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Evaluating the correlation between mammography and MRI for screening women with increased breast cancer risk

Janie M. Lee, MD, MS, Elkan F. Halpern, PhD, Elizabeth A. Rafferty, MD, and G. Scott Gazelle, MD, MPH, PhD

Massachusetts General Hospital, Department of Radiology

Abstract

Rationale and Objectives—Breast magnetic resonance imaging (MRI) is increasingly being added to mammography for screening asymptomatic women at increased risk of breast cancer. Because the direction and extent of correlation between mammography and MRI could potentially result in over- or under-estimation of the diagnostic gain related to using MRI as an adjunct to mammographic screening, we performed an analysis to evaluate the extent of correlation between mammography and MRI.

Materials and Methods—We reviewed the published literature to identify multimodality breast cancer screening studies reporting the sensitivity of mammography and MRI, alone and in combination, for breast cancer diagnosis. After calculating the expected sensitivity of combined mammography and MRI under conditions of test independence (no correlation), we compared the calculated and observed sensitivities for combined mammography and MRI. We then calculated correlation coefficients for mammography and MRI.

Results—Seven studies of multimodality screening in women at increased risk of developing breast cancer were included for analysis. Of these studies, the correlation between film mammography and MRI was positive in three studies, negative in two studies, and not identified in two studies. The calculated correlation coefficients ranged from -0.38 to 0.18. In 6 of 7 studies, the 95% confidence interval for the correlation coefficient included 0.0, indicating no significant correlation.

Conclusion—Evidence from published trials of multimodality breast cancer screening identified no statistically significant correlation between film mammography and MRI. Using both tests for breast cancer screening is likely to improve the early detection of breast cancer in women at increased risk.

Keywords

Mammography; MRI; screening; technology assessment

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Corresponding author: Janie M. Lee, MD, MS, Massachusetts General Hospital, Institute for Technology Assessment, 101 Merrimac Street, 10th Floor, Boston, MA 02114, Phone: 617-724-4445, Fax: 617-726-9414 jlee45@partners.org.

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INTRODUCTION

Mammography is the current clinical standard for breast cancer screening. The accuracy of mammography in the general population is relatively high, with a meta-analysis of screening mammography reporting sensitivity in the range of 83-95% and specificity of 94-99% (1). However, the sensitivity of mammography in women at increased risk of breast cancer, including BRCA gene mutation carriers, is substantially lower, in the range of 33 - 56% (2-5). This is thought to be related to multiple factors such as the younger age at screening for these women, increased breast radiodensity, as well as pathologic and imaging characteristics of breast cancers in this population. Recent studies indicate that breast magnetic resonance imaging (MRI) is highly sensitive and can detect breast cancers not seen on mammography, particularly in women at increased risk (6-11), and the American Cancer Society has endorsed the use of breast MRI as an adjunct to mammography for screening these women (12).

When two diagnostic tests are combined, a positive combined test can be defined in two ways: 1) either test with positive results is considered positive, or 2) both tests with positive results are required for the combined test to be considered positive (13,14). In the published studies and in current clinical practice, a positive finding on either screening mammography or breast MRI is followed by further diagnostic evaluation. Thus the two-test combination is considered positive if either individual examination is positive.

While additional tests often increase the diagnostic information available over that from a single test alone, the direction and extent that two diagnostic tests are correlated affects the diagnostic gain achievable when the tests are combined (13). If disease detection by one test is unrelated to disease detection by the other, the two tests are considered to be independent. Using the "either test positive" criterion, the overall sensitivity of the combined tests will be greater than the sensitivity of either test alone. However, if disease detection by two diagnostic tests is based on similar or overlapping disease features, then the two tests are often positively correlated. In this situation, a condition detected by one test is likely to also be detected by the other test. The combined improvement in disease detection from applying both tests is reduced, and the combined sensitivity of the two test strategy (as calculated under the assumption of test independence) is over-estimated. The reverse is true for negatively correlated tests.

When considering mammography and MRI, the two tests could potentially be positively or negatively correlated, or independent. The detection of breast cancer by MRI is dependent on the physiologic changes related to cancer vascularity as well as tumor morphology. The high soft tissue contrast of MRI has the advantage of demonstrating cancers in radiodense breasts. Mammography is thought to be more sensitive than MRI in detecting microcalcifications associated with some in situ (DCIS) and invasive ductal carcinomas. Because the development of calcifications and neovascularity may represent different aspects of malignant tumor progression, it is possible that mammography and MRI are complementary, or negatively correlated tests. However, because size, morphology, and distribution are all lesion features evaluated by both mammography and MRI, it is also possible that the two tests are positively correlated. Another consideration is that no single common feature underlies the detection of malignancy by both mammography and MRI. In that case, there would be no correlation between the two tests, otherwise known as test independence.

To better understand the potential diagnostic gain related to using breast MRI and mammography for screening, we reviewed the medical literature to identify relevant studies, and examined the extent of correlation between mammography and MRI for screening women at increased risk of breast cancer.

MATERIALS AND METHODS

Study selection and data abstraction

We reviewed the published medical literature to identify studies using breast MRI as an adjunct to mammography for breast cancer screening. In generating its latest guidelines for breast MRI screening (12), the American Cancer Society convened an expert review panel which evaluated articles published between September 2002 and July 2006. This review identified 6 nonrandomized studies performed to determine the benefit of adding annual MRI to film mammography for women at increased risk of breast cancer, primarily based on documented genetic mutation or strong family history of breast cancer (6-11). We performed the following search to identify additional subsequently published studies of breast cancer screening with MRI and mammography. First, we performed a MEDLINE search for additional publications by the authors of the 6 studies included in the American Cancer Society guidelines. We also performed additional MEDLINE searches using the following search terms: 1) “breast MRI” and 2) “breast” AND “magnetic resonance imaging.” We chose these broad search terms in order to identify as many potential references as possible. The list of identified references was limited to English language articles, human subjects and publication years 2006 - 2008. Subsequently, the titles and abstracts of the identified references were reviewed by a single investigator to select original articles describing screening with both mammography and MRI for article retrieval and additional review.

Data abstracted from the retrieved articles included: study population characteristics, number of screening rounds, mean number of screening exams per patient, criterion for a positive screening examination, reference standard confirmation of breast cancer diagnosis by histopathologic examination and confirmation of negative breast cancer status via clinical follow-up, and data required to calculate the sensitivity of mammography alone, MRI alone, and combined mammography and MRI. A study was excluded if any of the modality-specific or combined sensitivity values were not calculable from the data presented in the article. Due to the possibility of verification bias, a study was also excluded if confirmation of both positive and negative test results was not obtained.

Testing the independence of mammography and MRI

In the published screening trials, and in current clinical practice, a positive finding on either screening mammography or breast MRI is followed by further diagnostic evaluation, thus the two-test combination would be considered positive if either individual examination was positive. Using this “either test positive” criterion, the expected combined sensitivity of two diagnostic tests, under conditions of statistical independence, is calculated using the following equation:

$$\text{Expected combined sensitivity} = \text{Sensitivity of Test 1} + (1 - \text{Sensitivity of Test 1}) * (\text{Sensitivity of Test 2}) \quad (\text{Eq.1})$$

For the studies included in this analysis, the expected sensitivity of the mammography and MRI combination, assuming statistical independence, was calculated and compared with the observed sensitivity of the two test combination. Subsequently, using the observed sensitivities of mammography and MRI, alone and in combination, a correlation coefficient (ρ) was calculated to determine the direction and to quantify the magnitude of positive or negative correlation, as described by Shen, et al., (15) (Eq.2). For tests which are independent, the correlation coefficient is equal to zero.

$$\rho = \frac{\text{Sens Test 1} + \text{Sens Test 2} - (\text{Sens Test 1} * \text{Sens Test 2}) - \text{Sens Observed Combination}}{\text{Sqrt}[\text{Sens Test 1} * \text{Sens Test 2} * (1 - \text{Sens Test 1}) * (1 - \text{Sens Test 2})]} \quad (\text{Eq. 2})$$

The standard error for the correlation coefficient was also calculated (16).

RESULTS

The 6 studies identified by the American Cancer Society guidelines for breast screening with MRI were selected for review (6-11). A search for additional publications by the authors of those studies identified 3 articles (17-19) that were selected for review. One of these studies (18) was a follow-up study with a greater number of patients and replaced the earlier study from the same group (11). The MEDLINE search for “breast MRI” for publication years 2006 - 2008 identified 111 references and abstracts. These abstracts were reviewed, and the full text of three references (20-22) was obtained for further review. The search for “breast” AND “magnetic resonance imaging” for the same period identified 124 references and abstracts. Following abstract review, the full text of one additional reference (23) was obtained for further review.

After reviewing the 12 selected studies, 5 studies were excluded for the following reasons: confirmation of breast cancer status in women with negative breast MRI results was not performed (n=2), the article did not contain an estimate of sensitivity for either modality (n=1), insufficient data could be abstracted to confirm the reported sensitivities (n=1), the sensitivity of combined mammography and MRI was not reported (n=1). The remaining 7 articles (7-9, 18-20,23) were included in the analysis.

Table 1 presents a summary of the included studies. All studies included women at increased risk of breast cancer, ranging from lifetime risk exceeding 20% (using models dependent on family history) to known BRCA gene mutation carriers. While all patients underwent screening with film screen mammography and MRI, some studies included ultrasound and/or clinical breast examination as well. The number of women screened in the studies ranged from 116 to 649. The number of cancers detected ranged from 12 to 43. The number of screening rounds ranged from 1 to 6, with the average number of screens per patient ranging from 1.0 to 2.9.

Table 2 presents the summary of diagnostic test performance reported in the studies, the calculated combined sensitivity of film mammography and MRI, assuming test independence, as well as the identified direction of test correlation, calculated correlation coefficient (ρ), and standard error. Figure 1 provides a graphic representation of the correlation coefficient and 95% confidence intervals. For 6 of the 7 studies, the 95% confidence interval for the correlation coefficient included 0.0, indicating no significant correlation between mammography and MRI. One study (8), in which the largest number of women underwent screening, and which identified the second highest number of cancers (n = 35), significant and negative correlation was identified between mammography and MRI. Due to variation among the positivity criteria among the selected studies, a pooled summary correlation coefficient was not calculated.

DISCUSSION

We examined the published multimodality screening studies including both film screen mammography and breast MRI to assess for correlation between the two tests. Based on analysis of the studies available in the current medical literature, we found no statistically significant correlation between film mammography and MRI. This suggests that the two tests are independent, and that additional, different diagnostic information is gained when mammography and MRI are used in combination.

When considering the diagnostic gain from combining two tests, it is important to note that if each test, when used alone, has high sensitivity for disease detection, it is very likely that, when combined, the two-tests together will find many of the same lesions because they are highly sensitive, not necessarily because they are positively correlated. If the tests are good at detecting disease, they will do so even when they are statistically independent tests.

For example, consider two tests which are statistically independent, each of which has a sensitivity of 90%. When used together to evaluate 100 patients with cancer, each test will identify 90 of 100 cancers, and 81 of the 90 cancers will have been identified by both tests. Each test will also identify 9 additional cancers which the other test does not. Overall, the two-test combination will identify 99 of 100 cancers ($81 + 9 + 9 = 99$). Thus, given two statistically independent tests, the vast majority of detected cancers would be identified by both tests.

Correlation between tests affects how frequently the two tests are both positive. If the two tests were positively correlated, the number of cancers identified by both tests would be greater than 81, and overall, the two-test combination would detect less than 99 of 100 cancers. If the two tests were perfectly positively correlated (correlation coefficient = 1), only 90 cancers would be identified, and each cancer would be identified by both tests. Similarly, if the two tests were negatively correlated, the number of cancers identified by both tests would be less than 81, and greater than 9 cancers would be identified by a single test alone.

In the published studies included in this analysis, thousands of women who are at increased risk of breast cancer have been screened. However, the number of cancers identified in each study was relatively small, ranging from 12 to 43. The small number of cancers contributes to the observed variation in reported sensitivity values, as well as to the calculated correlation coefficients and standard errors. The calculated correlation coefficients ranged from negative to positive, and the 95% confidence intervals for 6 of 7 studies included 0.0, indicating no significant correlation.

The results of this analysis identified correlation coefficients which ranged from -0.38 to 0.18, with 4 of 7 values falling within the range of -0.1 to 0.1. The confidence intervals for the point estimates of correlation spanned a wider range, from -0.70 to 0.63. It is possible that correlation underlying mammography and MRI might exist but cannot be statistically identified due to the relatively small numbers of cancers studied to date. In this analysis, the single study which demonstrated a negative significant correlation (8) had the largest study population and second highest number of cancers. Should undetected correlation exist, the results of this analysis provide likely estimates for the upper and lower extent of correlation. It remains likely that substantial additional diagnostic information can be gained from adding MRI to screening mammography.

Differences in the criteria used to define a positive MRI examination could also influence the reported sensitivity across studies. In all studies, the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) (24), or an equivalent scale was used for image interpretation. For 5 of 7 included studies (7,9,18,19,23), a BI-RADS assessment of Category 4 (Suspicious) or 5 (Highly Suspicious) was used to define a positive MRI examination. One study (8) used BI-RADS assessments of Category 0 (Needs additional evaluation), 3 (Probably benign), 4 (Suspicious) or 5 (Highly suspicious) to define a positive result. In these studies, the positivity criteria were consistently applied between mammography and MRI within each individual study. One study (20) used a 5 point classification system recommended by its national breast cancer screening program, with scores of 3 (Uncertain), 4 (Probably malignant) and 5 (Malignant) considered positive. Because sensitivity at differing thresholds was not provided in the primary studies, a more direct comparison across studies, including calculation of a pooled summary estimate of correlation, was not performed.

When estimating the diagnostic gain of using two tests over one, assuming test independence is often a simplifying assumption. Even when diagnostic tests are evaluated in a head-to-head manner, studies of diagnostic test performance may or may not report test performance for each modality alone and in combination. Because diagnostic test performance information for film screen mammography and MRI was available, both alone and in combination, via several multi-modality breast screening trials, we used the opportunity to evaluate for the presence or absence of correlation between the two tests, rather than assuming that none exists.

This analysis identifies no significant correlation between film screen mammography and MRI. In addition to suggesting that substantial additional diagnostic information can be gained from adding MRI to screening mammography, these results also suggest that if MRI were to be combined with another x-ray based breast imaging modality, such as digital mammography or digital tomosynthesis, those additional two-test combinations would likely demonstrate little or no test correlation. Exploration of the potential diagnostic gain of these test combinations using decision analysis and modeling approaches, incorporating data from this analysis and single modality studies, could be pursued in advance of more definitive clinical trials. In addition, modeling “what-if” scenarios could provide insight into the diagnostic consequences of varying degrees of both positive or negative correlation, information unobtainable from clinical trials.

An inherent limitation of secondary analysis of primary studies is the quality of the studies selected for analysis. The multimodality screening trials included in this analysis were prospective nonrandomized studies conducted in the United Kingdom, Canada, Germany, Italy, Austria, and Norway. Three of the seven included studies (8,18,20) were multicenter trials, with the number of centers ranging from 5 to 22. While there is heterogeneity in eligibility criteria, patient demographic and risk factors, MRI technique, and interpretation thresholds across the studies, each of these factors was clearly presented in the each study. In addition, consistent application of the chosen reference standard, prospective interpretation of studies occurred throughout, and sufficient data to allow the calculation of sensitivity of mammography and MRI, alone and in combination, were presented in each article. The above limitations are thus unlikely to affect the statistical analysis and results presented.

Based on the evidence available from published multimodality breast screening studies conducted on women at increased risk of breast cancer, our analysis identified no significant correlation between film mammography and breast MRI. These results suggest that additional and different diagnostic information is gained by combining the two examinations. Using both mammography and MRI for breast cancer screening is thus likely to improve the early detection of breast cancer in women at increased risk.

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Figure 1. Correlation coefficients for mammography and MRI

For 6 of 7 studies, the 95% confidence intervals for the correlation coefficients (identified by error bars) included 0.0, indicating no significant correlation between mammography and MRI.

Table 1

Summary of studies included for analysis

Study	Warner, et al. (7)	Leach, et al. (8)	Kuhl, et al. (9)	Trecate, et al. (19)	Sardanelli, et al. (18)	Hagen, et al. (20)	Riedl, et al. (23)
Year published	2004	2005	2005	2006	2007	2007	2007
Study population	BRCA1/2 carriers	BRCA1/2, TP53 carriers	Lifetime risk 20%, and 21-40%, and mutation carriers	BRCA1/2 carriers, first degree relatives of carriers, or strong family history	BRCA1/2 carriers, first degree relatives of carriers, or strong family history	BRCA1/2 carriers	BRCA1/2 carriers, strong family history or high risk based on Claus model
No. women screened	236	649	529	116	278	491	327
No. cancers detected	22	35	43	12	18	25	28
<i>Invasive</i>	16	29	34	11	15	21	16
<i>DCIS</i>	6	6	9	1	3	4	12
No. screening rounds	3	5	5	1	2	3	6
Ave no. screens / pt	1.9	2.9	2.7	1.0	1.4	1.6	2.1

Table 2

Mammography and MRI sensitivity and correlation

Study	Warner, et al. (7)	Leach, et al. (8)	Kuhl, et al. (9)	Trecate, et al. (19)	Sardanelli, et al. (18)	Hagen, et al. (20)	Riedl, et al. (23)
Positivity Criterion	BIRADS 4,5	BIRADS 0,3,4,5	BIRADS 4,5	BIRADS 4,5	BIRADS 4,5	Norwegian scale value 3,4,5	BIRADS 4,5
Mammography alone							
Sensitivity	0.348	0.400	0.326	0.364	0.588	0.522	0.500
MRI alone							
Sensitivity	0.739	0.770	0.907	1.000	0.938	0.864	0.857
Combined (observed)							
Sensitivity	0.826	0.940	0.93	1.000	1.000	0.905	0.929
Combined (calculated)							
Sensitivity	0.830	0.862	0.937	1.000	0.974	0.935	0.929
Correlation (direction)	Positive	Negative	Positive	Independent	Negative	Positive	Independent
Correlation coefficient (ρ)	0.018	-0.378	0.054	0.000	-0.216	0.175	0.000
Standard error	0.224	0.161	0.156	0.316	0.244	0.205	0.196