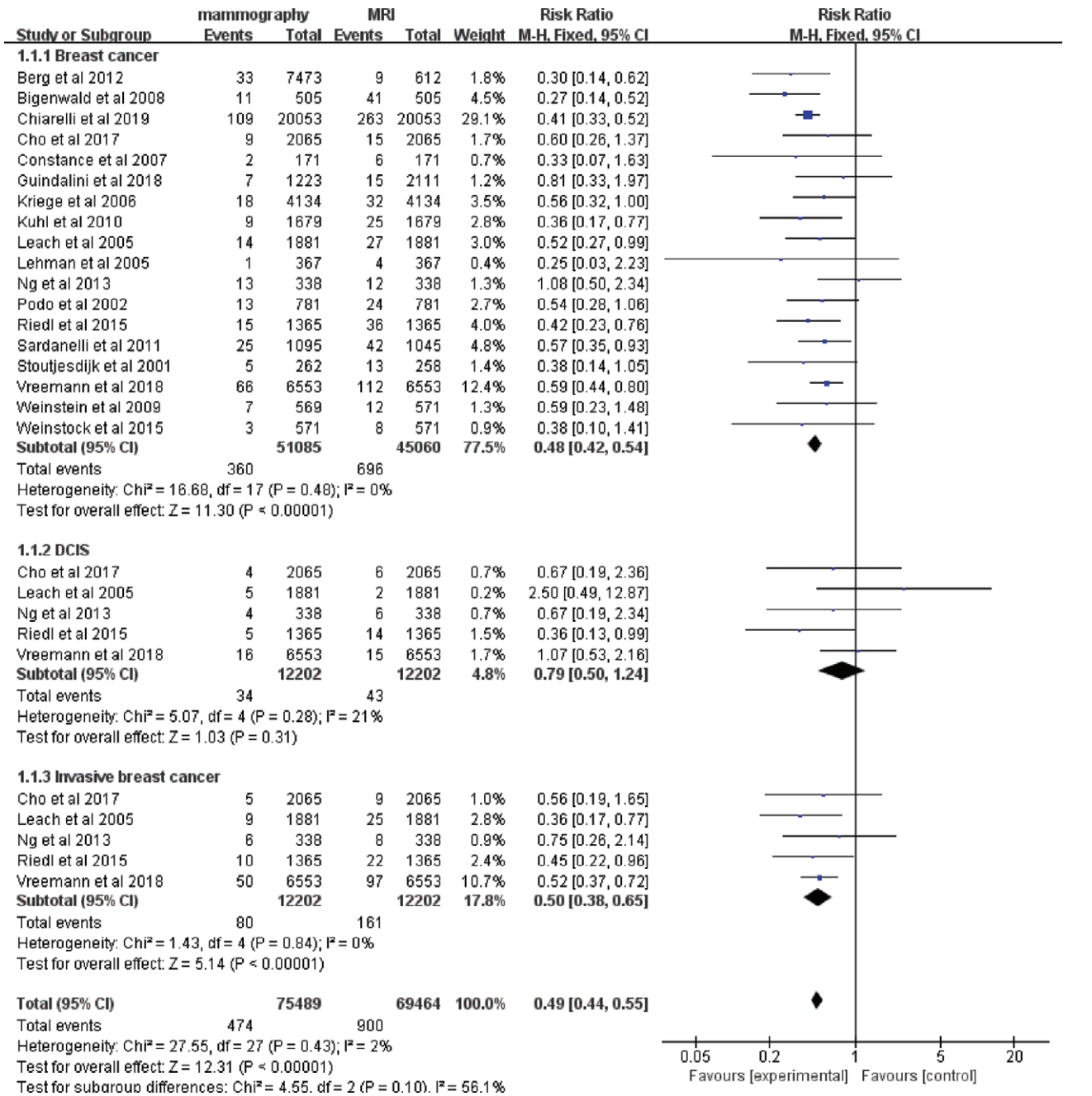

Figure 2. Forest plot of detection rate of breast cancer, DCIS and invasive breast cancer screening by mammography alone versus MRI alone. DCIS = ductal carcinoma in situ, MRI = magnetic resonance imaging.

mammography alone (RR 0.48, 95% CI 0.42–0.54; Fig. 2), and the rate of invasive breast cancer detection was increased by 6 (RR 0.50, 95% CI 0.38–0.65; Fig. 2). Regarding the rate of ductal carcinoma in situ (DCIS), there was no clear evidence to support a difference between the two interventions (RR 0.79, 95% CI 0.50–1.24; Fig. 2). Accordingly, the recall rate of patients in MRI alone group was significantly higher than that in mammography alone group (RR 0.46, 95% CI 0.39–0.54; Fig. 3).

Subgroups were analyzed to assess whether the variation between studies could be explained by patient's age, research type, and BRCA1/2 mutation carriers. The results showed that the diagnostic efficacy of MRI alone on breast was significantly better than that of mammography alone in each subgroup (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/I566).

3.2. Meta-analysis MRI alone versus mammography plus MRI

The mean CDR of MRI was 15.4‰ (696/45,060), and the mean CDR of MRI plus mammography was 16.7‰ (743/44,449). The fixed-effects model was used/conducted because there were no heterogeneities (I^2 = 0%, P = .61) between these data. Among the 1000 screened women, MRI plus mammography increased the detection rate of breast cancer by 1 compared with MRI alone (RR 0.86, 95% CI 0.78–0.96; Fig. 4), while regarding the rate of DCIS and invasive breast cancer, there was no clear evidence to support the difference between the two interventions (RR 0.71, 95% CI 0.47–1.05 and RR 0.93, 95% CI 0.75–1.15; Fig. 4). Accordingly, the recall rate of patients in MRI plus mammography group was significantly higher than that in the MRI alone group (RR 0.83, 95% CI 0.74–0.92;

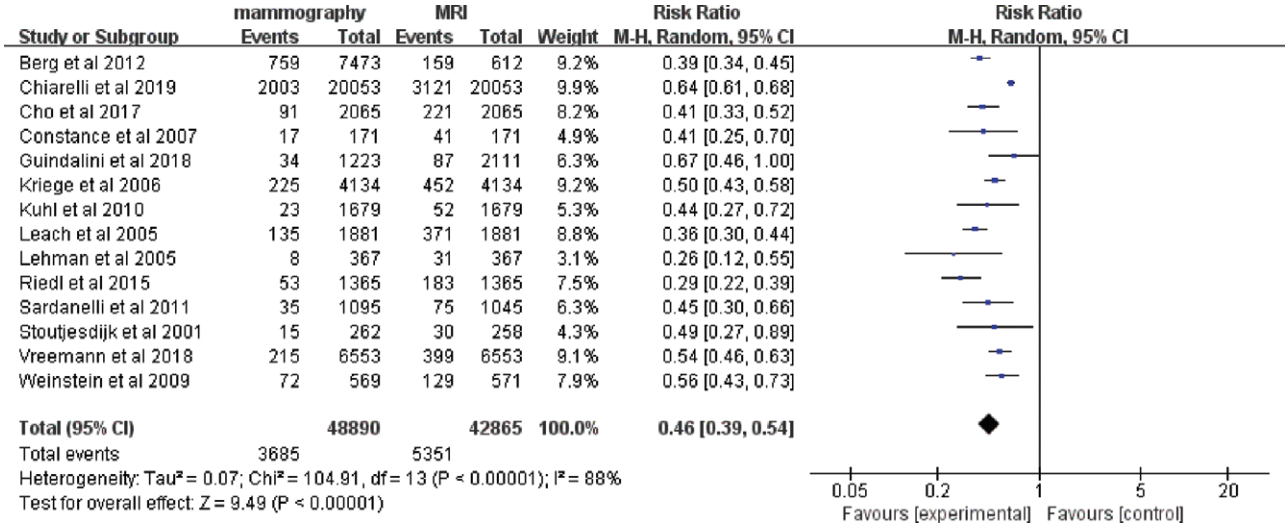

Figure 3. Forest plot of recall rate of breast cancer screening by mammography alone versus MRI alone. MRI = magnetic resonance imaging.

Fig. 5). Subgroup analysis showed that the diagnostic efficacy of MRI plus mammography in prospective studies was obviously better than that of MRI alone. But in the subgroup less than 50 years old, the subgroup older than 50 years old, the subgroup of retrospective studies or the subgroup of BRCA mutation carriers, the detection rate of MRI plus mammography for cancer was not significantly better than that of MRI alone (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/I567).

3.3. Risk of bias and applicability

Figure 6 showed the risk of bias corresponding to the inclusion of the study. Most studies reported the selection criteria and index test of the patients to be at low risk of bias in this respect. However, most studies were evaluated as having a high or unclear risk of bias in the reference test, since the pathologists who evaluated the pathological and biopsies results had prior knowledge of the screening tests. Follow-ups were also evaluated as a high or unclear risk of bias since patients who were not recalled missed the reference test. Therefore, the risk of this bias was high, which may reduce the quality of the publications.

4. Discussion

In order to provide clinicians with convincing evidence to make decisions, we conducted a systematic review to examine the benefits and harms of screening with mammography, MRI or both for women at high risk of breast cancer. Our meta-analysis focused on the latest studies, which revealed that adding breast MRI to mammography could increase the detection rate of asymptomatic breast cancer. However, due to the potential corresponding risks of increased false positive findings, the degree of this trade-off was uncertain.

It has been recognized that large-scale screening and early treatment are extremely important to improve cancer prognosis and reduce the burden of medical treatment.[31] Currently, the common radiological tools of breast cancer are mammography, ultrasound and MRI. Ultrasound is a good way to evaluate palpable abnormalities, distinguish between cystic and solid lesions, and classifying solid masses. However, it also has limitations as a screening method because it is difficult to detect microcalcification in DCIS. In contrast, mammography is a simple and convenient method for diagnosis of DCIS, but its diagnostic sensitivity is affected by the radiation density of breast tissue, especially in oriental women.[32,33]

There is no doubt that mammography is the main imaging screening method for breast cancer screening. Nevertheless, screening mammography is associated with low-dose radiation to the breast, which can increase the genetic risk of breast cancer in high-risk women.[34–36] According to the results of in vitro studies, there is evidence that breast tissues with BRCA mutations may be more vulnerable to ionizing radiation than genetically intact breast tissues.[37–39] One recent study estimated that BRCA mutation carriers have a 1.5 times higher risk of radiation-induced breast cancer than non-carriers.[40] Therefore, considering the high risk and early onset of breast cancer, current recommendations for breast cancer screening may not be sufficient for high-risk patients.

Breast MRI not only has no electrical radiation, but also has higher diagnostic sensitivity than mammography. Meanwhile, the sensitivity of breast cancer diagnosis is not affected by dense tissue. Therefore, MRI has been recommended as supplemental screening for women at high risk of breast cancer who have a lifetime risk of 20% to 25% or greater based on family history, radiation history of anterior chest wall, or known or suspected BRCA or other high-risk genetic mutations.[41] The combination of MRI and mammography will have higher diagnostic sensitivity, because when two imaging methods were combined for diagnosis, the higher category was categorized as the final imaging diagnosis. However, it is also for this reason that the recall rate increased accordingly. The results of this study showed that combining MRI and mammography seemed to improve the positive rate of breast cancer screening, but it could also increase the recall rate of breast cancer screening. The mean cancer detection rate of combing MRI plus mammography was 16.7‰, and this strategy increased the cancer detection rate by 1/1000 compared with screening with MRI alone. However, the recall rate would also increase significantly. The recall rate of patients in MRI plus mammography group was 16.2%, which was 4 percentage points higher than that of screening with MRI alone.

High recall rates lead to high false positive diagnostic results which can lead to unnecessary and invasive diagnostic procedures, such as needle biopsy. Although there is evidence that women are more likely to be recalled frequently to investigate false positive results, since delays and misdiagnoses can lead to adverse evolution.[42] In order to save medical resources, it is best to carry out personalized screening according to the risk degree of patients.

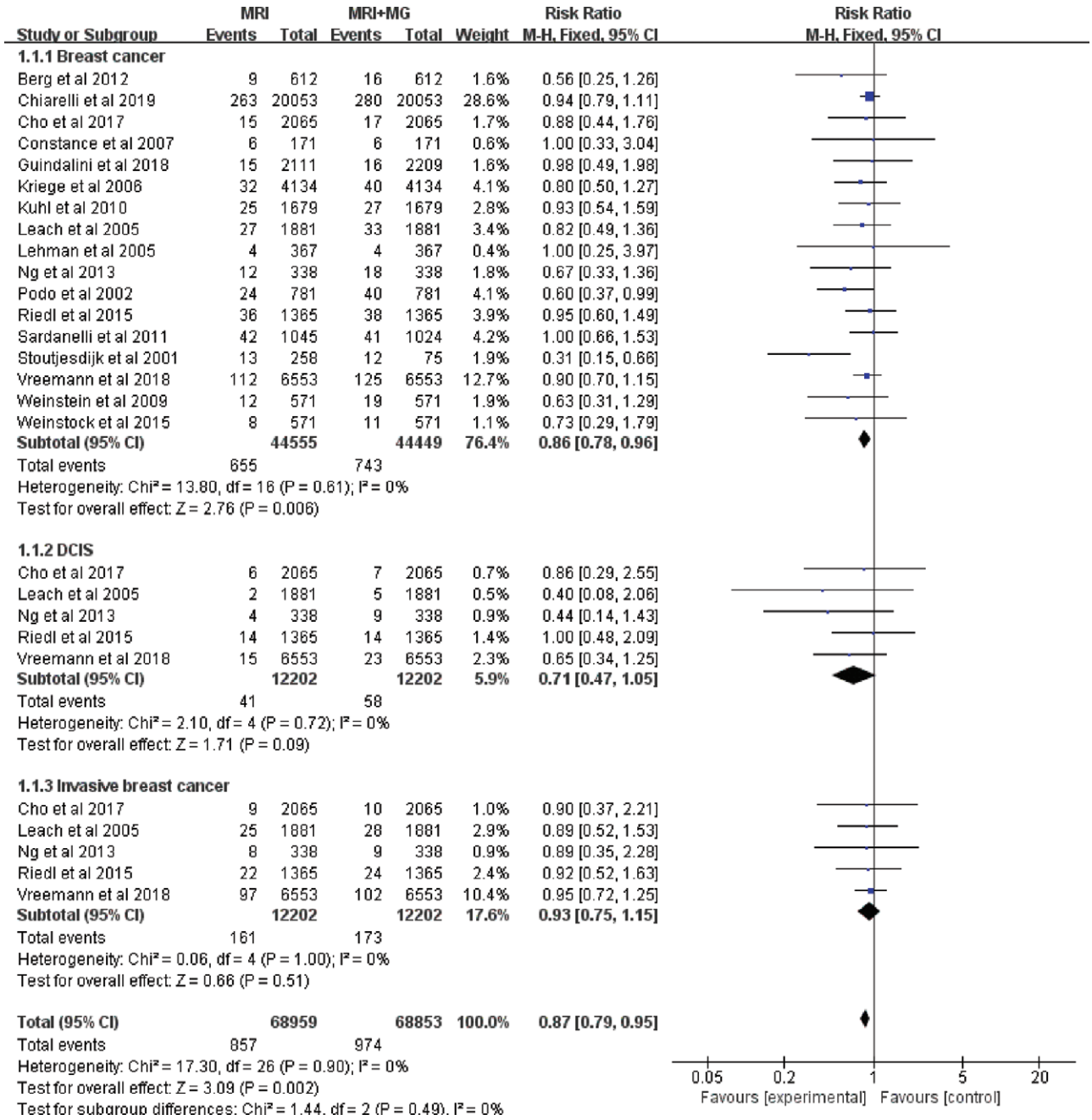

Figure 4. Forest plot of detection rate of breast cancer, DCIS and invasive breast cancer screening by MRI alone versus mammography plus MRI. DCIS = ductal carcinoma in situ, MRI = magnetic resonance imaging.

Women are likely to be divided to different screening imaging methods, which may increase the number of women and provide a more sensitive screening technique than mammography.[43]

Limitations of this study include the fact that the included studies lack complete follow-up data. Due to the lack of sufficient follow-up data, the absolute sensitivity of MRI and mammography is likely to be overestimated. Thus, although there is strong evidence that the addition of MRI contributes to the early detection of more breast cancer cases than traditional screening methods, the benefits of early detection in improving patient prognosis have not been quantified.

5. Conclusions

In conclusion, our findings support MRI as a screening tool for high-risk women. Although combined mammogram and MRI screening can increase the cancer detection rate slightly, it may also increase the potential corresponding risks of radiation and false positive findings. Therefore, screening with MRI alone might be the best choice for women at high risk of breast cancer.

Author contributions

Conceptualization: Wu Ding, Zaiwei Fan, Yuehuai Xu, Chunshou Wei, Zhian Li.
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Funding acquisition: Wu Ding, Zaiwei Fan, Yuehuai Xu, Chunshou Wei, Guodong Ruan.

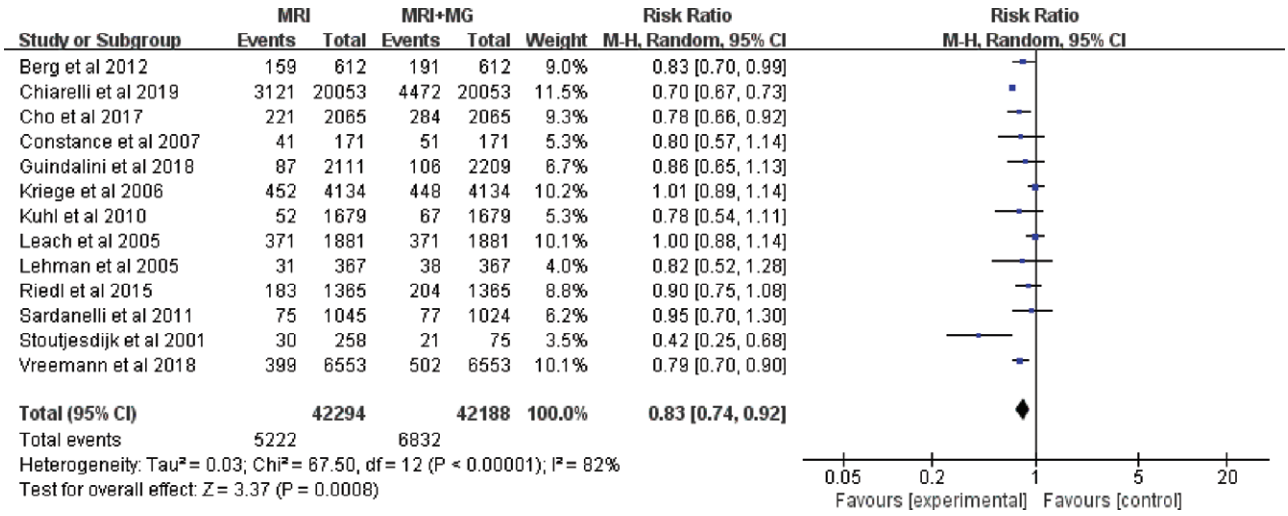

Figure 5. Forest plot of recall rate of breast cancer screening by MRI alone versus mammography plus MRI. MG = mammography, MRI = magnetic resonance imaging.

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Figure 6. Risk of bias assessment according to QUADAS 2.

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