

Systematic Review: Using Magnetic Resonance Imaging to Screen Women at High Risk for Breast Cancer

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Background: A sensitive and acceptable screening regimen for women at high risk for breast cancer is essential. Contrast-enhanced magnetic resonance imaging (MRI) of the breast is highly sensitive for diagnosis of breast cancer but has variable specificity.

Purpose: To summarize the sensitivity, specificity, likelihood ratios, and posttest probability associated with adding MRI to annual mammography screening of women at very high risk for breast cancer.

Data Sources: English-language literature search of the MEDLINE, EMBASE, and Cochrane databases from January 1995 to September 2007, supplemented by hand searches of pertinent articles.

Study Selection: Prospective studies published after 1994 in which MRI and mammography (with or without additional tests) were used to screen women at very high risk for breast cancer.

Data Extraction: Methods and potential biases of studies were assessed by 2 reviewers, and data were extracted and entered into 2 × 2 tables that compared American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) scores of MRI plus mammography, mammography alone, or MRI alone with results of breast tissue biopsies.

Data Synthesis: Eleven relevant, prospective, nonrandomized studies that ranged from small single-center studies with only 1 round

of patient screening to large multicenter studies with repeated rounds of annual screening were identified. Characteristics of women that varied across study samples included age range, history of breast cancer, and *BRCA1* or *BRCA2* mutation status. Studies used dynamic contrast-enhanced MRI with axial or coronal plane images (European studies) or sagittal images (North American studies) that were usually interpreted without knowledge of mammography results. The summary negative likelihood ratio and the probability of a BI-RADS–suspicious lesion (given negative test findings and assuming a 2% pretest probability of disease) were 0.70 (95% CI, 0.59 to 0.82) and 1.4% (CI, 1.2% to 1.6%) for mammography alone and 0.14 (CI, 0.05 to 0.42) and 0.3% (CI, 0.1% to 0.8%) for the combination of MRI plus mammography, using a BI-RADS score of 4 or higher as the definition of positive.

Limitations: Differences in patient population, center experience, and criteria for positive screening results led to between-study heterogeneity. Data on patients with nonfamilial high risk were limited, and no data were available on recurrence or survival.

Conclusion: Screening with both MRI and mammography might rule out cancerous lesions better than mammography alone in women who are known or likely to have an inherited predisposition to breast cancer.

Ann Intern Med. 2008;148:671-679.

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Since the discovery in the mid-1990s that inherited autosomal-dominant mutations in the *BRCA1* or *BRCA2* genes increase the lifetime risk for breast cancer by up to 85%, with substantial risk beginning at age 30 years (1), great attention has been focused on how to screen women who are at very high risk. Although inheritance of a *BRCA* mutation or another rare breast cancer predisposition gene is the strongest known risk factor for breast cancer (1), other women at high risk include untested first-degree relatives of known mutation carriers, those who have multiple relatives with early-onset breast or epithelial ovarian cancer, those who received therapeutic chest irradiation before 30 years of age (2), those with lobular carcinoma in situ or atypical ductal or lobular hyperplasia (3), and those with very dense breasts (4–8).

The alternative to breast screening for women at very high risk is bilateral prophylactic mastectomy, which reduces mortality by more than 90% (9). Therefore, a recommendation for screening is justified only if it will detect most of the tumors before invasion (ductal carcinoma in situ [DCIS]) or at a very early stage of invasion (node-negative tumors ≤1 cm in diameter), when the recurrence rate is less than 10% (10–12). However, in studies of women with inherited *BRCA* mutations who had conventional mammography-based screening (13–16), the inter-

val cancer rate was 35% to 50%, few in situ cases were detected, 40% to 78% of the invasive tumors were larger than 1 cm, and 20% to 56% of patients had lymph node involvement. Because most women at high risk decline prophylactic mastectomy, development of an effective and acceptable screening regimen is essential.

Because mammography remains the only screening test linked to reduced breast cancer mortality in any population, the approach has been to add 1 or more tests to mammography for high-risk patients. The most promising test to date is contrast-enhanced magnetic resonance imaging (MRI) of the breast, which has greater than 94% sensitivity in the diagnostic setting (17, 18). Unlike mammography, MRI is unaffected by breast density and does not use ionizing radiation. The use of breast MRI for screening

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Context

Some experts use mammography and magnetic resonance imaging (MRI) to screen women with an inherited predisposition to breast cancer.

Contribution

This review summarized data from 11 prospective studies that screened women at very high risk for breast cancer with mammography plus MRI. Assuming a 2% pretest probability of disease, negative findings on mammography and MRI reduced the probability of suspicious biopsy lesions to 0.3%, whereas a negative mammogram alone reduced the probability of suspicious lesions to 1.4%.

Caution

Criteria for suspicious lesions varied across studies.

Implication

Screening women at very high risk for breast cancer with both MRI and mammography might rule out cancerous lesions better than mammography alone.

—The Editors

the general population is not practical because of its high cost, limited availability, and relatively low specificity and the difficulty of sampling lesions visible only on MRI; limiting its use to a very high-risk population is more appropriate.

We performed a systematic review of prospective studies in which women at very high risk for breast cancer were screened with both MRI and mammography. We sought to summarize the sensitivity, specificity, likelihood ratios, and posttest probability associated with combining these 2 tests.

METHODS**Data Sources and Searches**

We searched EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials to September 2007 by using subject and text word search terms for magnetic resonance imaging or MRI, breast cancer, and the concept of high risk. We excluded studies with the search terms “health education,” “health promotion,” “retrospective studies,” “questionnaires,” or “health surveys” as subject terms or “case reports,” “letter,” “editorial,” “comment,” or “news” as publication types. One investigator with experience in literature searches and systematic review conducted the search. Two reviewers selected and reviewed relevant articles, and we searched the reference lists from all sources for additional studies.

Study Selection

We included prospective studies that examined use of MRI plus mammography, with or without ultrasonography and clinical breast examination, to screen women at

very high risk for breast cancer. Studies had to report sensitivity, specificity, positive or negative predictive value, tumor stage, or survival and be published in a peer-reviewed journal. No minimum length of study follow-up was required. Our target population consisted of women at high risk for breast cancer, defined as having a known mutation in *BRCA1*, *BRCA2*, or another gene associated with hereditary breast cancer; being an untested first-degree relative of a person with such a gene mutation; or having a family history consistent with a hereditary breast cancer syndrome, atypical or lobular carcinoma in situ on previous biopsy, or radiation therapy to chest (before age 30 years and at least 8 years previously). We included only English-language studies because of lack of translation resources and only studies published after 1994 to exclude outdated technology.

Data Extraction and Analysis

Two reviewers independently abstracted all data. We did not numerically score the validity or quality of studies; however, we assessed the methodology and conduct of studies and paid particular attention to issues that might bias findings, such as double reading of images. We extracted data on patient population; additional screening tests; MRI technique; reporting of blinding of image assessment; compliance, drop-out rates and reasons, and completeness of follow-up; total number of centers, patients, and screens; number of prevalent, incident, and interval cases of cancer detected; number of in situ versus invasive tumors detected, with size and nodal status of the latter; and reported sensitivity and specificity. We also extracted raw data to tabulate the number of false-positive, false-negative, true-positive, and true-negative screening results for mammography, MRI, and the combination of the 2 tests.

After study review, it became clear that conducting a meta-analysis without regard for the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) score used in each study to classify a positive test would be inappropriate and misleading. We therefore conducted all of the analyses separately whenever possible, using BI-RADS scores of 0 (indeterminate), 3 (short follow-up interval required), 4 (suspicious), and 5 (highly suspicious and requiring biopsy) as the definition of positive and then using only BI-RADS scores of 4 or 5 as positive, even if 1 of these criteria was not chosen a priori.

We used the methods described by Littenberg and Moses (19), Moses and colleagues (20), and Devillé and colleagues (21) to evaluate the heterogeneity among the included studies and to generate and compare summary receiver-operating characteristic (ROC) curves for the 2 tests separately and in combination. We used Meta-DiSc software (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain; available at www.hrc.es/investigacion/metadisc_en.htm) for our analysis. We estimated summary sensitivity by specificity, diagnostic odds ratio, positive likelihood ratio, and negative like-

Table 1. Prospective Studies of Screening Breast Magnetic Resonance Imaging and Mammography*

Study, Year (Reference)	Previous Breast Cancer Included?	Ages Allowed, y	Risk Criteria in Addition to Proven Mutation	Additional Tests†	MRI Plane	Image Assessment‡
Kuhl et al., 2005 (22)	Yes	≥30 (or 5 y before youngest family member); median, 40	High familial risk (≥20% lifetime)	Ultrasonography, semiannual CBE	Axial	Blinded
Kriege et al., 2004 (23)	No	25–70; mean, 40	High familial risk (≥15% lifetime)	Semiannual CBE	Axial	Blinded
Leach et al., 2005 (24)	No	35–49; median, 40	High familial risk (≥0.9% annual)	None	Coronal	Blinded
Warner et al., 2001 (25)	Yes	25–60; mean, 43	High familial risk (≥25% lifetime)	Ultrasonography, semiannual CBE	Coronal	Blinded
Warner et al., 2004 (26)	Yes	25–65; mean, 47	None	Ultrasonography, semiannual CBE	Coronal (first 38 patients), then sagittal	Blinded
Trecate et al., 2006 (27)	Yes	23–81	High familial risk	Ultrasonography, CBE	Axial	NR
Hartman et al., 2004 (28)	Yes	≥25; median, 42.5	High familial risk (>1% annual)	Ductal lavage, semiannual CBE	Sagittal§	NR
Lehman et al., 2005 (29)	Yes	≥25; mean, 45	High familial risk (>25% lifetime)	CBE	Sagittal	Blinded
Lehman et al., 2007 (31)	Yes	≥25; mean, 45	High familial risk (>20% lifetime)	Ultrasonography, CBE	Sagittal	Blinded
Sardanelli et al., 2007 (30)	Yes	≥25; mean, 46	High familial risk	Ultrasonography, CBE	Axial or coronal	Blinded
Hagen et al., 2007 (32)	Yes	19–79; mean, 41	None	None	Coronal (4 centers) or axial (1 center)	Blinded

* CBE = clinical breast examination; MRI = magnetic resonance imaging; NR = not reported.

† Tests were performed at the same time as MRI and mammography unless otherwise specified.

‡ Images from the different tests were evaluated independently for blinded assessments.

§ Only study that imaged breasts sequentially.

likelihood ratio from the data by using a random-effects model and calculated the probabilities after both a positive and a negative test result, assuming a 2% prevalence from the

pooled study results. We assessed the heterogeneity of these measures by using both a chi-square test for heterogeneity and the I^2 value; we considered a P value less than 0.1 on the

Table 2. Cancer Detected in Studies of Screening Magnetic Resonance Imaging and Mammography*

Study, Year (Reference)	Centers, n	Patients, n	Screening Examinations, n		Cancer Characteristics						
			Total	Mean per Patient	Total Cases, n†	Cases of Interval Cancer, n	Patients with In Situ Disease, %	Tumor Size, %‡			Patients with Node-Positive Disease, %§
								≤1 cm	1.1–2 cm	>2 cm	
Kuhl et al., 2005 (22)	1	529	1452	2.7	43	3	23	29	42	6	16
Kriege et al., 2004 (23)	6	1909	4169	2.2	45¶	4	12	38	28	22	14
Leach et al., 2005 (24)	22	649	1881	2.9	35	2	17	37	26	11	17
Warner et al., 2001 (25)	1	196	196	1	7	NA	14	86	NR	NR	0
Warner et al., 2004 (26)	1	236**	457	1.9	22	1	27	41	32	0	12
Trecate et al., 2006 (27)	1	116	116	1	12	NA	8	50	42††		NR
Hartman et al., 2004 (28)	1	41	41	1	1	NA	100	NR	NR	NR	NR
Lehman et al., 2005 (29)	13	367	367	1	4	NA	25	33	67	0	0
Lehman et al., 2007 (31)	6	171	171	1	6	NA	0	67‡‡		17	20
Sardanelli et al., 2007 (30)	17	278	377	1.4	18	0	22	44	22	11	21
Hagen et al., 2007 (32)	5	491	867	1.7	25	5	12	44	28	16	26

* NA = not applicable; NR = not reported.

† Some cases of cancer may have been detected by ultrasonography rather than by magnetic resonance imaging or mammography.

‡ Proportion of cases of invasive cancer detected, if this information was provided.

§ Proportion of cases of invasive cancer with positive nodes, of those for which nodal status was reported.

|| Only reported for the 31 cases of cancer in unaffected women.

¶ Included in sensitivity and specificity analysis; 51 cases of cancer reported.

** Included in sensitivity and specificity analysis; 1542 total surveillance rounds reported.

†† >1 cm.

‡‡ ≤2 cm.

Table 3. Studies Comparing MRI with Mammography*

Study, Year (Reference)	Definition of Positive Result†	Mammography			MRI			MRI and Mammography		
		Sensitivity, %	Specificity, %	PPV, %	Sensitivity, %	Specificity, %	PPV, %	Sensitivity, %	Specificity, %	PPV, %
Kuhl et al., 2005 (22)	BI-RADS score 4 or 5	32	97	24	91	97	50	93	96	42
Kriege et al., 2004 (23)‡	BI-RADS score 4 or 5	33	99	27	64	96	16	NR	NR	NR
	BI-RADS score 0, 3, 4, or 5	40	95	8	71	90	7	89§	NR	NR
Leach et al., 2005 (24)‡	BI-RADS score 4 or 5	14§	98§	15§	51§	96§	21§	60§	95§	20§
	BI-RADS score 0, 3, 4, or 5	40	93	10	77	81	7	94	77	7
Warner et al., 2001 (25)¶	BI-RADS score 4 or 5	43	99§	75§	86	91	26	100	NR	NR
Warner et al., 2004 (26)‡	BI-RADS score 4 or 5	36	100	88	77	95	46	86§	95§	48§
	BI-RADS score 0, 3, 4, or 5	36§	99§	80§	82§	81§	18§	90§	80§	19§
Trecate et al., 2006 (27)	BI-RADS score 4 or 5	33	100	100	100**	97	79§	100¶	97	79§
Hartman et al., 2004 (28)	BI-RADS score 4 or 5	0	NR	NR	100	75§	9§	100	NR	NR
Lehman et al., 2005 (29)	BI-RADS score 4 or 5	25	98§	11§	100	93§	13§	100	91§	11§
Lehman et al., 2007 (31)	BI-RADS score 3, 4, or 5††	33	91	12	100	79	15	100	73	12
Sardanelli et al., 2007 (30)	BI-RADS score 4 or 5	59	99§	77	94	98§	63	100	NR	NR
Hagen et al., 2007 (32)‡‡	BI-RADS score 3, 4, or 5††	32§	NR	NR	68§	NR	NR	80	NR	NR

* BI-RADS = Breast Imaging Reporting and Data System; MRI = magnetic resonance imaging; NR = not reported; PPV = positive predictive value.
 † In the BI-RADS system, 0 = indeterminate; 1 = negative; 2 = benign finding; 3 = short follow-up interval required; 4 = suspicious abnormality, biopsy should be considered; and 5 = highly suspicious for malignancy.
 ‡ The reported sensitivity and specificity were based on considering a BI-RADS score of 0, 3, 4, or 5 positive. However, the investigators also provided alternate cutoff information, which is reported here for comparability with the other included studies.
 § Calculated from data provided.
 || The study used an alternate scoring system, but the investigators claim that a positive result in this system is equivalent to a BI-RADS score of 0, 3, 4, or 5. When the 2 readers reached discrepant conclusions, the higher score was assigned.
 ¶ References 25 and 26 have at least some participants in common.
 ** Excludes 1 patient for whom MRI was not performed.
 †† No BI-RADS scores of 0 were assigned.
 ‡‡ The investigators reported 86% sensitivity with MRI and 50% sensitivity with mammography, but this was at time of diagnosis for patients who had imaging with those tests at diagnosis. These calculated values assume that interval cancer results were false negative with both MRI and mammography.

chi-square test or an I^2 value greater than 50% to be evidence of statistical heterogeneity. We used an equally weighted least-squares model to estimate the parameters of the summary ROC curves. We judged whether any cut-off effect was present on the basis of the slope parameter of the curve. To allow inclusion of studies with zero patients in a cell of the contingency table, we added 0.5 to those cells.

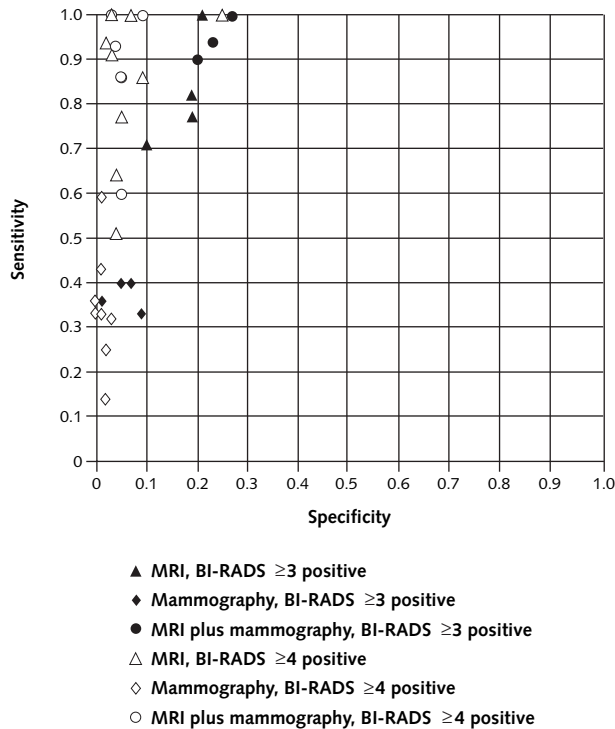
The diagnostic odds ratio, a measure of the overall accuracy of a test, is the ratio of the odds of a positive result among those with the disease to the odds of a positive result among those without. The greater the diagnostic odds ratio, the more discriminatory power the test has. A cut-off effect occurs when different studies have different implicit cut-off values for the test being evaluated. These implicit differences can occur even when studies are reported as having applied the same explicit standard (such as BI-RADS) because clinicians may interpret these standards in subtly different ways or study samples may differ.

When a cut-off effect is present, the diagnostic odds ratio is not constant across the range of sensitivities and specificities and must be interpreted with caution (19–21). If the slope of the summary ROC curve differs statistically significantly from zero, a cut-off effect is likely (19–21). The positive likelihood ratio indicates the increase in the odds of a person having the disease after a positive test result; the negative likelihood ratio is the similar value for the decrease in odds with a negative test result.

RESULTS

We did not identify any randomized trials. After reviewing the titles and abstracts of 217 articles identified in the electronic search and removing duplicates, we selected 40 for full-text review. Of these, we identified 11 articles (22–32) describing 11 prospective studies comparing MRI with mammography (Table 1). We included only the most

Figure. Sensitivity versus specificity of studies of MRI and mammography.



In the BI-RADS system, 0 = indeterminate; 1 = negative; 2 = benign finding; 3 = short follow-up interval required; 4 = suspicious abnormality, biopsy should be considered; and 5 = highly suspicious for malignancy. BI-RADS = American College of Radiology Breast Imaging Reporting and Data System; MRI = magnetic resonance imaging.

recent report for any study, unless relevant unreprinted data were found in the earlier reports. For the study by Kriege and colleagues, we used a follow-up report to compare results from initial (23) and subsequent (33) screens. The study by Hagen and colleagues (32) was unique in that it lacked specificity data.

The studies varied in size and scope, ranging from small single-center studies with only 1 round of patient screening to large multicenter studies with repeated rounds

of annual screening. Two studies (26, 32) included only patients with proven *BRCA1* or *BRCA2* mutations. All other studies included patients with various family history criteria in addition to those with proven breast cancer predisposition genes (Table 1). Leach and colleagues (24) only included women between the ages of 35 and 49 years, whereas ages ranged from 23 to 81 years in the study by Trecate and colleagues (27). In the 10 studies reporting mean or median age, the range was 40 to 47 years. All but the 2 largest studies (23, 24, 33) included women with a history of breast cancer.

All included studies used dynamic contrast-enhanced MRI with T1-weighted imaging based on spoiled gradient-recalled MRI with gadolinium diethylenetriamine pentaacetic acid as the contrast agent and obtained multiple sets of postinjection images to provide information about tumor enhancement kinetics. The level of reported technical detail varied widely. Image quality varied somewhat among the provided images because of differences in hardware (magnets and coils) and software (pulse sequences). Imaging was performed in either the axial or the coronal plane in the European studies (22–24, 27, 30, 32), which account for most of the data, whereas the North American studies (26, 28, 29, 31) used sagittal imaging. In all studies, mammography and MRI were conducted within 90 days of each other and usually on the same day. In studies with 2 or more rounds of screening (22–25, 26, 30, 32), the screening interval was 1 year. In all but 2 studies (24, 32), screening ultrasonography or clinical breast examination was also performed, and 1 study included ductal lavage (28).

All but 2 single-center studies specifically reported that each screening test was assessed independently of the others. The study by Leach and colleagues (24) was unique in that each imaging study was read by 2 different readers and the more conservative (higher BI-RADS score) reading was used. Hagen and colleagues (32), Trecate and colleagues (27), Sardanelli and colleagues (30), and Hartman and colleagues (28) did not discuss adherence or follow-up. In the study by Kuhl and colleagues (22), 8.5% of the patients who received only 1 round of screening were excluded

Table 4. Studies Reporting Sensitivity and Specificity, by Number of Previous Screenings*

Study, Year (Reference)	Mammography				MRI			
	First		Subsequent		First		Subsequent	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Kriege et al., 2004 (23)	36	94	29	95	82	87	77	92
Leach et al., 2005 (24)	40	93	40	94	75	82	80	81
Warner et al., 2004 (26)	38	99.6	43	100	85	93	71	97
Sardanelli et al., 2007 (30)	40	NR	86	NR	91	NR	100†	NR

* MRI = magnetic resonance imaging; NR = not reported.

† Excludes 1 patient with cancer for whom MRI was not performed and 1 for whom results were indeterminate because of motion artifact.

from the analysis. Common reasons for patient withdrawal included prophylactic mastectomy, claustrophobia from the MRI, pregnancy, and recurrence of cancer.

With the exception of the study by Hagen and colleagues (32), the interval cancer rate was less than 10% in the studies with more than 1 round of screening. In the studies with higher overall detection rates for DCIS (22, 26, 30), most noninvasive cases were detected by MRI only, whereas in the studies with lower rates of DCIS (23–25), most noninvasive cases were detected by mammography only. Overall, more than 50% of the detected tumors were either in situ or no larger than 1 cm. Twelve percent to 21% of invasive tumors were node-positive (Table 2). In the few studies for which data were available by year of screening (23, 24, 26, 30), tumor stage was similar for prevalent and incident screens. No study provided data on relapse-free or overall survival.

All studies considered biopsy-confirmed cancer the definitive positive result for sensitivity calculations (Table 3). However, some considered BI-RADS scores of 3, 4, or 5 to be positive, whereas others considered only BI-RADS scores of 4 or 5 to be positive. Three studies (23, 24, 26), provided enough data to calculate sensitivity and specificity by using both methods. In most studies, BI-RADS scores of 0 were ultimately reclassified; however, a few were included in the BI-RADS 3 tally because both scores generate further imaging. The sensitivity of MRI was higher than that of mammography in all studies that used either criterion for positivity. Reported sensitivity of the combination of MRI and mammography ranged from 80% to 100%, compared with 25% to 59% for mammography alone. In every study except the one by Kuhl and colleagues (22), the specificity of MRI was lower than that of mammography; specificity of the combined tests ranged from 73% to 93%. As expected, sensitivity was higher but specificity lower in the studies that scored BI-RADS 3 lesions as positive (Table 3 and Figure).

Three studies reported sensitivity and specificity by round of screening (first vs. subsequent), and in a fourth study (30), we were able to calculate sensitivities separately for the first and second rounds of screening. In 2 of the 3 studies, MRI specificity was higher on the subsequent screens, probably because false-positive lesions found on the first screen and determined to be benign would no longer be rated as “positive” on subsequent screens (Table 4). In studies that included additional screening tests (22, 23, 25–31), those tests detected very few cases of cancer missed by both MRI and mammography.

Of the 11 included studies, we excluded 1 (32) from the meta-analysis (Table 5) because of insufficient reporting of the number of true- and false-positive and true- and false-negative results. Not all studies reported sufficient data to be included in every aspect of the meta-analysis (Table 5). The slope of the summary ROC curve did not statistically significantly differ from zero for any subanalysis, indicating that a cut-off effect of interest was probably not present. Most of the subanalyses revealed statistical heterogeneity (heterogeneity chi-square *P* value <0.10) among the studies. When we used a BI-RADS score of 4 or higher as the definition of positive, the combination of MRI and mammography was associated with the highest diagnostic odds ratio (124.8 [95% CI, 36.4 to 427.4]), compared with an odds ratio of 45.9 (CI, 17.5 to 124.8) for BI-RADS scores of 3 or higher. When we used a BI-RADS score of 4 or higher as the definition of positive and assumed a 2% pretest probability of disease, the negative likelihood ratio for the combination of MRI plus mammography was 0.14 (CI, 0.05 to 0.42), compared with 0.7 (CI, 0.59 to 0.82) for mammography alone, and the probability after a negative test result for the combination was 0.3% (CI, 0.1% to 0.8%), compared with 1.4% (CI, 1.2% to 1.6%) for mammography alone. The positive likelihood ratio and probability after a positive test result for MRI plus mammography were 16.4 (CI, 11.1 to 24.1) and

Table 5. Meta-analysis of Studies*

Screening Technique and BI-RADS Cutoff Value (Reference)	Studies/Screening Examinations/Tumors, n/n/n	Diagnostic Odds Ratio (95% CI)	Sensitivity (95% CI), %	Specificity (95% CI), %
Mammography				
≥3 (23, 24, 26, 31)	4/6678/108	14.7 (6.1–35.6)§	39 (37–41)	94.7 (93.0–96.5)§
≥4 (22–24, 26, 27, 29, 30)	7/8818/178	38.5 (15.9–93.3)§	32 (23–41)§	98.5 (97.8–99.2)§
MRI				
≥3 (23, 24, 26, 28, 31)	5/6719/109	18.3 (11.7–28.7)	77 (70–84)	86.3 (80.9–91.7)§
≥4 (22–24, 26–30)	8/8857/178	88.7 (34.6–227.5)§	75 (62–88)§	96.1 (94.8–97.4)§
Mammography and MRI				
≥3 (25, 26, 31)	3/2509/63	45.9 (17.5–120.9)	94 (90–97)	77.2 (74.7–79.7)§
≥4 (22, 24, 26, 27, 29)	5/4272/115	124.8 (36.4–427.4)§	84 (70–97)§	95.2 (93.7–96.6)§

* BI-RADS = Breast Imaging Reporting and Data System; MRI = magnetic resonance imaging; ROC = receiver-operator characteristic.

† Posttest probabilities calculated assuming 2% prevalence.

‡ Based on 95% CI of likelihood ratio.

§ Associated with considerable statistical heterogeneity (chi-square *P* value < 0.1).

25.0% (CI, 18.4% to 33.0%), respectively, compared with 24.8 (CI, 11.6 to 53.0) and 33.6% (CI, 10.1% to 51.9%) for mammography alone.

DISCUSSION

We found 11 prospective, nonrandomized studies in which women at high risk for breast cancer were screened with both annual MRI and mammography. However, our quantitative summary estimates are uncertain because the studies were heterogeneous in terms of patient population, sample size, number of screening examinations, and center experience. We may also have missed 1 or more key studies that were published in a language other than English or that are not yet published. Overall, the combination of MRI and mammography with a BI-RADS score of 4 or higher as positive provided the best balance of performance in terms of all measures investigated (sensitivity, specificity, diagnostic odds ratios, likelihood ratios, and posttest probabilities). The summary negative likelihood ratio and probability of a BI-RADS–suspicious lesion (given negative test findings and assuming a 2% pretest probability of disease) for the combination of MRI plus mammography were 0.14 and 0.3%, respectively, compared with 0.70 and 1.4% for mammography alone.

The studies differed in several ways that affected their comparability. First, the sensitivity and specificity of MRI or mammography may have differed among patient samples according to risk status. In addition, because tumor growth rates vary inversely with age and are higher in women with *BRCA* mutations (34), studies with a younger patient population or a greater proportion of women with mutations might have a higher rate of interval cancer or later-stage tumors. Second, the sensitivity estimates, which were based on no more than 45 cases of cancer in any study, would be particularly imprecise for the smaller studies. Third, the tumors detected by these techniques might otherwise have been interval cancer or might have been

detected on a subsequent mammography or MRI screen. However, few cases of cancer were detected by additional tests alone. Fourth, the experience level of the MRI technologists and radiologists undoubtedly varied, and technical differences in the performance of the MRI scans may also be important. Fifth, differences in patient adherence to the protocol and follow-up may have biased the reported sensitivity and interval cancer rates. Finally, one might expect higher sensitivity of MRI relative to mammography in the first round of screening if patients had previously been screened with mammography alone. Specificity would also be expected to improve after the first round of screening (Table 4).

Given the many differences among the studies, the relative consistency of the results is reassuring from a clinical point of view. However, although the available evidence strongly supports the addition of MRI to mammography for screening women at high risk because of family history or genetic status, many questions remain unanswered.

Although all 11 studies used a screening interval of 1 year, this may not be the ideal screening interval for all risk groups and ages. The lower age of eligibility in the reported studies ranged from 25 to 35 years; thus, we do not know the optimal age at which to begin MRI screening. We have no data about the upper age limit because few studies included a substantial proportion of older women.

With the exception of women who have a predisposing mutation or are close relatives of a person with such a mutation, selecting appropriate women for MRI screening on the basis of family history is not always a simple matter. Various models have been developed to help estimate lifetime risk and the probability of carrying a *BRCA1* or *BRCA2* mutation. The recent American Cancer Society guideline on MRI screening describes the use and limitations of these models (35).

All studies to date have focused on women at increased

Table 5—Continued

Summary ROC Curve Slope P Value	Positive Likelihood Ratio (95% CI)	Probability after Positive Test Result† (Range‡), %	Negative Likelihood Ratio (95% CI)	Probability after Negative Test Result† (Range‡), %
0.141	8.7 (4.4–17.5)§	15.1 (8.2–26.3)§	0.64 (0.55–0.75)	1.3 (1.1–1.5)
0.30	24.8 (11.6–53.0)§	33.6 (19.1–51.9)§	0.70 (0.59–0.82)§	1.4 (1.2–1.6)§
0.46	4.2 (3.0–5.9)§	8.0 (5.8–10.8)§	0.29 (0.21–0.41)	0.6 (0.4–0.8)
0.29	16.6 (11.1–25.0)§	25.3 (18.4–33.8)§	0.22 (0.12–0.43)§	0.4 (0.2–0.9)§
0.97	4.1 (3.6–4.7)	7.7 (6.8–8.7)	0.09 (0.04–0.23)	0.2 (0.08–0.4)
0.20	16.4 (11.1–24.1)§	25.0 (18.4–33.0)§	0.14 (0.05–0.42)§	0.3 (0.1–0.8)§

risk because of family history or genetic status. The benefit of MRI in other high-risk populations is unknown and could differ in subgroups of patients with similar cancer risk but a different profile of risk factors. Nevertheless, the recent American Cancer Society guidelines also recommend MRI of the breast for screening women who had chest irradiation before age 30 years (35). Great caution should be taken before extrapolating these results to women at lower risk, such as those with a previous diagnosis of atypical hyperplasia, lobular cancer in situ, dense breasts, or previous breast cancer.

The possible reasons why the sensitivity of mammography in this setting was so much lower than the sensitivity reported for screening the general population include the young age of these patients (mean age, early 40s), which would be associated with higher breast density; the pathology of *BRCA1*-related cancer (fewer cases of DCIS or fleshy tumors with pushing margins), which might cause these tumors to be less visible on mammography; and the possibility that cancer detected by MRI alone might have been detected by mammography on a subsequent round of screening. Indeed, the relatively small increase in cancer detection observed with the addition of mammography to MRI raises the possibility that MRI alone could be a reasonable screening strategy. However, although all groups have reported a higher sensitivity for MRI than mammography for invasive cancer, in the 2 large multicenter studies (23, 24), mammography was more sensitive than MRI for DCIS. This is probably because of the “MRI learning curve,” which is steeper for DCIS because of its more subtle presentation. Accordingly, MRI should be used in addition to mammography, even in young women. If mammography reveals cancer on a particular round of screening, MRI is still indicated, because multiple primary lesions occur fairly commonly in this population (22, 30).

The clinical effectiveness of any screening regimen depends on its ability to reduce mortality, as opposed to simply increasing lead time. The greatest challenge in reviewing the evidence on the effectiveness of MRI screening is the lack of randomized trials. Now that preliminary evidence from comparative studies of MRI and mammography is available, randomized trials may no longer be feasible and would be ethically complicated. Longer follow-up of the patients in these comparative studies is needed so that recurrence and survival data can be obtained.

A final caveat is that very high-risk women who are choosing between risk-reducing mastectomy and screening should be counseled that although the sensitivity of MRI in combination with mammography is excellent and will probably improve as further experience is gained with this technique, it will always be less than 100%. In addition, some very small tumors will already be incurable at the time of detection. Therefore, women who opt for screening should strongly consider other risk-reducing measures (such as chemoprevention or oophorectomy) and must be willing to accept some risk.

In conclusion, annual screening with MRI and mammography using a BI-RADS score of 4 or 5 to define positivity is currently the most accurate means of screening women with a strong familial or genetic predisposition to breast cancer.

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Acknowledgment: The authors thank Dr. Steve Hanna of McMaster University for his assistance with the meta-analysis.

Grant Support: The Program in Evidence-based Care is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario.

Potential Financial Conflicts of Interest: *Stock ownership or options (other than mutual funds):* D. Plewes (GE Healthcare, Sentinelle Medical).

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