WHEN DENSITY INDEX IS COMBINED WITH RISK CALCULATION, DEDICATED BREAST MRI YIELDS MORE EARLY CANCERS NOT SEEN ON MAMMOGRAPHY

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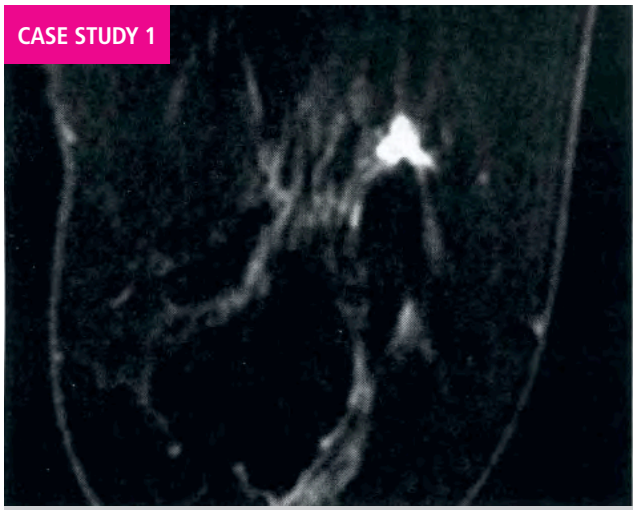
INTRODUCTION

In 2007, the American Cancer Society (ACS) issued new guidelines for screening women "at high-risk" for breast cancer. The recommendations, based primarily on published literature from clinical trials, were for annual screenings with mammography and with breast magnetic resonance imaging (bMRI) –either alternately every six months or at the same time. The guidelines defined "high-risk" as a lifetime risk of approximately 20% to 25% or greater as defined by BRCAPRO or other models that are largely dependent on family history (FH). The ACS task force placed emphasis on familial and genetic risk for breast cancer because this risk category alone was used for entry into all of the prospective MRI screening trials. The ACS's definition of "high-risk" has proven to be highly debatable.

Today breast MRI plays a major role in both the diagnosis and clinical management of many breast cancer patients. The use of dedicated, high-resolution breast MRI yields anatomical and physiological information that may benefit women at all levels of risk.

At Mercy Health Center, where we have an Aurora® 1.5T Dedicated Breast MRI System –we have developed an in-house protocol combining calculated risk and breast density for MRI screening recommendations. Using our protocol and our dedicated breast MRI system, we are finding more cancers early, when they are most treatable, in women who otherwise wouldn't be considered candidates for breast MRI (according to the current guidelines). Our yield-to-date through breast MRI screening, at least on prevalence scans, is comparable to those studies that have relied on risk alone for entry. From our experience since 2003, we strongly believe that the screening criteria for mammography and complementary breast MRI should be expanded – rather than tightened or limited.

CASE STUDY 1



Breast MRI in a 53 year-old female whose sister was diagnosed with breast cancer at age 48. Although this was the only traditional risk factor for the patient, mammographic density was extreme, in and of itself an additional risk factor, as well as a predictor of low mammographic sensitivity. A 1.8 cm, grade 1, node negative, invasive ductal carcinoma was identified on MRI screening.

STUDY DESIGN

At Mercy Women's Center we had established an in-house protocol as an extension of our risk assessment/genetic testing program before any organization or society had announced formal guidelines. Thus, we had no precedent on which to build. We were prompted to consider high-risk screening based on a retrospective study published in 2003 in the American Journal of Radiology that evaluated 367 consecutive high-risk patients with normal findings on mammography and examination.[1] MRI detected 13 cancers in the 367 patients – a 3.5% yield in these women. Knowing that mammography is not as effective in women with dense breasts, we considered breast density to be equal to risk calculation as a determinant of the benefits of bMRI.

> "Using our protocol and our dedicated breast MRI system, we are finding more cancers early, when they are most treatable, in women who otherwise wouldn't be considered candidates for breast MRI (according to ACS guidelines)."
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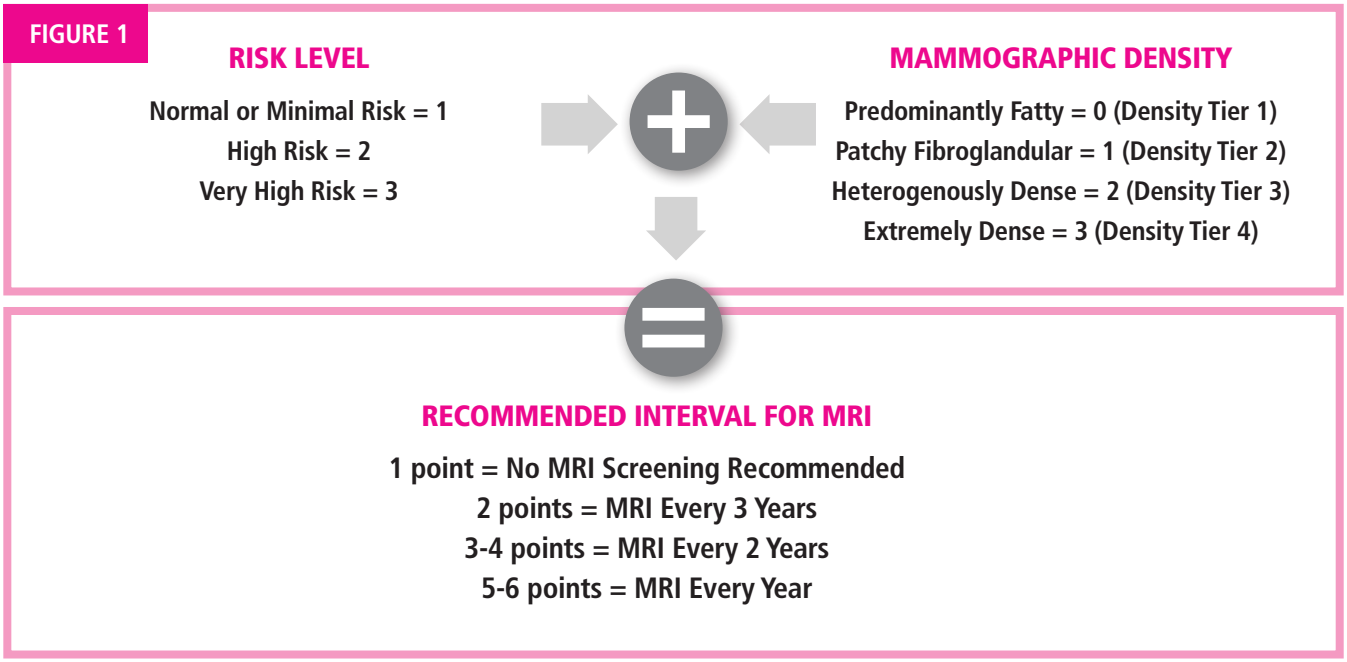
> - Dr. Rebecca Stough

We use a combined point system for risk level[2] and for mammographic density[3], weighting them equally. By using risk categories and not numbers, we avoided age discrimination that accompanies strategies utilizing lifetime risks wherein remaining risk declines over time. The median age of the patients was 54 and they ranged in age from 41 to 75. Figure 1 below summarizes the Risk Assessment and Recommendation System:

FIGURE 1



**Evidence for biennial and triennial screening is taken from mammography screening trials, no evidence to date for MRI at any interval other than annual

Women for whom bMRI is recommended every three years (2 points) are being monitored closely to see if any benefit of bMRI can be demonstrated with this longer interval. Studies recommend bMRI annually or not at all. However, we believe there is a biologic basis for considering longer intervals in some women, particularly older women, where tumor doubling times are longer, even in those women with hereditary risk.[4] Also, bMRI is not a stand-alone screening tool, so a longer interval does not leave patients "out-in-the-cold."

RESULTS

With our protocol and the Aurora MRI System, we identified 26 cancers in 24 women with normal mammograms and normal examination. Of the 26 MRI-discovered cancers, 6 were DCIS (25%) and 18 were invasive carcinomas (75%). All 18 invasive cancers were node-negative, 2 were clinically node negative (cN0) as the surgeon opted to leave the axilla untouched. The median invasive tumor size was 1.0 cm – the same as in mammography – and the mean size was 1.1 cm **(see Table 1)**.

Most notable is that the majority of these women would not have qualified for screening with MRI if the decision had been based on family history or other models, and if density had not been a factor. More than half – 14 of 24, 58% - failed to qualify for MRI screening using the most lax ACS guidelines and/or the National Comprehensive Cancer Network (NCCN) guidelines. Of the 24 patients, 5 qualified for BRCA testing, but still would have been excluded from MRI based on the ACS criteria which requires that a first-degree relative already be confirmed as a BRCA mutation carrier. Only 2 of the 24 would have qualified using the Gail model, none using the Claus model and only 6 using the Tyrer-Cuzick model **(see Table 1)**.

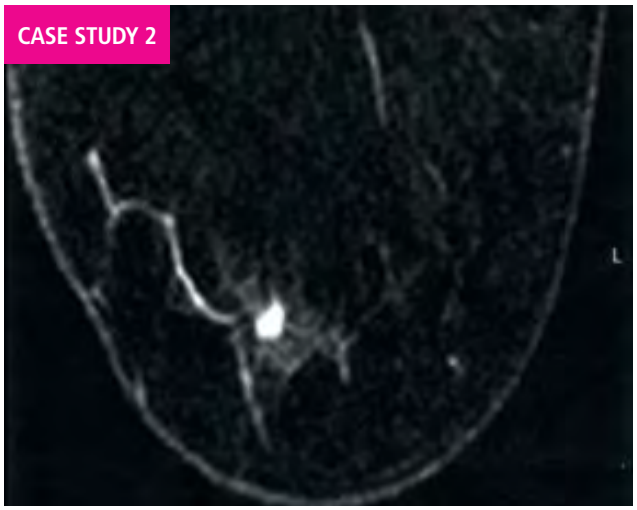
TABLE 1

Mercy Women's Center - Cancers discovered by MRI alone in patients with normal exam/normal mammograms

*Lifetime Risk

	AGE	RISKS	DENSITY TIER	GAIL*	CLAUS*	T-CUZICK*	BRCA PROBABILITY	PATHOLOGY
1	53	mod.FH	3	16%	7%	15%	5%	0.5cm IDC
2	49	ADH	2	15%	N/A	36%	-	0.6cm IDC
3	58	mod. FH	3	15%	6%	12%	5%	DCIS
4	75	weak FH +ADH	4	15%	N/A	21%	-	1.0cm IDC
5	51	ADH	3	13%	N/A	20%	-	1.0cm IDC
6	53	mod. FH	4	16%	10%	14%	5%	1 8cm IDC
7	50	mod. FH	4	19%	12%	19%	5%	DCIS
8	53	(density)	4	11%	N/A	10%	-	1.5cm ILC
9	53	(density)	4	10%	N/A	9%	-	1.2cm IDC
10	58	weak FH	3	15%	5%	13%	-	0 7cm IDC
11	54	(density)	4	9%	N/A	8%	-	DCIS
12	71	strong FH	4	9%	3%	8%	20%	DCIS
13	49	strong FH	4	18%	18%	27%	7%	2.2cm ILC
14	63	mod. FH	3	15%	7%	7%	8%	BIL 0.9cm ILC & DCIS
15	72	mod. FH + ADH	3	19%	5%	21%	5%	0.8cm IDC
16	76	strong FH	1	14%	N/A	6%	30%	DCIS
17	65	mod. FH	2	11%	7%	8%	7%	IDC x2 (1 0 & 0.9cm)
18	54	mod. FH	3	16%	8%	17%	5%	DCIS with 0 2cm IDC
19	53	implants + FH	4	7%	7%	10%	12%	1.0cm IDC
20	41	strong FH	3	19%	17%	18%	7%	DCIS- multicentric
21	59	strong FH	4	16%	9%	15%	7%	1.5cm IDC
22	61	strong ~H	3	40%	16%	33%	11%	2.5m IDC
23	66	strong FH	3	21%	15%	12%	11%	0.4cm IDC
24	51	(density)	4	12%	8%	14%	-	1.9cm ILC

CASE STUDY 2



Although this 49 year-old female had reasonable mammographic sensitivity (patchy fibroglandular tissue, tier 2 according to ACR guidelines), she had a solitary identifiable risk factor- atypical ductal hyperplasia (ADH)- that had been previously diagnosed in the opposite breast. Breast MRI screening revealed a 0.6 cm invasive ductal carcinoma, grade 1, node negative.

DISCUSSION AND CONCLUSION

The cost of the breast MRI for screening may be higher than mammography screening, but the downstream costs of treating a cancer when it has advanced beyond its early stages are far greater. While further investigation is warranted, our study strongly suggests that breast density should be a factor in determining candidacy for augmented screening with breast MRI. We found that risk + density or density alone allowed for maximal detection of cancer. Given that the mammography screening trials have confirmed breast cancer as vulnerable to early detection (mortality reductions in screened populations), the next step in the evolution of screening should not be to back down on screening recommendations. We should, in fact, be focused on identifying those women who are most likely to benefit through more aggressive screening with complementary breast MRI.

> "Our yield to date through breast MRI screening, at least on prevalence scans, is comparable to those studies that have relied on risk alone for entry, yet few of our cancer patients would have met minimum risk levels for entry to those prospective trials"
>
> - Dr. Alan Hollingsworth

SOURCES:

1. Moms EA, LibermanL, Ballon DJ, et al: MRI of occult breast carcinoma in a high-risk population. Am J Radiol 2003; 181:619-626.
2. Hollingsworth AB, Singletary SE, Morrow M, et al. Current comprehensive assessment and management of women at increased risk for breast cancer. Am J Surg 2004; 187:349-362.
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4. Tilanus-Linthorst MM, Kriege M, Boetes C, et al: Hereditary breast cancer growth rates and its impact on screening policy. Eur J Cancer 4111610-1617,2005.