Frequency of Malignancy Seen in Probably Benign Lesions at Contrast-enhanced Breast MR Imaging: Findings from ACRIN 6667

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Purpose:
To determine the frequency of malignancy in probably benign lesions seen at magnetic resonance (MR) screening of the contralateral breast in patients with known breast cancer enrolled in American College of Radiology Imaging Network (ACRIN) protocol 6667.

Materials and Methods:
ACRIN conducted a prospective multi-institutional MR imaging screening trial of the contralateral breast in women in whom breast cancer had been diagnosed recently. Each participating institution obtained institutional review board approval before patient accrual and was compliant with HIPAA. Informed consent was obtained from the patients. At enrollment, all women had negative clinical breast examination results and negative mammograms of the study breast. At image interpretation, radiologists scored lesions by using the Breast Imaging and Reporting and Data System (BI-RADS) lexicon. Of the 969 women who comprised the final study group, 106 were classified as having a BI-RADS category 3 lesion as their highest scoring lesion at MR imaging. There were 145 BI-RADS category 3 lesions in 106 patients.

Results:
In the 106 patients with at least one BI-RADS category 3 lesion, there were 37 masses (25.5%), 59 areas of non-mass enhancement (40.7%), and 47 foci of enhancement (32.4%). In two (1.4%) of these patients, no findings were reported. Eighty-three (78.3%) of the 106 patients had no evidence of malignancy in the study breast after 2 years of follow-up; the remaining 23 (21.7%) received a tissue diagnosis. Seventeen (16.0%) of the 106 patients elected to undergo biopsy. Biopsy was recommended in the remaining six patients (5.7%) on the basis of follow-up imaging findings. The biopsy results were benign in 18 (78%) of the 23 patients, whereas they showed atypical hyperplasia in two (9%). One (4%) of the 23 patients had ductal carcinoma in situ. Overall, malignancy was diagnosed in one (0.9%) of the 106 patients.

Conclusion:
In a multi-institutional study, the frequency of malignancy in MR-detected BI-RADS category 3 lesions was 0.9% (95% confidence interval: 0.02%, 5.14%).

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Short-term follow-up is the accepted management for mammographic lesions that are probably, but not definitely, benign. For these lesions to be classified as Breast Imaging Reporting and Data System (BI-RADS) category 3 lesions, they must fit the criteria of probably benign features, as described in the BI-RADS atlas (1). Several authors have reviewed the outcome of mammographic BI-RADS category 3 lesions and consistently reported the malignancy rate to be less than 2% (2–6). This malignancy rate is considered acceptable by the radiology community. The potential delay in cancer diagnosis that results from short-interval follow-up is outweighed by the potential to minimize the number of unnecessary benign biopsies and decrease the health care expenditure that would have resulted had category 3 lesions been sampled for biopsy immediately rather than followed up. If the BI-RADS category 3 criteria are applied appropriately, the outcome of more than 98% of these lesions will be benign. For the lesions that are ultimately diagnosed as malignant, short-term follow-up allows for close surveillance of the lesions. Given that the average estimated doubling time of breast cancers is 100–180 days, short-interval follow-up would still lead to early detection of potential cancers without compromising patient survival.

A magnetic resonance (MR) imaging lexicon, similar to the mammographic BI-RADS lexicon, has been developed. In comparison to the mammographic BI-RADS lexicon, which was developed in the 1980s, the MR imaging BI-RADS lexicon is relatively new. The MR imaging BI-RADS lexicon was first published in the 2003 edition of the American College of Radiology BI-RADS Atlas (1). Although MR imaging is highly sensitive in depicting invasive breast cancers, the estimated specificity of the modality has varied across studies (7–13). Because the MR imaging lexicon is relatively new, it has not been as widely studied as the mammographic lexicon. Our goal was to determine the frequency of malignancy in probably benign lesions seen at MR evaluation of the contralateral breast in patients with known breast cancer enrolled in American College of Radiology Imaging Network (ACRIN) protocol 6667.

Materials and Methods

ACRIN, funded by the National Cancer Institute, conducted a prospective multi-institutional breast MR imaging study (protocol 6667) with the goal of evaluating the diagnostic yield of MR imaging in the detection of cancer in the contralateral mammographically and clinically negative breast in women in whom unilateral breast cancer (intraductal or invasive cancer) had been recently diagnosed (14). Patient recruitment began April 1, 2003, and ended June 10, 2004. Twenty-five institutions participated in the study. Each participating institution obtained institutional review board approval before patient accrual and was compliant with the Health Insurance Portability and Accountability Act. Informed consent was obtained from the patients. The study’s quality control committee evaluated the image quality of MR images and the biopsy capability of each institution. The women recruited for the study had benign or negative findings on mammograms and negative clinical breast examination findings in the study breast within 90 days of enrollment. All participating women underwent contrast-medium–enhanced MR imaging.

Patient Selection

Patients were included in ACRIN 6667 if they received a diagnosis of breast cancer within 60 days of MR imaging and they had negative (BI-RADS category 1) or benign (BI-RADS category 2) mammographic findings and negative clinical breast examination results in the contralateral breast within 90 days of enrollment. Patients were not eligible to enroll in the study if they were younger than 18 years, had a contraindication to gadolinium-containing contrast agents or MR imaging, were unable to give full consent, had previously undergone biopsy of the study breast within 6 months of study entry, or had undergone chemotherapy within the past 6 months. Patients were also excluded if they were undergoing hormonal therapy for breast cancer, had undergone MR imaging of the study breast within the past 12 months, had new breast symptoms needing additional evaluation, or had a remote history of breast cancer.

Advance in Knowledge

In our study, the malignancy rate of MR-detected Breast Imaging Reporting and Data System (BI-RADS) category 3 lesions fell within the accepted range for mammographically detected BI-RADS category 3 lesions.

Implication for Patient Care

Although the MR imaging BI-RADS lexicon does not give specific imaging feature guidelines for BI-RADS category 3 lesions, if the lesions have a high likelihood of being benign and lack suspicious imaging features, the lesions may be placed in the probably benign category and followed up rather than sampled for biopsy.
Breast Imaging Technique
Contrast-enhanced breast MR imaging was performed with a 1.5-T or greater imager with a dedicated breast coil. Images were acquired before and after gadolinium administration. Unenhanced and contrast-enhanced three-dimensional T1-weighted gradient-echo sequences were required with a repetition time of less than 60 msec and an echo time of less than 20 msec. Patients underwent at least one unenhanced series and at least two contrast-enhanced series. The first contrast-enhanced sequence was performed less than 4 minutes after contrast material administration, and the second sequence was performed within 8 minutes after contrast material administration. For breasts imaged in the axial or coronal planes, the protocol required a field of view of 36 cm or less with a 256 × 512 matrix. If the sagittal plane was used for imaging, the protocol required a field of view of 20 cm or less with a 128 × 256 matrix. Other requirements included a voxel size of less than 0.9 mm in the frequency-encoding direction and 1.8 mm in the phase-encoding direction. All images were acquired with 3-mm-thick sections and fat suppression.

MR Image Interpretation
The radiologists interpreting the MR images met the minimum standard criteria of competency. All readers had to have interpreted at least 50 breast MR images and had to have performed at least five breast MR-guided procedures to participate in the study. The readers were instructed to interpret the MR images by using American College of Radiology BI-RADS criteria (1). The six MR imaging assessment categories used at initial interpretation were as follows: 0, need additional imaging evaluation; 1, negative; 2, benign; 3, probably benign; 4, suspicious abnormality; and 5, highly suggestive for malignancy. For BI-RADS category 0 lesions, additional imaging was performed. For BI-RADS category 3 lesions, short-term follow-up MR imaging was to be performed, as recommended by the initial interpretation.

The findings of all MR examinations were evaluated and recorded with regard to the lesion type, shape, margin, distribution, and internal architecture. An enhancing lesion smaller than 5 mm was categorized as a focus of enhancement. Nonmass enhancement was categorized as an area of enhancement greater than or equal to 5 mm. Kinetic information was obtained by drawing a region of interest over the most intensely enhancing area to measure the intensity of the pixels on the unenhanced image and the two contrast-enhanced images. The readers were asked to classify the initial enhancement phase as not applicable, slow, medium, or rapid. The readers were also asked to classify the delayed enhancement phase after 2 minutes or after the curve began to change from the following options: not applicable, persistent, plateau, or washout. The initial kinetic enhancement was reported for 114 lesions and was not applicable for 29; no lesions were reported in two patients. The delayed enhancement kinetics were reported for 115 lesions and were not applicable for 28. For lesions smaller than 3 mm in diameter, kinetic information was not reported due to the small size. Kinetic information was not reported for two lesions.

At follow-up MR imaging, a definitive negative, benign, or suspicious recommendation had to be rendered. Further details of the study already have been reported (14).

The cancer status of the study participants was followed up for 730 days after MR imaging. During this time, the results of the imaging tests, pathologic and clinical examinations, and surgeries were documented. The patients who had documented histologic diagnosis of cancer in the study breast within 730 days of the study MR imaging were classified as having findings that were positive for cancer. The remaining patients were considered to have findings that were negative for cancer.

Data Collection and Analysis
ACRIN performed data collection and management. Data were analyzed at the Biostatistics Center of ACRIN, which is located at the Center for Statistical Sciences of Brown University (Providence, RI). Site personnel performed patient registration and data entry via the Internet. Exact confidence intervals were computed for the rate of cancer among the patients with BI-RADS category 3 lesions. We used χ² tests for proportions and t tests for means to compare patient characteristics for lesions assigned a BI-RADS score of 3 and those with BI-RADS scores of 0, 1, 2, 4, or 5. These results are listed in Tables 1 and 2. Computations were performed with SAS software (SAS Institute, Cary, NC).

Results
A total of 1007 women were recruited into the ACRIN 6667 contralateral breast screening trial; 969 women made up the final study group. Twenty patients were determined to be ineligible on the basis of the entry criteria. Eighteen additional patients were excluded for the following reasons: fourteen did not undergo MR imaging, and four withdrew from the study. Of the 909 women who constituted the final study group, 106 (10.9%) were assigned a BI-RADS category 3 lesion as their highest scoring lesion.

The mean age of the patients assigned a final BI-RADS category 3 lesion was 50.4 years (range, 28–80 years). Twenty patients had a first-degree relative with breast cancer; eleven patients had mothers in whom breast cancer was diagnosed, and 10 had sisters in whom breast cancer was diagnosed. Both the menopausal status and the parity status of the women at the time of enrollment are listed in Tables 1 and 2.

At the final 2-year follow-up, malignancy was diagnosed in only one of the 106 patients with a BI-RADS category 3 lesion (0.9%; 95% confidence interval: 0.02%, 5.14%). Eighty-three (78.3%) of the 106 patients had no evidence of malignancy in the study breast after 2 years of clinical follow-up; the remaining 23 (21.7%) received a tissue diagnosis. Seventeen (16.0%) of the 106 patients with BI-RADS category 3 lesions opted to receive a tissue diagnosis rather than undergo imaging follow-up. Eight of those 17 women elected to undergo bilateral mastectomy at the time of their definitive surgery for their known breast
cancer in the nonstudy breast. Biopsy was recommended for the remaining six (5.7%) of 106 patients on the basis of findings at follow-up imaging. The patients underwent the following procedures: mastectomy (n = 8), excisional biopsy (n = 4), core needle biopsy (n = 9) and fine-needle aspiration (n = 2); 83 patients did not undergo a procedure. In the 23 patients who underwent biopsy, results were as follows: eighteen patients (78%) had benign findings, two patients (9%) had atypical ductal hyperplasia, two patients (9%) had atypical lobular hyperplasia, and one patient (4%) had ductal carcinoma in situ.

In the 106 patients with at least one BI-RADS category 3 lesion, 143 probably benign lesions were identified. Of the 37 masses, 19 (51%) were oval, 10 (27%) were round, seven (19%) were lobulated, and one (3%) was irregular. Thirty (81%) of the 37 masses had smooth margins and seven (19%) had irregular margins. Twenty-five (68%) of the 37 masses had homogeneous internal enhancement, seven (19%) had hypointense internal septations, two (5%) had rim enhancement, and three (8%) had heterogeneous internal enhancement. Twenty-nine (78%) of the 37 masses had moderate internal enhancement, four (11%) had minimal enhancement, and four (11%) had marked enhancement.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BI-RADS 0, 1, 2, 4, or 5 (n = 963)</th>
<th>BI-RADS 3 (n = 106)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>.0507</td>
</tr>
<tr>
<td>American Indian or Alaskan native</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>19 (2.2)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>42 (4.8)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>0</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>782 (90.8)</td>
<td>98 (92.4)</td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>8 (0.9)</td>
<td>0</td>
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</tr>
<tr>
<td>Unknown</td>
<td>12 (1.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td>.4215</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (4.1)</td>
<td>36 (4.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>822 (95.8)</td>
<td>103 (98.0)</td>
<td></td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td>.0241</td>
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<tr>
<td>Privately Insured</td>
<td>577 (71.1)</td>
<td>81 (81.5)</td>
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<td>Medicare, Medicaid, or Veterans Administration</td>
<td>234 (28.8)</td>
<td>18 (18.1)</td>
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<td>Menopausal status</td>
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<td></td>
<td>.0002</td>
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<td>Postmenopause or surgical menopause</td>
<td>510 (59.2)</td>
<td>42 (40.0)</td>
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<td>Pre- or perimenopause</td>
<td>351 (40.7)</td>
<td>63 (60.0)</td>
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<td>Previous benign breast biopsy</td>
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<td>Yes</td>
<td>128 (14.8)</td>
<td>12 (11.3)</td>
<td></td>
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<tr>
<td>No</td>
<td>735 (85.1)</td>
<td>94 (88.6)</td>
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<td>History of hormone use</td>
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<td></td>
<td>.7985</td>
</tr>
<tr>
<td>Yes</td>
<td>685 (79.3)</td>
<td>86 (81.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>178 (20.8)</td>
<td>20 (18.8)</td>
<td></td>
</tr>
<tr>
<td>First-degree relative (mother or sister) had breast cancer</td>
<td></td>
<td></td>
<td>&gt; .99</td>
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<tr>
<td>Yes</td>
<td>166 (23.7)</td>
<td>20 (22.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>532 (76.2)</td>
<td>67 (77.1)</td>
<td></td>
</tr>
<tr>
<td>Family history of breast cancer (relative of any degree)</td>
<td></td>
<td></td>
<td>.7478</td>
</tr>
<tr>
<td>Yes</td>
<td>532 (62.3)</td>
<td>67 (64.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>321 (37.6)</td>
<td>37 (35.5)</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Data are numbers of patients. Data in parentheses are percentages. Results are reported for patients who answered questions. Not all patients answered all questions or knew all answers. Thus, totals do not always add up to the total number of patients.

### Nonmass Lesions

There were 59 nonmass enhancing lesions that were at least 5 mm in diameter. Of those 59 lesions, the nonmass enhancement was classified as diffuse in seven (12%), regional in 20 (34%), segmental in seven (12%), affecting multiple regions in seven (12%), linear in five (8%), ductal in three (5%), and at least 5 mm in diameter in 10 (17%). The internal characteristics of nonmass enhancement were described as clumped in seven lesions (12%), heterogeneous in 25 (42%), homogeneous in 12 (20%), and stippled or punctate in 15 (25%).

### Enhancing Foci

There were 47 enhancing foci smaller than 5 mm in diameter. Due to the small size of the foci, internal enhancement characteristics were not reported.

### Kinetic Features

The kinetic features of the probably benign lesions were assessed in 115 lesions. During the initial enhancement phase, enhancement was classified as rapid in 29 (25.2%) of the 115 lesions, medium in 52 (45.2%), and slow in 34 (29.6%). The delayed enhancement features were also reported. Persistent enhancement was seen in 63 (56.1%) of lesions, plateau was seen in 41 (35.3%), and washout was seen in 10 (8.6%). Kinetic information was reported as not applicable for 29 lesions in the initial phase and 28 lesions in the delayed phase. In two patients, no lesions were reported. Because of the small size of some of the lesions, it was not possible to obtain kinetic information about these lesions.
At 2-year follow-up, ductal carcinoma in situ was diagnosed in one (0.9%; 95% confidence interval: 0.02%, 5.14%) of the 106 patients. The remaining 105 patients remained cancer free at 2-year follow-up. The one category 3 lesion that was ultimately proved to be malignant was diagnosed at mastectomy. On MR images, the lesion was a focal area of nonmass-like enhancement smaller than 5 mm in diameter. Kinetic information was not determined because of its small size. The patient elected to undergo bilateral mastectomy shortly after the initial MR examination. At histologic evaluation, a 4-mm well-differentiated ductal carcinoma in situ was found.

**Discussion**

When Sickles wrote his landmark article describing the outcome of BI-RADS category 3 lesions (2), he strictly defined the criteria used to evaluate mammographic BI-RADS category 3 lesions. When the criteria for probably benign lesions were closely adhered to, he found the malignancy rate to be 0.3% (17 of 3184 lesions) (2). These results have been corroborated by other researchers (3–6). It is crucial, however, that the mammographic lesions fit the criteria for probably benign characteristics as defined by Sickles. If the criteria are not closely followed, cancers may be incorrectly placed into the probably benign category (15,16). Unlike BI-RADS category 3 mammographic lesions, BI-RADS category 3 MR imaging lesions have not been well studied. Although the probably benign category is included in the American College of Radiology MR imaging BI-RADS lexicon, the specific imaging feature guidelines are not defined in the BI-RADS atlas other than that the lesions should have a high likelihood of being benign. Few studies have examined the malignancy rate among lesions classified as probably benign at MR imaging (17–20).

Sadowski and Kelcz (17) reported a 0% malignancy rate in a retrospective study of 473 women. The authors classified 79 patients (17%) as having BI-RADS category 3 lesions. Liberman et al (18) reported a 7%–10% malignancy rate in their retrospective study of 367 high-risk women with normal mammograms. Their probably benign assignment rate was 24% (89 of 367 patients). In 2000, Kuhl et al (19) screened 192 women who were proved or suspected to be BRCA1 or BRCA2 carriers. Of the 192 women, 19 (10%) were classified as having MR imaging BI-RADS category 3 lesions. At follow-up, one of the 19 patients was classified as having invasive ductal carcinoma. Eby et al (20) also looked retrospectively at the malignancy outcome of MR imaging BI-RADS category 3 lesions. The authors report a cancer yield of 0.6% (one of 160 cases) on the basis of 1–1.5-year follow-up. The malignancy rates reported by Sadowski and Kelcz (17) and Liberman et al (18) were substantially higher than...
In our prospective multi-institutional study, we found a malignancy rate of 0.9% (one of 106 patients). In addition, in our study, the probably benign category was assigned as the highest level of assessment in 106 (10.9%) of 969 patients. These rates are more in line with the results reported by Eby et al (20) and Kuhl et al (19). In the literature, the percentage of probably benign mammographic diagnosis is reported to be 3%–10% (2–6,21). Our malignancy rate and frequency of the probably benign category more closely approximates the rates reported with the mammographic BI-RADS category 3 lesions.

There may be several factors why the results of our study more closely approximate the malignancy rate reported for mammographic BI-RADS category 3 lesions than those previously reported by Sadowski and Kelcz (17) and Liberman et al (18). First, the American College of Radiology MR imaging BI-RADS lexicon was available as a reference, giving the radiologists at the participating institutions a standard lexicon to follow during the conduct of ACRIN 6667. However, the MR imaging BI-RADS lexicon was not available at the time the patients in the studies by Sadowski and Kelcz (17) and Liberman et al (18) underwent imaging. Second, in our study, a group of radiologists with a similar experience level interpreted breast MR images. To be a reader for the ACRIN 6667 study, the radiologist had to meet minimum requirements, as reported in the Materials and Methods section. This allowed us to have a group of radiologists with a similar level of experience in the interpretation of MR images. Third, all studies were performed to meet minimum standards set by the protocol. This gave us a set of images with uniform quality obtained in a short period of time. In the study by Sadowski and Kelcz (17), the MR studies were performed from 1994 to 2002. During this time, there were improvements in MR technology that would allow for improved image quality and, hence, enhanced detection of malignant lesions in the later years of the study period. Similarly, our MR studies were performed 3–4 years after the study by Liberman et al (18), and this difference of only a few years, during which improved imaging and biopsy techniques were developed, may have resulted in improved detection. Finally, in the study by Sadowski and Kelcz (17), patients had mammographic findings or abnormalities that prompted the breast MR imaging study. Some of the patients had mammographic abnormalities that corresponded to the probably benign MR imaging lesions, and some of the MR imaging BI-RADS category 3 lesions were followed up with mammography or ultrasonography and not MR imaging. Having a mammographic finding in conjunction with the MR imaging finding may have led to a higher malignancy rate in that study. Our patients had negative mammograms, as did the patients in the study by Liberman et al (18), although both groups of patients in the studies were in the high-risk category.

Our study had several limitations. First, tissue diagnosis was available for only 22 patients. The remaining patients had no evidence of cancer at 2-year follow-up. Because some of the lesions that were classified as probably benign at MR imaging were small and some of the patients underwent chemotherapy for their index breast cancer, the 2-year follow-up may have been too short for the malignancies to manifest. A 2-year imaging follow-up period or an MR examination at 2 years was not required by the protocol. All available clinical data, however, were collected and reviewed. Furthermore, because all patients received a diagnosis of breast cancer, it is likely that they were closely followed up with, at a minimum, conventional imaging. Second, our patient population was limited to women in whom unilateral breast cancer had been recently diagnosed. Therefore, our data may not be applicable to the general population. Finally, the readers had to meet minimum criteria as set forth in the protocol. Despite their level of experience, readers in our study used descriptors, such as irregular, ductal, and linear washout kinetics, that would not ordinarily be considered probably benign features. This attests to the lack of specific descriptors or guidelines for BI-RADS category 3 lesions that are currently available to the interpreting radiologists.

In conclusion, our results suggest that the malignancy rate in lesions classified as probably benign with MR imaging is in the accepted range for malignancy detected in mammographic BI-RADS category 3 lesions. Our malignancy rate of 0.9% is in line with the malignancy rate of less than 2% found in mammographic BI-RADS category 3 lesions. Our frequency of BI-RADS category 3 assignments also fell within the range reported in the literature for the mammographic probably benign lesions. With continuing improvements in technology and increasing reader experience in breast MR imaging, additional studies may help corroborate our findings.

References


