Comparison of Breast Magnetic Resonance Imaging, Mammography, and Ultrasound for Surveillance of Women at High Risk for Hereditary Breast Cancer

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Purpose: **Recommended surveillance for *BRCA1* and *BRCA2* mutation carriers includes regular mammography and clinical breast examination, although the effectiveness of these screening techniques in mutation carriers has not been established. The purpose of the present study was to compare breast magnetic resonance imaging (MRI) with ultrasound, mammography, and physical examination in women at high risk for hereditary breast cancer.**

Patients and Methods: **A total of 196 women, aged 26 to 59 years, with proven *BRCA1* or *BRCA2* mutations or strong family histories of breast or ovarian cancer underwent mammography, ultrasound, MRI, and clinical breast examination on a single day. A biopsy was performed when any of the four investigations was judged to be suspicious for malignancy.**

Results: **Six invasive breast cancers and one noninvasive breast cancer were detected among the 196 high-risk women. Five of the invasive cancers occurred in mutation carriers, and the sixth occurred in a woman with a previous history of breast cancer. The prevalence of invasive or noninvasive breast cancer in the 96 mutation carriers was 6.2%. All six invasive cancers were detected by MRI, all were 1.0 cm or less in diameter, and all were node-negative. In contrast, only three invasive cancers were detected by ultrasound, two by mammography, and two by physical examination. The addition of MRI to the more commonly available triad of mammography, ultrasound, and breast examination identified two additional invasive breast cancers that would otherwise have been missed.**

Conclusion: **Breast MRI may be superior to mammography and ultrasound for the screening of women at high risk for hereditary breast cancer.**

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WOMEN WHO CARRY a constitutional mutation of the *BRCA1* gene or the *BRCA2* gene face a high lifetime risk of breast cancer. The cancer risk is significant in these women at age 25, and by the age of 70, approximately 80% of mutation carriers will have developed invasive breast cancer.[1] After breast cancer is diagnosed in one breast, there is a 30% risk of developing cancer in the contralateral breast within 5 years.[2] Although there is evidence that breast cancer risk can be reduced by prophylactic mastectomy,[3] oophorectomy,[4] and tamoxifen,[5] few women choose these interventions, and no preventive measure will eliminate the risk of breast cancer completely. Current recommendations for the management of high-risk women include semi-annual clinical breast examination and annual mammography beginning between the ages of 25 and 35.[6] Despite widespread endorsement of mammographic screening for high-risk women, no evidence to date has shown that routine mammography reduces cancer mortality in *BRCA1* or *BRCA2* carriers. Most hereditary breast cancers occur in premenopausal women, and the value of screening mammography is significantly lower for women below age 50.[7-9]

If breast cancer screening is to be successful, the majority of cancers among screened women must be detected when tumors are small and before the occurrence of distant or nodal metastases. It may be that a combination of imaging modalities will be superior to any single screening technique. Magnetic resonance imaging (MRI) is a new breast imaging technique that is gaining popularity.[10,11] With the use of gadolinium-DTPA as an intravenous contrast agent, breast MRI has been shown to be capable of detecting early breast cancer[12] with 94% to 100% sensitivity.[13,14] The enhancement of the breast lesion reflects local tissue changes in blood flow, capillary permeability, and extracellular volume.[15,16] These changes are thought to be characteristic of tumor-related angiogenesis and help to distinguish tumors from surrounding stromal and fatty tissues. MRI quality is not influenced by breast density, which is believed to limit the effectiveness of mammography in

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young women. The use of MRI as a screening method for the general population is not practical at present because of its high cost and inadequate specificity[17,18]; however, it may be an appropriate screening tool for high-risk populations.

In the general population, ultrasound is not in use as a breast cancer screening tool but is commonly used to evaluate breast abnormalities found at mammography or on physical examination. However, among high-risk women, ultrasound in combination with other methods may have a role in breast cancer screening. To determine whether MRI increases the ability to detect small breast cancers in high-risk women, beyond that of mammography, clinical breast examination, and ultrasound, we screened a series of 196 high-risk women using all four modalities.

PATIENTS AND METHODS

Study Population

Study subjects were recruited between November 1997 and May 2000 from the following six familial cancer clinics in southern Ontario: Toronto-Sunnybrook Regional Cancer Centre, Women's College Hospital, North York General Hospital, University Health Network, Mt Sinai Hospital, and London Regional Cancer Centre. Eligible women were age 25 to 60 and at high risk for breast cancer because of either (1) a germline *BRCA1* or a *BRCA2* mutation, (2) a first-degree relative with a *BRCA1* or *BRCA2* mutation (but an unknown personal mutation status), or (3) three or more relatives on the same side of the family with breast cancer diagnosed before age 50 or ovarian cancer. A woman with a past history of unilateral breast cancer who satisfied the criteria was also eligible if her contralateral breast had not been removed. In this case, she could be included among the affected relatives under (3) above.

Pregnant or lactating women were asked to defer their participation. Women with metallic foreign objects in their bodies, a history of bilateral breast cancer, or known metastatic disease were excluded.

Participation in the study was offered to eligible women (and to their eligible first-degree relatives) in the context of genetic counseling. These women were invited to contact the study coordinator directly if they wished to participate.

Study Protocol

The study was approved by the institutional review boards of the participating institutions. Eligible women were invited to begin the screening protocol at least 1 year after their last mammogram. The protocol included evaluation by the following four modalities: clinical breast examination, mammography, screening ultrasound, and MRI, all performed at the Sunnybrook campus of the Sunnybrook and Women's College Health Sciences Centre on the same day after informed written consent was obtained. For premenopausal women, screening was performed during the second week of the menstrual cycle to minimize the occurrence of breast densities or enhancing masses related to the menstrual cycle. For women with a past history of breast cancer who had undergone breast-conserving surgery with or without radiation, bilateral breast screening was performed, and for those who had undergone unilateral mastectomy, contralateral breast screening was performed.

Physical Examination

Physical examination of the breasts and regional lymphatic areas was performed by one of two physicians experienced in breast examination. Each examination was coded as normal, suggestive of benign disease, or suspicious for malignancy.

Mammography

Conventional four-view film/screen mammograms were conducted and were reviewed by a single radiologist. Further views were done where necessary. Mammograms were scored on a five-point scale, using the following American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) categories: 1, negative; 2, benign finding; 3, probably benign finding, short follow-up interval suggested; 4, suspicious abnormality, biopsy should be considered; and 5, highly suggestive of malignancy.[19]

The mammographic density of the breast tissue was evaluated from the screening mammogram. The total percentage of dense breast was calculated as the ratio of the area of dense breast compared with the total breast area using a standard protocol.[20,21] In addition, the density of the breast tissue surrounding the breast cancer was compared to the overall breast density. In these cases, the location of the breast cancer was estimated by reference to the MRI image.

MRI

Simultaneous bilateral magnetic resonance was done using a General Electric Signal 1.5 Tesla magnet (Milwaukee, WI). The first 65 patients were imaged with a single-turn elliptical coil after a bolus injection of 0.1 mmol/kg of gadolinium-DTPA. After appropriate imaging to localize the breast, bilateral three-dimensional spoiled gradient recalled (SPGR) images were collected in the coronal plane (repetition time [TR]/echo time [TE]/flip angle = 12.9 msec/4.3 msec/20° with 28 slices of 4- to 6-mm thickness) before injection and after injection for a period of 10 minutes. The scan time for each three-dimensional data set was 90 seconds. For the remaining 131 patients, a phased-array coil arrangement was used, which provided high-quality bilateral sagittal images and a 2.5-fold greater signal-to-noise ratio. The technique allows simultaneous imaging of both breasts using dual three-dimensional sagittal TR-interleaved SPGR sequences (TR/TE/flip angle = 18.4 msec/4.3 msec/40° from 28 partitions per breast).[20] The coil support apparatus was designed to provide breast immobilization with gentle medial-lateral compression, thereby optimizing coil coupling to each breast. The precontrast images were subtracted from the contrast-enhanced images to improve visualization of the enhancing structures.

In cases where a potentially suspicious area of enhancement (anything other than an obvious benign structure such as a blood vessel or scar) was detected, an additional set of dynamic, unilateral MRI scans of the suspicious breast was conducted. This scan involved a series of nine adjacent, two-dimensional images (SPGR, TR/TE/flip angle = 150 msec/4.2 msec/50°), which allowed dynamic monitoring of tissue enhancement with a temporal resolution of 20 seconds. These images were used to further track tracer kinetics and to help characterize the lesion for clinical management.

MRI results were scored in a pattern similar to the BI-RADS classification using a combination of morphology and enhancement kinetics.[22] Criteria that were considered included overall lesion configuration, lesion margins, internal architecture (eg, internal septations or central clearing), and the time course of signal intensity changes.

Ultrasound

Shortly after the study began, the protocol was modified to include ultrasound as a fourth screening modality. The first 10 patients did not receive ultrasound. High-resolution ultrasound was performed by an experienced physician blinded to the other imaging studies using a 7.5-MHz transducer. The reports were coded in a pattern similar to the BI-RADS categories. Any solid lesion, unless obviously benign by criteria established by Stavros,[23] was considered suspicious enough for cancer to warrant a biopsy.

Breast Biopsies

A biopsy was recommended if either the clinical breast examination, the mammogram, the MRI examination, or the screening ultrasound was judged to be suspicious for cancer (BI-RADS categories 4 or 5). If the MRI screening test was abnormal (BI-RADS 3, 4, or 5), but no other modality was abnormal, then a high-resolution MRI follow-up sequence was performed approximately 4 weeks later. Cases that remained suspicious for malignancy on repeat MRI examination proceeded to biopsy.

Core and excisional biopsies were performed under ultrasound or stereotactic guidance, with the exception of two women in whom the abnormality was visualized by MRI but was not seen with directed ultrasound or mammography. In these cases, an excisional biopsy was performed using an MRI-guided wire localization device.[18] This consisted of a needle guide plate that provided medial-lateral compression of the breast and contained an array of 4,000 holes drilled on 2.5 mm centers as well as MR-visible fiducial markings to allow accurate definition of the location of the tumor. The appropriate hole was used to guide the needle into the tumor for final wire localization.

Pathologic Analysis

The biopsy specimens were processed according to standard protocols.[24] Tumor grade was determined according to the modified Bloom-Richardson classification.[25] Immunohistochemistry was performed as described previously for the assessment of estrogen and progesterone receptor status,[26] p27 levels,[27] Her-2/*neu* overexpression,[28] and the presence of stable p53 protein.[29] In addition, microvessel density was determined using immunohistochemistry for factor VIII–related antigen and scored according to the method of Weidner.[30] Microvessel counts were performed in areas of highest vascularity (hot spots) using a ×40 objective and a ×10 eyepiece (magnification of ×400). Single endothelial cells and vessels were counted. Four fields were randomly selected from the hot spots and scored. The results were expressed as the average number of vessels/four ×40 high-power fields. Microvessel densities above 15 were considered high. Fibroadenomas were scored in a similar manner.

RESULTS

The characteristics of the 196 study subjects are listed in Table 1. Their mean age at the time of screening was 43.3 years (range, 26 to 59 years). Ninety-six of the patients (49%) had a *BRCA1* or *BRCA2* mutation. Seventeen patients had unknown mutation status but had a first-degree relative with a mutation. Eighty-three patients had a strong family history of breast or ovarian cancer, but no mutation had been identified. In this category, there were 66 women for whom testing had been performed for the family, but a mutation had not yet been identified. There were 17 women for whom testing had not been performed. This group included six women who had no living affected relative available for testing and 11 women who chose not to undergo testing for other reasons. Fifty-five of the patients (28%) had a past history of breast cancer, including 34 of those with a *BRCA1* or *BRCA2* mutation. The majority (71%) of the women had a screening mammogram within the previous 15 months, but none had a previous MRI. Sixty-four percent performed regular breast self-examination.

Table 1. Characteristics of the Study Subjects (N = 196)

	No.	%
Age, years		
Mean	43	
Range	26-59	
Race or ethnic group		
Ashkenazi Jewish	60	31
Other white	111	57
Other	25	13
Mutation status		
BRCA1 carrier	59	30
BRCA2 carrier	37	19
Unknown	100	51
Cancer history		
Previous breast cancer	55	28
Menopausal status		
Premenopausal	123	63
Postmenopausal	73	37

Fourteen eligible women contacted the study coordinator to discuss participation but did not complete the study protocol. Seven patients declined after the study protocol was described to them in detail. Three women agreed to participate initially but could not be reached to schedule an appointment. Two women presented for an MRI examination but experienced claustrophobia and withdrew before the examination was completed. One patient became pregnant after enrolling, and her participation has been deferred. One patient discovered a lump in her breast shortly after her examination was scheduled and withdrew from the study.

Breast Cancers

A total of 33 patients underwent a biopsy because an abnormality was detected on one or more screening tests. Six invasive cancers and one case of ductal carcinoma in situ (DCIS) were detected. All six invasive tumors were detected by MRI examination, three were detected by ultrasound, two by physical examination, and two by mammography. The mammograms of the four patients for whom the tumor was missed by that modality were all classified as BI-RADS 1. The characteristics of the tumors and the screening results are presented in Table 2. Five of the women with invasive tumors were mutation carriers, and

Table 2. Characteristics of Patients, Screening Results, Breast Density, and Pathologic Features for Invasive Cancers

Patient Factors				Screening Results				Breast Density		Tumor	
ID	Age	Mutation Status	Previous Breast Cancer	CBE	Mammo	US	MRI	At Lesion	Entire Breast (%)	Size (cm)	MF
63	52	*BRCA1*	Yes	−	+	+	+	Low	14	0.7	−
122	33	*BRCA1*	Yes	−	+	+	+	Low	16	1.0	+
19	46	*BRCA1*	No	−	−	−	+	High	51	0.5	+
5	50	*BRCA1*	No	−	−	−	+	High	52	0.5	+
23	49	*BRCA2*	No	+	−	N/D	+	High	37	1.0	+
81	53	Fhx	Yes	+	−	+	+	High	20	1.0	−

Abbreviations: Fhx, family history of breast cancer, no mutation identified; CBE, clinical breast examination; US, ultrasound; Mammo, mammography; N/D, not done; MF, medullary features.

the other woman had a past history of breast cancer. The DCIS was detected only by mammography and occurred in a 52-year-old *BRCA2* carrier with a past history of breast cancer. The prevalence of cancer was 6.2% in the subgroup of mutation carriers. Four cancers occurred in women with a previous history of breast cancer, and all were in the contralateral breast. Among the women in whom cancer was not detected on this study, no interval cancers have been diagnosed to date within 1 year of screening, with a median follow-up of 18 months (range, 8 to 38 months). The screening characteristics of the individual modalities are discussed below.

MRI

MRI tests were completed for 196 women. Follow-up sequence studies were performed for 32 cases (16%). One hundred seventy-three women had a result that was judged to be normal or of low suspicion, and 23 women had a result that was suspicious for cancer (BI-RADS categories 4 and 5) and have had a biopsy. For 15 of these women, the MRI was the only abnormal screening test, and for eight women, at least one additional screening test was suspicious. Cancer was detected in six (26%) of the 23 women who had a biopsy. For two of the six women with cancer, the MRI was the only abnormal screening test. The women who underwent biopsy but did not have cancer were found to have fibroadenoma (seven patients), stromal fibrosis (five), proliferative fibrocystic changes (three), fat necrosis (one), and an intramammary lymph node (one).

Mammography

Four women with positive mammograms (BI-RADS 4 or 5) proceeded to biopsy. Two of these had invasive cancer, one had DCIS, and one had a radial scar. Both invasive cancers were seen on MRI and ultrasound. The DCIS was not detected by any other modality.

Physical Examination

Three women had breast examinations that were considered suspicious for cancer, and biopsies were recommended. Two of the three women were found to have cancer. Both cancers were detected by at least one of the imaging studies.

Ultrasound

Ultrasound screening examinations were performed on 186 of the 196 women. Sixteen women had results that were suspicious for malignancy and proceeded to biopsy. Three of these 16 women were found to have cancer. All three women with cancer also had suspicious MRI examinations. Eight women had a suspicious result on ultrasound alone, and no cancers were detected in these women.

Comparison of Screening Modalities

The sensitivities, specificities, and positive and negative predictive values for invasive cancer associated with the four screening modalities are presented in Table 3. In the absence of MRI, a total of 19 biopsies would have been done and four cancers detected. With MRI alone, 23 biopsies would have been performed and six cancers identified. The addition of MRI to the screening protocol incurred the need for 14 additional biopsies, and two additional cancers were detected.

Pathologic Features

All six invasive tumors detected were node-negative and were 1 cm or less in size (range, 0.5 to 1.0 cm). All had high-grade histologic features. Four patients had tumors with medullary features, evidenced by pushing margins, syncytial arrangement of tumor cells, and a loose fibrovascular stroma containing a lymphoplasmacytic infiltrate. These patients had documented *BRCA1* or *BRCA2* mutations. The tumors of the other two women showed histologic features typical of invasive breast cancer, not otherwise specified. One of these women was a *BRCA1* carrier and the other had a personal and family history of breast cancer. There was no evidence of lymphatic invasion, and none of the cases showed a detectable in situ component.

All tumors were estrogen and progesterone receptor–negative, all had low p27 levels, and none showed evidence

Table 3. Performance Characteristics of Screening Modalities*

Modality	Total Screens	Abnormal Screens	Cancers Detected	Sensitivity (%)	Positive Predictive Value (%)	Specificity (%)	Negative Predictive Value (%)
CBE	196	3	2	33	66	99.5	97
Mammography	196	3	2	33	66	99.5	97
Ultrasound†	186	16	3	60	19	93	99
MRI	196	23	6	100	26	91	100

NOTE. The terms sensitivity and specificity here are based on the data available and are presented for comparison across the modalities in the study. Sensitivity: number of cancers detected by a particular modality divided by the total number of cancers detected by the four modalities (six); positive predictive value: number of cancers detected by a particular modality divided by the total number of abnormal tests which resulted in a biopsy; specificity: number of normal tests (no biopsy indicated) in women who did not have cancer detected by any modality divided by the total number of women who did not have cancer detected by any modality; negative predictive value: number of normal tests (no biopsy indicated) in women who did not have cancer detected by any modality divided by number of normal tests including false negatives.

*The patient with DCIS was excluded from this analysis.

†One patient with cancer did not receive an ultrasound screening examination, and she was excluded from the totals based on ultrasound.

of Her-2/*neu* overexpression or stable p53 protein. Microvessel density was high in all tumors. The range of values extended from 17 to 22 vessels per high-power field (mean, 18.5 vessels). The seven fibroadenomas detected on MRI showed values from 12 to 14 vessels per high-power field (mean, 13 vessels).

Breast Density

The measured breast densities for the total breast (expressed as a percentage) and for the areas surrounding the tumors are presented in Table 2. The mean percentage of dense breast tissue for the two mammographically detected tumors was 15%, compared with the mean of 40% for the four tumors not identified by mammography. Breast density correlated with the histological presence of stromal fibrosis in the tissue surrounding the tumors (Fig 1). In the two cases identified by mammography, breast density in the vicinity of the tumors was low, and tumors were surrounded by adipose tissue (Fig 1, cases 63 and 122, A-C). In the four cases not detected by mammography, breast density was high, and the tumors were either partially or completely surrounded by stromal fibrosis (Fig 1, cases 19, 5, 23, and 81, A-C).

DISCUSSION

The objective of the present study was to compare breast MRI with mammography, screening ultrasound, and physical examination in women at high risk for hereditary breast cancer. We identified six stage I invasive cancers and one noninvasive breast cancer in our population of 196 women. All six invasive cancers were detected by MRI. In contrast, only three invasive cancers were detected by ultrasound, two by mammography, and two by physical examination. Two cancers were missed by all screening modalities other than MRI.

Our estimates of sensitivity of the four screening modalities (Table 3) were based on only six tumors that were detected at the first round of screening. It is possible that we missed some cancers that will become clinically apparent over the next few years. As a result, our estimate of 100% sensitivity for MRI is likely to be high. However, no interval cancer was reported in this cohort of women to date, after a mean follow-up period of 18 months. We expect that the cancers detected in future screening rounds will be smaller on average than the mean size of 0.8 cm for cancers detected by this prevalence screen.

Our results suggest that mammography is less sensitive than MRI for surveillance of *BRCA1* and *BRCA2* mutation carriers. Only two of six invasive tumors were identified by mammography. The poor sensitivity of mammography in this population may have been related both to the young age of the women and to the characteristics of hereditary breast cancer. The majority of hereditary breast cancers are diagnosed in premenopausal women in whom breast density is on average higher than in older women.[31] Several groups of investigators have reported lower sensitivity of screening mammography and higher rates of interval cancers in women with dense breasts compared with those with fatty breasts, after adjustment for age, menopausal status, and other possible confounding factors.[32-34] Interestingly, the two tumors that were detected by mammography in our study were situated in areas of low breast density, whereas those tumors not detected by mammography occurred in areas with high breast density and were either partially or completely surrounded by stromal fibrosis. In a small study of Asian women, it was found that the breast density was higher in women with *BRCA1* mutations than in age-matched controls,[35] but this finding has not been replicated in the North American population. In addition, *BRCA1*-associated tumors are less likely than sporadic tumors to

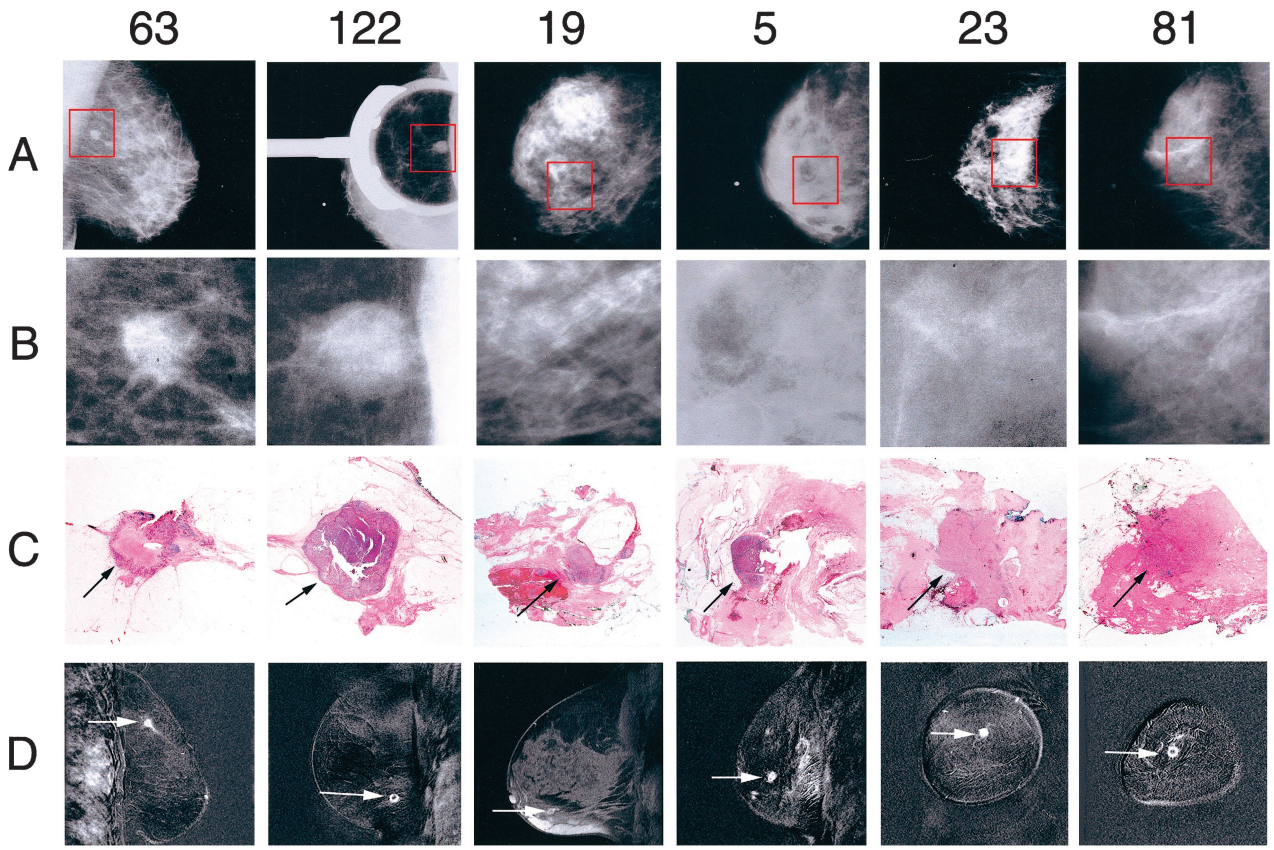

Fig 1. Imaging features and pathologic characteristics of the six invasive breast cancers. Row A, mammography, medio-lateral-oblique (cases 63, 19, 5, and 81) and cranio-caudal (cases 122 and 23) views; row B, mammography, magnification views; row C, tumor specimens; row D, MRI, sagittal (cases 63, 122, 19, and 5) and coronal views (cases 23 and 81).

have associated DCIS,[36] which often presents with microcalcifications that lead to detection by mammography.

Detection by MRI depends on the visualization of intravascular contrast media and is proportionate to the density of blood vessels at a given site.[37] In this study, 13 false-positive results were obtained using MRI. Seven of these resulted from the detection of fibroadenomas, which were shown to have microvessel densities approaching that of the tumors. Vascular benign lesions can often but not always be distinguished from cancers on the basis of enhancement kinetics.[22] Although the positive predictive value of MRI was low (26%), we chose to biopsy all lesions for which there was even a fairly low suspicion of malignancy. The majority of these patients underwent core biopsy by directed ultrasound. We are currently evaluating new techniques that we hope will help distinguish benign from malignant areas of enhancement on MRI in order to reduce the number of biopsies. It is expected that the biopsy rate on MRI screens subsequent to the initial screen will be lower.

One previous study from Germany reported results similar to ours. Kuhl et al[38] performed screening MRI examinations on 192 asymptomatic, high-risk women. They found invasive or in situ cancers in six (3.1%) of 192 women at the first MRI screening round and in three (3.0%) of 101 women at the second screening round. Genetic testing was not done on all patients, but of the nine women with cancer, six were carriers of a *BRCA1* mutation, and one carried a *BRCA2* mutation. Of the nine MRI-detected cancers, only three were apparent on mammography.

It is not yet possible to establish which high-risk women would benefit from MRI surveillance, but it seems that priority should be given to women who are known to carry a *BRCA1* or *BRCA2* mutation. In our study, six of seven cancers were detected in women who were mutation-positive. In the German study, seven of nine women with cancer had a *BRCA1* or *BRCA2* mutation.[38] It remains to be seen whether or not women without an identified mutation but with a significant family history of cancer are at sufficiently high risk to warrant

intensive surveillance. Future studies should explore whether breast density can be helpful in selecting other groups of high-risk women most likely to benefit from MRI screening in addition to mammography.

Our results suggest that MRI may be superior to mammography, ultrasound, and physical examination of the breasts for the surveillance of women at high risk for hereditary breast cancer. The invasive tumors we detected were node-negative and 1 cm or less in maximum dimension. These preliminary findings are encouraging but need to be confirmed on larger samples and with longer follow-up. Furthermore, it is not yet known what proportion of MRI-detected tumors will ultimately be cured. Large trials similar to ours are now underway in the United States and Europe.[39] In the absence of a randomized screening study, the best test of the utility of MRI screening will be to document long-term survival of a cohort of the *BRCA1* and *BRCA2* mutation carriers with MRI-detected tumors, using combined data from all MRI screening trials.

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