Serendipity in Diagnostic Imaging: Magnetic Resonance Imaging of the Breast

William F. Lawrence, Wenchi Liang, Jeannie S. Mandelblatt, Karen F. Gold, Matthew Freedman, Susan M. Ascher, Bruce J. Trock, Polun Chang

Background: Magnetic resonance imaging (MRI) of the breast has been proposed as a noninvasive diagnostic test for evaluation of suspicious (“index”) lesions noted on mammography and/or clinical breast examination (CBE). However, women may have incidental (“serendipitous”) lesions detected by MRI that are not found on mammography or CBE. To understand better whether or not biopsy procedures should be performed to evaluate serendipitous lesions, we estimated the breast cancer risk for women with this type of lesion. Methods: A decision analysis model was used to estimate the positive predictive value (i.e., the chance that a woman with a serendipitous lesion has cancer) of MRI for serendipitous lesions in women who had an abnormal mammogram and/or CBE suspicious for cancer (where a biopsy procedure is recommended). We restricted the analysis to data from women whose index lesions were noncancerous and used meta-analysis of published medical literature to determine the likelihood ratios (measures of how test results change the probability of having cancer) for MRI and the combination of CBE and mammography. The positive predictive value of MRI was calculated using the U.S. population prevalence of cancer (derived from registry data) and the likelihood ratios of the diagnostic tests. Results: Under a wide variety of assumptions, the positive predictive value of MRI was extremely low for serendipitous lesions. For instance, assuming sensitivity and specificity values for MRI of 95.6% and 68.6%, respectively, approximately four of 1000 55- to 59-year-old women with serendipitous lesions would be expected to have cancer (positive predictive value = 0.44%, 95% confidence interval = 0.24%–0.67%). Conclusion: In women with a suspicious lesion discovered by mammography and/or CBE that is found to be benign, serendipitous breast lesions detected by MRI are extremely unlikely to represent invasive breast cancer. Immediate biopsy of such serendipitous lesions may, therefore, not be required. [J Natl Cancer Inst 1998;90:1792–800]

Mammography and clinical breast examination (CBE) are the current standard measures for breast cancer screening and initial evaluation of breast signs and symptoms. The combination of mammography and CBE has a moderate sensitivity and high specificity for breast cancer. However, the positive predictive value of these tests for cancer, especially when done for screening and in young women, may be quite low, due to a low prior probability of cancer. For example, in a large Canadian screening study, only 12% of women aged 40–49 years who were recommended to have a biopsy procedure as a result of an abnormal screening mammogram or CBE actually had breast cancer (1). An estimated 600 000 breast biopsies are performed annually in the United States (2); as many as 85% of these yield benign results (3–6). Thus, the potential economic and quality-of-life (7–12) impact of alternative diagnostic pathways could be substantial.

To reduce the number of biopsies performed on women who will ultimately be diagnosed with benign lesions, several intermediate diagnostic tests have been proposed (13,14). Such tests would need to have high sensitivity, so that there are few missed cancers, and ideally also have high specificity, so that women without breast cancer would not be required to undergo an unnecessary invasive procedure.

One test currently under investigation as an intermediate diagnostic test is magnetic resonance imaging (MRI) of the affected breast. Studies suggest that MRI will be quite sensitive but may not be very specific, with specificity as low as 30% (15). Also, MRI of the breast has been reported to show breast lesions not found on either the initial mammogram or CBE. We refer to these lesions as “serendipitous lesions”—lesions found incidentally in the work-up of another breast lesion (16). These lesions raise a diagnostic dilemma: If the MRI has a higher sensitivity than conventional procedures, then cancer, if present, would be more likely to be detected by the MRI than the mammogram; on the other hand, if the specificity is truly much lower, then these serendipitous lesions are much more likely to be false-positive lesions than if they were originally found on mammography or CBE. In addition, localizing these lesions for biopsy procedure would be quite difficult if other diagnostic modalities cannot detect them; in this case, an MRI-guided biopsy procedure may be necessary to ensure localization of the lesion.

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If the suspicious lesion that prompted MRI evaluation is found to be benign, what should be done diagnostically to evaluate these serendipitous breast lesions found on MRI? Using decision analysis and the best estimates from a comprehensive literature review, we estimate the positive predictive value of these serendipitous lesions found on MRI or the probability that women with serendipitous lesions truly have invasive breast cancer. These data, while preliminary, provide clinicians and patients with a framework for decision making.

Methods

There are no published data that specifically address the question of risk of cancer in a serendipitous MRI lesion detected in the course of diagnostic evaluation. Although this study is concerned with the diagnosis of invasive breast cancer, we separately analyzed breast cancer results; 3) the study sample consisted of women at risk for cancer, defined as having a suspicious finding on CBE and/or mammogram, and where the index lesion is not malignant, and was not suspected by either the index mammogram or CBE.

The conceptual approach to the construction of the model is shown in Fig. 1. As noted above, we define the index lesion as the lesion found on mammogram and/or CBE that prompted a recommendation for biopsy procedure and further evaluation. A serendipitous lesion represents a lesion seen on MRI that was not suspected by either the index mammogram or CBE. The conceptual approach to the construction of the model is shown in Fig. 1. A woman having a biopsy procedure for the index lesion will either have a benign or a malignant lesion. We assume that if the index lesion is malignant, the clinician may wish to pursue the serendipitous lesions for the possibility of a multicentric cancer, and these women are excluded from this analysis. If the woman has an index lesion that is benign, we assume that her initial probability of cancer is the U.S. population average for her age and race. We also assume that the woman does not have a personal history of breast cancer; this history could raise her initial probability of disease. By definition, the mammogram and the CBE for this woman were negative in the area of the serendipitous lesion, which lowers the probability of cancer. Her probability of cancer given these prior negative tests is calculated using a Bayesian revision of probability (17) and is influenced by her probability of cancer before the test and the sensitivity and specificity of the index mammography and CBE. The positive MRI raises her probability of cancer; this probability is affected by the sensitivity and specificity of MRI. Thus, overall, our model calculates the probability of cancer given the positive MRI, a negative mammogram and CBE, and the initial probability of disease for women of different ages and races.

Model Parameters

We estimated three parameters for this model: the likelihood ratio positive of MRI, the likelihood ratio negative of the combination of mammography and CBE, and the initial prevalence of breast cancer. The likelihood ratio positive is the ratio of one minus the sensitivity to specificity and represents the degree to which a negative test raises the odds of diagnosis. The likelihood ratio negative is the ratio of sensitivity to one minus the specificity and represents the degree to which a positive test raises the odds of disease. Meta-analyses were conducted to estimate the likelihood ratios of MRI and mammography and CBE. Meta-analysis is a technique that can be used to summarize the results of good-quality studies (18-23) performed in diverse settings and populations. Such analyses are useful for new diagnostic tests, such as MRI, when no one study has sufficient power to address a particular question, and for summarization of the data across multiple studies on potentially different populations with different diagnostic thresholds for a positive test.

Sensitivity and specificity of MRI. Data for the sensitivity and specificity of breast MRI, used to calculate the likelihood ratio positive, came from the published medical literature. We performed a MEDLINE® (National Library of Medicine) search, from 1990 through 1997, using the terms "magnetic resonance imaging" and "breast neoplasms." We also searched references of relevant articles. Inclusion criteria for the abstraction of data from an article included the following: 1) sample size of 10 or greater; 2) data were available on MRI and breast cancer results; 3) the study sample consisted of women at risk for cancer, defined as having a suspicious finding on CBE and/or mammogram, but without known cancer at study entry; 4) the MRI readers were blinded to the final diagnosis; and 5) the article was written in English. We did not exclude articles in which the MRI readers had access to mammography or clinical examination data, since we assumed that in clinical practice the MRI reader would review these data when reading the MRI. For studies eligible for inclusion, the following data were abstracted: study design; patient selection; number and age of subjects; method for MRI; method for diagnosing breast cancer; and numbers of true-positive, false-positive, true-negative, and false-negative MRI results. Although this study is concerned with the diagnosis of invasive breast cancer, we include the diagnosis of ductal carcinoma in situ (DCIS) as a true-positive diagnosis for the purposes of calculating the sensitivity and specificity of MRI. This assumption results in a higher positive predictive value of MRI than would not including DCIS as a true-positive result; assuming otherwise would result lower the specificity of MRI, lowering the positive predictive value. Data could
not be found on the diagnostic accuracy of MRI in specific areas of the breast where the mammogram and CBE were negative. Thus, we assume that the sensitivity and specificity of MRI for the detection of breast cancer are the same for serendipitous lesions as they are for index lesions. Given the paucity of age-specific data, we also assume that the diagnostic accuracy of MRI is independent of age.

**Sensitivity and specificity of mammography and CBE.** Data for the diagnostic characteristics of CBE and mammogram were derived from the four major randomized trials of breast cancer screening that employed both CBE and two-view mammography (1,24–26). Although only one of these studies was conducted in the United States, we assume that the sensitivity and specificity of mammography and CBE are independent of the country in which the study was performed. Similar to MRI, data from these studies were abstracted to define true-positive, false-positive, true-negative, and false-negative results. We used the detection method (27) to calculate sensitivity of mammography and CBE. True positives were defined as screening-detected cancers, whether found by mammogram, CBE, or both. False negatives were defined as those who were diagnosed as having breast cancer in the interval between screening tests. False positives were defined as those participants undergoing biopsies for benign lesions. True negatives were those who did not clinically develop cancer during the study follow-up period. While probably not strictly true (28), we make the simplifying assumption that CBE and mammography combined test accuracy is independent of age. We examine this assumption in sensitivity analysis by calculating the effects of lower sensitivity for mammography and CBE for women under 50 years of age. While mammography may be less sensitive in this age group, these women also have a low prior probability of cancer. We also assume that the diagnostic accuracy of CBE and mammography is conditionally independent of that of MRI, conditioned on the presence or absence of cancer (29).

Thus, for example, if a woman has cancer and a positive MRI, her probability that the CBE and/or mammogram are positive is the same as it would be if she had cancer but a negative MRI.

**Breast cancer prevalence.** Yearly incidence rates of breast cancer will underestimate breast cancer prevalence since not all breast cancer will be detected in the year following the onset of the cancer. Data for the baseline prevalence of undiagnosed breast cancer in the U.S. population were derived from a simulation model of the natural history of breast cancer (30,31). This model uses breast cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) registry (32) as well as U.S. population data (33) to estimate the prevalence of cancer by age, race [as reported by Ries et al. (32): black, white, and total population], and incidence rate. We estimate prevalence of invasive breast cancer only; our data do not include the prevalence of DCIS in the population. Data from this model have been validated against Wisconsin and Iowa tumor registry data (30). That model was used to calculate a ratio of detected disease to undetected disease. Using this ratio, we then estimated the age- and race-specific prevalence of disease. We also calculated prevalences for “high-risk” women, using twice the average U.S. population incidence rates to represent those at high risk. We use this high-risk estimate to approximate the increased risk of having a first-degree relative with breast cancer (34–41) or of having previously had a biopsy showing benign breast disease (42–45).

**Analysis**

**Meta-analysis.** Using data from the literature of the sensitivity and specificity of the tests, we converted these data into likelihood ratios and pooled the data across studies using an analogue of a Mantel–Haenszel estimator. We use the ratio of the average sensitivities and complements of specificities to preserve the roles of the sensitivity and specificity in the calculation of the likelihood ratio in the estimator, and because this estimator is the closest analogue of the Mantel–Haenszel estimator of odds ratios (46). The estimator for the likelihood ratio positive for MRI \( \left( LR_{MRI} \right) \) was calculated using the formula:

\[
LR_{MRI} = \frac{\sum_{i} TP_{i}}{\sum_{i} \left( 1 - \frac{TN_{i}}{TN_{i} + FP_{i}} \right)} \frac{\text{sensitivity}}{1 - \text{specificity}}
\]

where \( TP_{i} \) is the number of true-positive diagnoses for study \( i \), \( TN_{i} \) is the number of false negatives, \( TP_{i} \) is the number of true positives, and \( FP_{i} \) is the number of false positives. The likelihood ratio negative for the combination of mammography and CBE \( \left( LR_{MAM, CBE} \right) \) was calculated in a similar fashion (see below). We obtained the 95% confidence intervals (CIs) by using jackknife estimation and recalculating likelihood ratios, leaving one study out for each study in the analysis (47). The standard errors (SEs) of the means of the likelihood ratios (\( LR \)) were calculated using the following formula:

\[
SE = \sqrt{\frac{n}{n-1} \times \sum_{i=1}^{n} (LR_{i} - LR)^{2}},
\]

where \( n \) is the number of studies in the analysis, and \( LR_{i} \) is the recalculated likelihood ratio leaving out study \( i \). The 95% CIs were then calculated by:

\[
95\% \text{ CI} = LR \pm 1.96 \times SE.
\]

Independent estimation of sensitivity and specificity of a diagnostic test using Mantel–Haenszel meta-analytic methodology may underestimate true sensitivity and specificity (48). Thus, we performed the meta-analysis on the likelihood ratios, to recognize the interdependence of these two measures of accuracy. Since underestimation of the sensitivity and specificity of MRI would result in an underestimation of the probability of disease given a positive MRI, we also examined the sensitivity and specificity of this test using the technique of the summary receiver-operating characteristic curve (48). This technique creates a receiver-operating characteristic (ROC) curve based on sensitivity and specificity data from multiple studies. This technique has the advantage, similar to our method of estimating likelihood ratios, of recognizing the interdependency of sensitivity and specificity. We also use this technique to test for homogeneity of the different MRI studies, looking for outliers on the summary ROC curve.

**Positive predictive value of MRI.** The probability of having cancer given a negative mammogram and CBE but positive MRI (the post-test probability) was calculated using the following equations:

\[
\text{Post-test odds} = \frac{\text{pre-test odds} \times LR_{MAM, CBE} \times LR_{MRI}}{1 - \text{pre-test probability}}
\]

where

\[
\text{Pre-test odds} = \frac{\text{test probability}}{1 - \text{test probability}}
\]

and post-test odds are converted to probability using the formula:

\[
\text{Post-test probability} = \frac{\text{post-test odds}}{1 + \text{post-test odds}}
\]

The post-test probability represents the positive predictive value of MRI given that the mammogram and CBE were negative in the area of the suspicious lesion found on MRI. We use a person-level analysis to calculate the positive predictive value of MRI as opposed to a lesion-level analysis; thus, the positive predictive value represents the probability that the woman has cancer given an MRI finding of a serendipitous lesion or lesions.

**Monte Carlo simulations.** We use Monte Carlo (49) stochastic simulations to calculate two-sided CIs for the positive predictive value of MRI, given starting age, race, and given that the mammogram, CBE, and index lesion biopsy are negative. In this simulation technique, each uncertain parameter (e.g., the likelihood ratio positive of MRI) is represented by a random variable that is chosen from a probability distribution reflecting the degree of uncertainty for that parameter. We used normal probability distributions to represent the three parameters in the model, each distribution was constrained to avoid illegal values. The probability of breast cancer and likelihood ratio negative of CBE and mammography were bounded between zero and one; the likelihood ratio positive for MRI was bounded as greater than or equal to one. The model was recalculated 5000 times.
Table 1. Model parameters*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>95% confidence interval†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity of mammography and CBE</td>
<td>82.2%</td>
<td></td>
</tr>
<tr>
<td>Specificity of mammography and CBE</td>
<td>98.8%</td>
<td></td>
</tr>
<tr>
<td>Likelihood ratio negative of mammography and CBE‡</td>
<td>0.18</td>
<td>0.12–0.24</td>
</tr>
<tr>
<td>Sensitivity of MRI</td>
<td>95.6%</td>
<td></td>
</tr>
<tr>
<td>Specificity of MRI</td>
<td>68.6%</td>
<td></td>
</tr>
<tr>
<td>Likelihood ratio positive of MRI§</td>
<td>3.05</td>
<td>2.00–4.11</td>
</tr>
</tbody>
</table>

*CBE = clinical breast examination; MRI = magnetic resonance imaging.
†Confidence intervals are shown only for the likelihood ratios, the parameters used in the study.
‡The likelihood ratio negative is defined as the ratio of one minus sensitivity to specificity.
§The likelihood ratio positive is defined as the ratio of sensitivity to one minus specificity.

for each set of parameters using a Monte Carlo simulation software package (@Risk version 3.0 for Windows; Palisade Corp., Newfield, NY). The 95% CIs for the likelihood ratios are shown in Table 1.

**Sensitivity analyses.** To test the effects of uncertainty in model parameters on model results, we performed several sensitivity analyses. These analyses involve varying the model parameters over a range of values. We performed sensitivity analyses on the initial prevalence of disease, the sensitivity and specificity of mammography and CBE, and the sensitivity and specificity of MRI. We also examined the effect of assuming that the combined sensitivity of mammography and CBE was lower for younger women than for older women, using an approximate ratio of sensitivity of mammography in younger women to that of older women based on the medical literature (28,50–53).

**RESULTS**

**Meta-analyses**

The results of the literature search for the MRI parameters revealed 360 MEDLINE entries identified, of which 14 met eligibility criteria for use in the meta-analysis. After removal of duplicated data, we used 12 studies in the meta-analysis; these studies are summarized in Appendix Table 1. Sensitivity of the studies ranged from 91% to 100%. The studies showed a wide range of specificity, ranging from 37% to 89%.

Parameter estimates for the likelihood ratios used in the analysis are shown in Table 1. The sensitivity and specificity for mammography and CBE and for MRI are included for reader information; the likelihood ratios were used for the model analyses. As can be seen in Table 1, the summary measure of sensitivity of MRI is quite high, but that of specificity is modest. The summary likelihood ratio positive for MRI, 3.05, is reasonably small. In comparison, the likelihood ratio positive of mammography and CBE would be 68.5, due to the very high specificity of the combination of these two tests.

Fig. 2 shows the summary ROC curve for the MRI studies along with the operating points of these studies. The curve shown is a partial ROC curve to avoid extrapolation past the range of available data. While we combined studies using different MRI techniques, no study was an outlier on the regression line computed. These figures represent roughly three times the SEER yearly incidence of disease. Among women having an abnormal mammogram (American College of Radiology categories 4 and 5) (54) and/or CBE who are recommended to have a biopsy procedure, where that biopsy is negative for cancer, the estimated positive predictive values of serendipitous lesions found on MRI are listed in Table 3. For our baseline analysis, the product of the likelihood ratio negative of mammography and CBE and the likelihood ratio positive of MRI is less than one. As a result, the age- and race-specific positive predictive values of MRI for serendipitous lesions are actually smaller than the initial prevalences of cancer shown in Table 2. Positive predictive values range from less than 1% chance of disease up to a high estimate of a 1.9% chance of cancer in an MRI lesion found in an 80-year-old high-risk woman. In general, the positive predictive value of MRI increases with age (Table 3). Older blacks tend to have a lower positive predictive value than older whites (although the CIs overlap), but the positive predictive values for blacks and whites under age 60 years are reasonably similar.

**Simulation Model Results**

Table 2 shows the calculated initial prevalence of disease for the overall population, whites, blacks, and women at high risk. These figures represent roughly three times the SEER yearly incidence of disease. Among women having an abnormal mammogram (American College of Radiology categories 4 and 5) and/or CBE who are recommended to have a biopsy procedure, where that biopsy is negative for cancer, the estimated positive predictive values of serendipitous lesions found on MRI are listed in Table 3. For our baseline analysis, the product of the likelihood ratio negative of mammography and CBE and the likelihood ratio positive of MRI is less than one. As a result, the age- and race-specific positive predictive values of MRI for serendipitous lesions are actually smaller than the initial prevalences of cancer shown in Table 2. Positive predictive values range from less than 1% chance of disease up to a high estimate of a 1.9% chance of cancer in an MRI lesion found in an 80-year-old high-risk woman. In general, the positive predictive value of MRI increases with age (Table 3). Older blacks tend to have a lower positive predictive value than older whites (although the CIs overlap), but the positive predictive values for blacks and whites under age 60 years are reasonably similar.

Table 2. Estimated age- and race-specific prevalence of breast cancer*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Total, %</th>
<th>White, %</th>
<th>Black, %</th>
<th>High risk, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–39</td>
<td>0.24</td>
<td>0.24</td>
<td>0.25</td>
<td>0.53</td>
</tr>
<tr>
<td>40–44</td>
<td>0.40</td>
<td>0.40</td>
<td>0.44</td>
<td>0.84</td>
</tr>
<tr>
<td>45–49</td>
<td>0.63</td>
<td>0.64</td>
<td>0.65</td>
<td>1.40</td>
</tr>
<tr>
<td>50–54</td>
<td>0.68</td>
<td>0.70</td>
<td>0.66</td>
<td>1.37</td>
</tr>
<tr>
<td>55–59</td>
<td>0.79</td>
<td>0.81</td>
<td>0.74</td>
<td>1.58</td>
</tr>
<tr>
<td>60–64</td>
<td>0.98</td>
<td>1.03</td>
<td>0.82</td>
<td>1.95</td>
</tr>
<tr>
<td>65–69</td>
<td>1.17</td>
<td>1.23</td>
<td>0.98</td>
<td>2.34</td>
</tr>
<tr>
<td>70–74</td>
<td>1.42</td>
<td>1.48</td>
<td>1.17</td>
<td>2.85</td>
</tr>
<tr>
<td>75–79</td>
<td>1.53</td>
<td>1.58</td>
<td>1.27</td>
<td>3.06</td>
</tr>
<tr>
<td>≥80</td>
<td>1.67</td>
<td>1.73</td>
<td>1.30</td>
<td>3.34</td>
</tr>
</tbody>
</table>

*Values expressed as a percentage; 1% would be equivalent to 1000 cancer cases per 100,000 women.
†A high-risk population is defined for this analysis as a population that has twice the age-specific incidence of breast cancer compared with the U.S. total population incidence.
Sensitivity Analyses

Cancer prevalence. The relationship between the initial prevalence of cancer and the positive predictive value of MRI given a negative mammogram and CBE is shown in Fig. 3. Under our baseline conditions of diagnostic accuracy, the positive predictive value of MRI for a serendipitous lesion is less than the starting prevalence of cancer. This finding is explained by the fact that, under our baseline estimates of diagnostic accuracy, the finding of a negative mammogram and CBE lowers the probability of disease more than the finding of a positive MRI raises the probability.

Sensitivity and specificity of MRI. Fig. 4 shows a graph of the specificity of MRI (for a constant sensitivity) versus the positive predictive value of the MRI, given a negative mammogram and clinical breast examination. For women of all ages, if the specificity of MRI were lower than our baseline estimate, then the positive predictive value of the test would be lower; if the specificity of MRI were to improve, then the positive predictive value of the test would improve. For example, for an average 60-year-old woman to have a 5% chance of cancer with a positive MRI in this setting, the specificity of MRI would have to be more than 95%. For all ages for women at average population age-specific risk of breast cancer, the specificity of MRI would need to be at least 94% to raise the positive predictive value to 5%. Improving the sensitivity of MRI will also slightly improve the positive predictive value, but the analysis is not as dependent upon this parameter. We also varied the likelihood ratio positive of MRI across the range of values represented in the summary ROC curve in Fig. 2, bounded by the range of specificities seen in the analyzed studies. If the most specific point on the summary ROC curve is used, the likelihood ratio positive for MRI is 8.3, and the product of the likelihood ratios would be 1.5. Thus, if future use of MRI for a particular finding demonstrated a sensitivity and specificity at this point on the curve (92% and 89%, respectively), the positive MRI could raise the probability of cancer, for example from a pre-test probability of 1.5%–2.3% for a 75-year-old average woman in the population.

Sensitivity and specificity of mammography and CBE. Fig. 5 shows a graph of the relation between the sensitivity of mammography and the positive predictive value of MRI. If mammography were more sensitive than our baseline estimate of 82%, the positive predictive value of MRI would be lower than estimated. As sensitivity of mammography and CBE decreases, the positive predictive value of the MRI increases, although even with a sensitivity of 40% for mammography and CBE, the positive predictive value of MRI does not reach 5% for average risk women. If the specificity of mammography and

Table 3. Age- and race-specific positive predictive values for cancer (with 95% confidence intervals [CIs]) for women with a serendipitous breast lesion found on MRI and a benign index lesion

<table>
<thead>
<tr>
<th>Age, y, Total</th>
<th>White</th>
<th>Black</th>
<th>High risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predictive value, % (95% CI)</td>
<td>Predictive value, % (95% CI)</td>
<td>Predictive value, % (95% CI)</td>
</tr>
<tr>
<td>35–39</td>
<td>0.13 (0.07–0.21)</td>
<td>0.13 (0.07–0.20)</td>
<td>0.14 (0.07–0.22)</td>
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<tr>
<td>40–44</td>
<td>0.22 (0.12–0.35)</td>
<td>0.22 (0.12–0.35)</td>
<td>0.24 (0.13–0.38)</td>
</tr>
<tr>
<td>45–49</td>
<td>0.35 (0.19–0.55)</td>
<td>0.35 (0.19–0.55)</td>
<td>0.36 (0.20–0.55)</td>
</tr>
<tr>
<td>50–54</td>
<td>0.38 (0.21–0.58)</td>
<td>0.39 (0.21–0.60)</td>
<td>0.33 (0.18–0.51)</td>
</tr>
<tr>
<td>55–59</td>
<td>0.44 (0.24–0.67)</td>
<td>0.45 (0.25–0.68)</td>
<td>0.41 (0.22–0.63)</td>
</tr>
<tr>
<td>60–64</td>
<td>0.54 (0.30–0.83)</td>
<td>0.57 (0.31–0.88)</td>
<td>0.45 (0.25–0.70)</td>
</tr>
<tr>
<td>65–69</td>
<td>0.65 (0.34–0.99)</td>
<td>0.68 (0.37–1.1)</td>
<td>0.54 (0.29–0.84)</td>
</tr>
<tr>
<td>70–74</td>
<td>0.78 (0.44–1.2)</td>
<td>0.82 (0.45–1.3)</td>
<td>0.65 (0.35–0.99)</td>
</tr>
<tr>
<td>75–79</td>
<td>0.84 (0.46–1.3)</td>
<td>0.87 (0.49–1.3)</td>
<td>0.70 (0.39–1.1)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.93 (0.51–1.4)</td>
<td>0.96 (0.52–1.5)</td>
<td>0.72 (0.39–1.1)</td>
</tr>
</tbody>
</table>

* A high-risk population is defined for this analysis as a population that has twice the age-specific incidence of breast cancer compared with the U.S. total population incidence.
CBE decreases, then the positive predictive value will improve, although the analysis is much less dependent on changes in this value. We also examined the effect of our assumption that the sensitivity of mammography and CBE are independent of age. In this sensitivity analysis, we assumed that the combined sensitivity of mammography and CBE for woman younger than 50 years old was 0.8 times our baseline sensitivity. This assumption did not cause large changes; the positive predictive value of MRI ranged from 0.3% for an average 35- to 39-year-old woman to 1.5% for a 45- to 49-year-old high-risk woman. The product of the likelihood ratios for this sensitivity analysis was 1.1; so the combination of negative mammography and CBE did not largely raise the probability of disease for these women whose initial prevalence of disease is small.

**Discussion**

We know of no other work that focuses on the issue of serendipitous breast lesions in women without known cancer. This work was initiated to help guide clinicians who were faced with decisions of whether or not to pursue serendipitous breast lesions found on MRI.

Our analysis has shown that the positive predictive value for cancer of serendipitous lesions found on MRI is quite low. There are several reasons that MRI has such low positive predictive values. First, the positive predictive value is affected by the probability of disease in the women who undergo the test. Overall, the general population prevalence of cancer is low.

Second, the mammogram and CBE add information to the MRI. The mammogram and CBE are, by definition, negative in the area that the serendipitous lesion was found. The fact that these two tests are negative lower the probability that a woman has cancer from her baseline. Our baseline estimates of the sensitivity and specificity of mammography and CBE suggest that the probability of cancer after these tests are negative is roughly one fifth the initial chance of cancer.

Finally, the lack of specificity of MRI contributes to the low positive predictive value of this test. For our baseline estimates of diagnostic accuracy, the specificity of MRI would have to be 83% to have a positive predictive value of MRI for a serendipitous lesion equal to the initial prevalence of cancer. While the studies we examined uniformly reported sensitivity more than 90% for MRI, the specificity of MRI ranged from 37% (55,56) to 89% (57). We have found on meta-analysis that the specificity is quite low; however, should future MRI techniques preserve current sensitivity while greatly improving specificity, then the positive predictive value may become high enough to warrant an immediate biopsy procedure for further evaluation. If the sensitivity of future techniques is similar, then the positive predictive values for serendipitous lesions found using these MRI techniques can be approximated by finding the appropriate value for a woman’s age and the technique’s specificity on the graph in Fig. 4.

Sensitivity analyses show that the probability of cancer in these serendipitous lesions remains extremely low over a wide range of assumptions. As noted above, the analysis was perhaps most dependent on the specificity of MRI, with higher positive predictive values for higher specificity. However, to have the positive predictive value for a 50-year-old woman raised to 5%, for example, the specificity of MRI would have to be 98% given our baseline estimate of sensitivity. Also, the lower the sensitivity of mammography and CBE combined, the better the positive predictive value of MRI; however, the sensitivity of mammography and CBE would have to be 55% for MRI to have a positive predictive value of 1% for 50- to 54-year-old average-risk women.

There are several caveats that should be considered when evaluating our results. First, while our results are based on the best estimates of MRI performance from currently available medical literature, none of the studies specifically address MRI characteristics for incidental lesions. Ideally, future research would include a multicenter, consecutive case series in which all patients with serendipitous lesions and benign index lesions either had an excisional biopsy, an MRI-guided biopsy procedure, or close clinical follow-up to determine the probability of cancer in these serendipitous lesions.

Second, we are currently unable to test the validity of the assumptions underlying this model. However, over a broad range of assumptions, our conclusions that MRI has a very low positive predictive value for serendipitous lesions do not change.

Third, we use a person level analysis, instead of a lesion level analysis. We use this level of analysis to calculate the probability that a woman with a serendipitous finding has cancer, instead of the probability that an individual lesion has cancer. Although we are more interested in the former probability, it is difficult to estimate whether a systematic bias is introduced for women with multiple serendipitous lesions due to lack of data on the risk of cancer with multiple serendipitous lesions compared with a single lesion. If each lesion were statistically independent, then our results, which present data for an average woman with serendipitous lesions, would overestimate the probability of cancer in women with a single serendipitous lesion and underestimate the probability for women with multiple lesions. If the risk of cancer in each of multiple lesions is highly correlated, then the probability of cancer will be similar, regardless of the number of lesions.
Fourth, we are interested in the probability of finding invasive breast cancer in this study; we do not include DCIS in the calculation for positive predictive value. Many women who are diagnosed with DCIS by biopsy do not develop invasive breast cancer (58), although if DCIS is diagnosed then treatment is recommended (59). While the incidence of diagnosed DCIS is currently less than that of invasive cancer (32), an autopsy study (60) suggests that the prevalence of undetected DCIS may be larger than that of undetected invasive cancer. Thus, if DCIS were included, the positive predictive value of MRI would increase over our estimates due to an increase in the pretest probability of having disease, albeit by including lesions of more questionable significance than invasive cancers.

These results apply to women who are "typical members of the population." We include high-risk women, e.g., someone with a strong family history of cancer or with a previous history of a biopsy for benign breast disease. This analysis does not apply to someone for whom there is a very high prior probability of cancer. Excluded from this analysis would be women who have a BRCA1 or BRCA2 breast cancer genetic susceptibility mutation, which put women at much higher lifetime risk of cancer than those with a family history but without a susceptibility mutation (61,62). Also excluded in this analysis are those women who have a high clinical suspicion of having a cancer; for instance, if the serendipitous lesion were found in a woman who is being worked-up for findings suspicious for metastases in other organs or a woman who has known breast cancer or prior breast cancer, the results of this analysis would not be applicable. Also, this analysis is specific to one point in time. There are currently no data on the positive predictive value of MRI for lesions that change over time. Lesions increasing in size on follow-up MRI, for example, may have a higher probability of being cancer than the one-time finding of a serendipitous lesion modeled here.

Finally, the optimal threshold positive predictive value for cancer for which a biopsy procedure of a suspicious lesion should be performed is not well established. This threshold probability would be dependent on a full evaluation of the risks and benefits of a biopsy procedure, for example, balancing the risks of an invasive procedure versus the consequences of potentially delaying diagnosis of a cancer. We provide the probabilities shown in Table 3 as data to assist clinicians and patients in making decisions about further evaluation of serendipitous MRI lesions. The results of this analysis indicate that the probability that a woman with serendipitous lesions found on MRI has breast cancer is lower than the approximately 15%–35% probability of finding cancer in women currently undergoing a biopsy procedure (3–6). Thus, it is unlikely that an immediate biopsy procedure would be the most beneficial strategy.

In summary, we have found that, in women with a suspicious lesion on mammogram and/or CBE found to be benign, serendipitous breast lesions found on MRI are extremely unlikely to be malignant. While the risk is certainly not zero, for a typical woman the probability of cancer in these lesions is low enough that an immediate biopsy procedure could be avoided.

**Appendix Table 1. Summary of magnetic resonance imaging (MRI) studies* used in analysis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study (reference No.)</th>
<th>Level of analysis†</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>No. of patients</th>
<th>Contrast MRI techniques‡</th>
<th>Pre- and post-contrast comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Cross et al. (55)</td>
<td>Lesion</td>
<td>95</td>
<td>37</td>
<td>41</td>
<td>RODEO</td>
<td>No</td>
</tr>
<tr>
<td>1993</td>
<td>Harms et al. (56)</td>
<td>Lesion</td>
<td>94</td>
<td>37</td>
<td>30</td>
<td>RODEO</td>
<td>No</td>
</tr>
<tr>
<td>1994</td>
<td>Boetes et al. (63)</td>
<td>Lesion</td>
<td>95</td>
<td>86</td>
<td>83</td>
<td>3D MP-RAGE</td>
<td>Turbo T1 SGE (60)</td>
</tr>
<tr>
<td>1994</td>
<td>Gilles et al. (64)</td>
<td>Person</td>
<td>95</td>
<td>53</td>
<td>144</td>
<td>T1 spin-echo</td>
<td>T1 spin-echo (6)</td>
</tr>
<tr>
<td>1994</td>
<td>Turket et al. (65)</td>
<td>Lesion</td>
<td>100</td>
<td>83</td>
<td>35</td>
<td>T2 spin-echo; T1 spoiled GRASS</td>
<td>T2 spin-echo; T1 spoiled GRASS</td>
</tr>
<tr>
<td>1995</td>
<td>Stomper et al. (66)</td>
<td>Lesion</td>
<td>92</td>
<td>65</td>
<td>49</td>
<td>T1; T2 spin-echo; T1 SPGR</td>
<td>T1; T2 spin-echo; T1 SPGR</td>
</tr>
<tr>
<td>1996</td>
<td>Heiber et al. (67)</td>
<td>Lesion</td>
<td>100</td>
<td>73</td>
<td>56</td>
<td>25 patients: T1; T2; 3D SPGR</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Obdeijn et al. (68)</td>
<td>Person</td>
<td>91</td>
<td>67</td>
<td>54</td>
<td>STIR</td>
<td>2D T1 SGE (3)</td>
</tr>
<tr>
<td>1996</td>
<td>Perman et al. (57)</td>
<td>Lesion</td>
<td>100</td>
<td>89</td>
<td>28</td>
<td>T1 Full Fourier</td>
<td>T1 Full Fourier</td>
</tr>
<tr>
<td>1997</td>
<td>Bone et al. (69)</td>
<td>Breast</td>
<td>92</td>
<td>72</td>
<td>220</td>
<td>3D T1 SGE</td>
<td>3D Dynamic Half Fourier (6)</td>
</tr>
<tr>
<td>1997</td>
<td>Helbich et al. (70)</td>
<td>Lesion</td>
<td>96</td>
<td>82</td>
<td>66</td>
<td>65 patients: T2; 3D T1 SGE 3 patients; T2; Dynamic T1 SGE</td>
<td>No</td>
</tr>
<tr>
<td>1997</td>
<td>Nunes et al. (71)</td>
<td>Person</td>
<td>96</td>
<td>79</td>
<td>192</td>
<td>T1 spin-echo; T2 spin-echo</td>
<td>67 patients: 2D SPGR</td>
</tr>
</tbody>
</table>

*All studies used machines with 1.5 Tesla MRI units except for Helbich’s study where a 0.5 Tesla machine was used on three patients. All studies gave doses of gadolinium of 0.1 mg/kg body weight except for Boetes (0.2 mg/kg) and Obdeijn (20 mL for all patients).

†Level of analysis refers to the unit used for calculating sensitivity and specificity.

‡RODEO = rotating delivery of excitation off-resonance; MP-RAGE = magnetization-prepared rapid gradient echo; SGE = spoiled gradient echo; GRASS = gradient-recalled acquisition in the steady state; SPGR = spoiled gradient-recalled echo; STIR = short tau inversion recovery; 2D, 3D = 2 or 3 dimensional. Numbers in parentheses represent the numbers of times images were acquired.


NOTES

1Editor’s note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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