Short Communication

Is Mammography Adequate for Screening Women with Inherited BRCA Mutations and Low Breast Density?

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Abstract

Background: Several observational studies have shown that magnetic resonance imaging (MRI) is significantly more sensitive than mammography for screening women over age 25 at high risk for hereditary breast cancer; however, MRI is more costly and less specific than mammography. We sought to determine the extent to which the low sensitivity of mammography is due to greater breast density.

Methods: Breast density was evaluated for all patients on a high-risk screening study who were diagnosed with breast cancer between November 1997 and July 2006. Density was measured in two ways: qualitatively using the four categories characterized by the Breast Imaging Reporting and Data System and quantitatively using the four categories characterized by the Breast Imaging Reporting and Data System and classified as (a) ≤10%, (b) 11% to 25%, (c) 26% to 50%, and (d) >50% density. Comparison of sensitivity of mammography and MRI for each individual density category and after combining the highest two and lowest two density categories was done using Fisher’s exact test.

Results: A total of 46 breast cancers [15 ductal carcinoma in situ (DCIS) and 31 invasive] were diagnosed in 45 women (42 with BRCA mutations). Mean age was 48.3 (range, 32-68) years. Overall, sensitivity of mammography versus MRI was 20% versus 87% for DCIS and 26% versus 90% for invasive cancer. There was a trend towards greater mammographic sensitivity for invasive cancer in women with fatter breasts compared with those with greater breast density (37-43% versus 8-12%; P = 0.1), but this trend was not seen for DCIS.

Conclusion: It is necessary to add MRI to mammography for screening women with BRCA mutations even if their breast density is low. (Cancer Epidemiol Biomarkers Prev 2008;17(3):706–11)

Introduction

Until recently, annual mammography was recommended as the sole imaging modality for screening high-risk women, including those with inherited BRCA mutations, who have a 50% to 80% lifetime risk of developing breast cancer (1, 2). This recommendation was based on extrapolation of strong evidence for mortality reduction from screening mammography in the general population. However, reports of mammography-based screening of women with BRCA mutations showed a high percentage of interval cancers that were large and/or had already spread to axillary lymph nodes (3, 4).

Several prospective single and multicenter observational studies have shown that for screening women at very high risk for breast cancer based on genetic testing or family history, breast magnetic resonance imaging (MRI) is significantly more sensitive than mammography (71-96% versus 28-43%; refs. 5-11). However, MRI is ~10 times more costly than mammography and has significantly lower specificity with accompanying higher rates of recalls, additional imaging, and biopsies for resolving ambiguous screening results (5-7, 9, 10).

Identifying specific subpopulations of very high risk women for whom mammography alone might be an adequate screening tool would be highly desirable. For screening the general population, the amount and percentage of radiodense breast parenchyma relative to fat is inversely correlated with mammographic sensitivity. The reported sensitivity of mammography for fatty breasts ranges from 80% to 92% compared to 30% to 69% for dense breasts (12-15). Based on these data, we sought to determine whether mammography would have acceptable sensitivity for screening very high risk women with low breast density.
Materials and Methods

Study Population. Between November 1997 and July 2006, 507 very high risk women ages 25 to 65 (395 with confirmed BRCA1 or BRCA2 mutations) were enrolled in the single center Toronto MRI Screening Study. Patient eligibility was restricted to women unaffected or with a past history of breast cancer who (a) were known BRCA mutation carriers, (b) were untested first-degree relatives of a BRCA mutation carrier, or (c) had three relatives on the same side of the family with breast cancer diagnosed before age 50 or epithelial ovarian cancer. The study was approved by the Human Subjects Review Board of Sunnybrook Health Sciences Centre, and informed consent was obtained from all patients.

Screening Protocol. An in-depth description of study methodology can be found in previous publications (5, 16). Eligible women were screened annually with film-screen mammography, MRI, and ultrasound and semiannually with clinical breast examination. All three annual imaging modalities were done successively on the same day at Sunnybrook Health Sciences Centre. Ultrasound screening was discontinued in May 2005 due to inadequate sensitivity and specificity.

Mammograms, ultrasound, and MRI examinations were classified using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) as follows: 0, needs further workup; 1, negative; 2, benign finding; 3, probably benign finding, short-term follow-up; 4, suspicious abnormality, biopsy should be considered; and 5, highly suggestive of malignancy (17). Biopsy was suggested if at least one screening modality was suspicious for malignancy (5).

Mammographic Density Measurement. The mammographic density of the ipsilateral breast of all women diagnosed with breast cancer in the study was categorized (a) qualitatively and (b) quantitatively. The ipsilateral breast was chosen for consistency across the patient population; the contralateral breast mammogram was not available/appropriate for patients with previous contralateral breast cancer and a previous ipsilateral mammogram was not available for all patients. Qualitative categorization determined by one of seven radiologists, who were experienced in breast imaging, was one of four BI-RADS categories: 1, mostly fatty (<25% dense); 2, scattered fibroglandular tissue (25-50% dense); 3, heterogeneously dense (51-75% dense); and 4, extremely dense (>75% dense; ref. 17). Interobserver variability was not formally assessed.

Quantitative breast density categorization has been described in detail in a publication by Byng et al. (18) and is shown in Fig. 1. In this study, the cranio-caudal view of the ipsilateral mammogram from the most recent round of screening was digitized using a Lumisys 85 digitizer at 260 μm pixel size and 12 bits precision. All mammograms were presented to an observer blinded to clinical data, including method of detection. Using the computer program Cumulus, the observer selected two threshold gray-level values: one to identify the overall breast area and the other for classifying the dense area (18, 19). Cumulus calculated only those pixels above the threshold values chosen. Percentage of mammographic density was defined as the area of

Figure 1. Computer-aided density quantification of a mammographic image. Pixels in red define the outline of the breast, whereas those in green outline pixel values above the density threshold. The percentage density is the ratio of the total number of “dense pixels” to the total number of pixels in the breast multiplied by 100.

Table 1. Patients and cancers

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. women</td>
<td>45</td>
</tr>
<tr>
<td>Mean age (range), y</td>
<td>48.3 (32-68)</td>
</tr>
<tr>
<td>Risk status</td>
<td></td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>23</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>19</td>
</tr>
<tr>
<td>First-degree relative BRCA1 carrier</td>
<td>1</td>
</tr>
<tr>
<td>High-risk family*</td>
<td>2</td>
</tr>
<tr>
<td>No. previous screens [median (range)]</td>
<td>2 (1-5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>15</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>30</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Invasive tumor size [mean (range)], cm</td>
<td>0.94 (0.4-3.0)</td>
</tr>
</tbody>
</table>

*Three or more relatives on the same side of the family with epithelial ovarian cancer or early onset breast cancer.
dense tissue divided by the overall breast area multiplied by 100 (Fig. 1).

**Statistical Analysis.** Qualitative and quantitative density categorizations were compared using linear regression analysis. Midpoints of the standard numerical density ranges of the BI-RADS categories (e.g., 12% we used for category 1 representing <25% dense) were used as the qualitative density value. These were correlated with percent densities calculated using the quantitative technique. Linear regression analysis was also used to plot the relationship between quantitative breast density and patient age.

To compute the sensitivity of mammography and MRI for different density categories, the following quantitative categories were defined: ≤10%, 11% to 25%, 26% to 50%, and >50% dense. Although different from the BI-RADS quartiles, these categories were created based on our data set in which there were only eight women with a quantitative breast density of >50%.

For both qualitative and quantitative categories, the two lower and two higher density categories were collapsed due to very low numbers in the highest and lowest categories. Sensitivity was defined as the number of cancers detected by an imaging modality divided by the total number of cancers detected in the study. Using Fisher’s exact tests, the sensitivities of mammography and MRI in the higher and the lower density categories were compared as were the overall sensitivities of both modalities.

**Results**

Forty-eight cancers were diagnosed in 507 women between November 1997 and July 2006. Two cases were excluded from density analysis because diagnostic mammograms done at the time of diagnosis were irretrievable. Two cancers developed in one woman while being followed on study. The demographics of these 45 women, of whom 42 had BRCA mutations, are shown in Table 1. Nine (45%) of 20 cancers in women with BRCA2 mutations were ductal carcinoma in situ (DCIS) compared with 5 (22%) of 23 cancers in women with BRCA1 mutations.

Linear regression analysis comparing qualitative and quantitative breast density categorization showed a moderate correlation ($R^2 = 0.47; P < 0.0001$; Fig. 2). The quantitative density measurements were generally lower than the qualitative BI-RADS. Comparison of age and ipsilateral percent breast density showed an inverse relationship ($R^2 = 0.18; P = 0.0032$).

By quantitative measurement, mean breast density of all 45 women was 26.7%. The mean density for women with BRCA1 mutations was 28.8% (range, 2.8-78.9%), not significantly different from the mean density for women with BRCA2 mutations, which was 23.2% (range, 4.4-71.6%).

Overall, as reported by others, mammography was significantly less sensitive than MRI for detecting breast cancer (24% versus 89%; $P < 0.001$; refs. 5-11). For women with BRCA1 versus BRCA2 mutations, the relative sensitivities of mammography and MRI were very similar (25% versus 25% for mammography and 84% versus 92% for MRI).

As illustrated in Table 2, the sensitivity of mammography was 33%, 33%, 16%, and 33% for BI-RADS categories 1 to 4, respectively. Using quantitative categorization, sensitivity was 31%, 27%, 20%, and 12.5% for lowest to highest density categories, respectively.

In contrast, MRI sensitivity was high for all density categories, ranging from 100% (BI-RADS 1) to 88% (BI-RADS 3) and detecting 2 of 3 (67%) BI-RADS 4 cases.

<table>
<thead>
<tr>
<th>Table 2. Sensitivity of MRI versus mammography by density</th>
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<tbody>
<tr>
<td>No. cancers detected/total [sensitivity (%)]</td>
</tr>
<tr>
<td><strong>BI-RADS</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td><strong>Quantitative</strong></td>
</tr>
<tr>
<td>≤10% dense</td>
</tr>
<tr>
<td>11-25% dense</td>
</tr>
<tr>
<td>26-50% dense</td>
</tr>
<tr>
<td>&gt;50% dense</td>
</tr>
</tbody>
</table>
With the quantitative measurement MRI sensitivity was 92%, 87%, 100%, and 75% for categories 1 to 4, respectively (Table 2). There was no statistically significant effect of density on MRI sensitivity.

After collapsing the four categories into two (low density and high density) for both density measurement methods, comparisons were made between the mammographic sensitivities in the low density and high density categories (Fig. 3). The sensitivity of mammography for women with low density was not significantly greater than for women with high density as measured by either quantitative analysis ($P = 0.49$) or qualitative analysis ($P = 0.30$).

The relative sensitivities of mammography versus MRI were almost identical for DCIS (20% versus 87%) and for invasive cancer (26% versus 90%). There was a trend towards lower mammographic sensitivity with increasing density for invasive cancers with both methods of density measurement (qualitative: 43% low density versus 12% high density, $P = 0.11$; quantitative: 37% low density versus 8% high density, $P = 0.10$). The opposite trend was seen for DCIS probably due to chance because of very small numbers (qualitative: 0% low density versus 28% high density, $P = 0.52$; semiquantitative: 0% low density versus 50% high density, $P = 0.53$).

**Discussion**

In this study, we found that in a population of women at very high risk for hereditary breast cancer, although there was a trend towards higher sensitivity of screening mammography for detecting invasive cancer in women with fattier breasts, mammographic sensitivity was still far lower than that of MRI (Fig. 4). The sensitivity of mammography for detecting DCIS was very low even in women with fatty breasts. Findings were similar regardless of how density was measured.

It is plausible that mammographic detection of early invasive cancer is adversely affected by breast density,
whereas early detection of DCIS is not. This is because mammographic detection of invasive cancer is generally dependent on the ability to visualize a mass or architectural distortion, features often obscured by background breast density. Mammographic detection of DCIS, however, is generally due to visibility of malignant calcifications, which is less affected by breast density. In fact, MRI detected the majority of DCIS cases in this series before the development of malignant calcifications. Similarly, in a recent series of 33 cases of pure DCIS in women who underwent both MRI and mammography at diagnosis, only 9 of the cases were detected by mammography, with 8 of the 9 detected due to the presence of calcifications. In addition, the ability of mammography to detect DCIS was not found to be related to breast density (7).

One might argue that our study overestimates the benefits of MRI, as over time these DCIS lesions might have developed calcifications, enabling them to be detected by mammography before the development of invasion on subsequent screening. However, this seems unlikely given the universally low prevalence of DCIS without invasion reported in women with BRCA (particularly BRCA1) mutations not screened with MRI (3, 4, 20, 21).

The sensitivity of mammography for women in this study was generally poor (24%) compared with the ~50% sensitivity reported when screening women with BRCA mutations using mammography without MRI. This is due, in part, to the much smaller size (and earlier stage) of the invasive cancers detected by MRI in this study (mean, 1.0 cm) compared with the size reported with mammography alone (mean, 1.3-1.7 cm; refs. 3, 20, 21). Some of the cancers detected by MRI, while still mammographically occult, would likely have been detected by mammography on a subsequent screen but at a larger size.

In our study, there was only a moderate correlation between qualitative and quantitative methods of breast density assessment with generally lower density values found with the quantitative technique. For example, using qualitative assessment, 27 of 45 cancers were rated as having >50% breast density, whereas the quantitative method identified only 8 cancers with this degree of density. This is not surprising in that the quantitative method is a simple binary threshold technique, whereas with the qualitative method the radiologist can take into account the degree of intensity of the densities and areas with density that is just below the quantitative threshold. On the other hand, the BI-RADS method of density assessment is limited, except at absolute extremes (that is, completely fatty or breasts composed entirely of dense fibroglandular tissue) due to its inherent nonquantitative techniques. In a recent report by Martin et al., although there was good correlation between quantitative estimates of breast density by trained radiologists and by an automated mammography density estimation program, there was poor correlation between the quantitative estimates and the qualitative assessments using BI-RADS categories (22).

One potential criticism of our study is that because the ipsilateral breast was used for density measurements, the presence of a tumor might have falsely elevated the measured density. However, because the mean tumor size was only 1 cm, such an effect was unlikely to have been significant. Moreover, similar results were obtained upon repetition of our analysis using the density of the contralateral breast for those patients without a history of contralateral breast cancer.

Corroborating our findings is a recent study by Lehman et al., investigating the sensitivity of MRI for detecting clinically and mammographically occult cancer in the contralateral breast at the time of a breast cancer diagnosis (23). In that study, MRI was just as likely to
detect mammographically occult cancer in women with fatty breasts (9 of 299 = 3%) as in women with dense breasts (20 of 666 = 3%).

In conclusion, although mammography may be somewhat more sensitive for detecting invasive cancers in very high risk women with fatty breasts than in those with greater breast density, even in women with low breast density sensitivity was <50%, which is clearly inadequate. It is, therefore, appropriate to recommend MRI screening for all women with BRCA mutations regardless of their breast density.

References

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