The American Cancer Society Guidelines for Breast Screening With Magnetic Resonance Imaging

An Argument for Genetic Testing

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BACKGROUND. The American Cancer Society (ACS) guidelines for screening with breast magnetic resonance imaging (MRI) recommend MRI for women who have a lifetime risk $\geq$20% of developing breast cancer. Genetic testing for breast cancer gene (*BRCA*) mutations is offered to women who have a risk $\geq$10% of carrying a mutation. The objectives of the current study were 1) to identify the number of women in a breast cancer screening population who had $\geq$20% lifetime breast cancer risk and, thus, were candidates for screening MRI; and 2) to determine the number of women who had $\geq$10% risk of *BRCA* mutation yet had <20% lifetime risk of breast cancer and, thus, may not have been identified as candidates for MRI screening.

METHODS. From 2003 to 2005, women who underwent screening mammography completed a self-administered questionnaire regarding breast cancer risk factors. For each patient, the lifetime breast cancer risk and the risk of *BRCA* mutation was determined by using the computerized BRCAPRO breast cancer risk-assessment model.

RESULTS. Of 18,190 women, 78 (0.43%) had $\geq$20% lifetime risk of breast cancer, all of whom had $\geq$10% risk of carrying a *BRCA* mutation. An additional 374 women (2.06%) had <20% lifetime breast cancer risk but $\geq$10% risk of mutation. Overall, there were 183 (1%) predicted mutation carriers, 27 women (0.15%) who had $\geq$20% lifetime risk of breast cancer, and 62 women (0.34%) who had $\geq$10% risk of mutation but <20% lifetime breast cancer risk.

CONCLUSIONS. The ACS guidelines for breast MRI screening may systematically exclude MRI screening for many women who have a substantial risk for *BRCA* mutation. The current results demonstrated a need for greater awareness of breast cancer risk factors in the screening mammography population, so that high-risk women can be identified and given access to genetic testing and counseling regarding all risk-reducing interventions. *Cancer* 2008;113:3116–20. © *2008 American Cancer Society.*

KEYWORDS: breast magnetic resonance imaging, breast cancer screening, breast neoplasm, BRCAPRO.

Magnetic resonance imaging (MRI) is being used increasingly for the screening and diagnosis of breast cancer. In April 2007, the American Cancer Society (ACS) released guidelines for the use of MRI as an adjunct to mammography in breast cancer screening.[1] In these guidelines, the recommendation for breast MRI screening is based on assessment of lifetime breast cancer risk. Specifically, the guideline panel recommended annual breast MRI for the following specific, high-risk groups: 1) breast cancer gene (*BRCA*) mutation carriers, 2) first-degree relatives of known *BRCA* mutation carriers

who have not undergone genetic testing, and 3) women with an approximate lifetime risk from 20% to ≥25%, as estimated by the computerized BRCA-PRO breast cancer risk-assessment model or by other models that largely are dependent on family history. At the same time, referral for *BRCA* mutation testing is recommended for patients who have a family history suggestive of hereditary breast and ovarian cancer syndrome and in patients of relatives who are known mutation carriers.[2] To our knowledge, there is no empiric evidence supporting the risk level at which genetic testing should be initiated; however, commonly, a 10% risk of mutation is used.

In patients who undergo risk assessment and are deemed appropriate candidates for genetic testing, studies estimate that only 59% ultimately will go through with mutation testing.[3] Thus, the vast majority of patients and their family members who undergo breast cancer screening have not undergone genetic testing; therefore, Part 3 of the ACS guidelines is the most relevant of the 3 parts to clinical practice.

The breast cancer risk-assessment model BRCA-PRO uses both family cancer history and personal history to estimate the risk of carrying deleterious *BRCA1* or *BRCA2* mutations and to predict the lifetime risk of breast cancer. Specifically, BRCAPRO predicts risk based on the history of breast and ovarian cancer among the patient's first- and second-degree relatives as well as the patient's personal cancer status. BRCAPRO has been well validated and reportedly is nearly as effective in patient risk stratification as experienced cancer risk counselors.[4,5]

The first objective of the current study was to determine the number of patients who met ACS criteria for MRI screening based on their lifetime breast cancer risk in a large breast cancer screening population that had undergone risk stratification by BRCA-PRO. The second objective of this study was to identify the number of high-risk patients who may be excluded systematically from screening MRI based on the ACS guidelines. Specifically, we used BRCA-PRO to predict the number of patients in our population who would and would not be mutation carriers. Of the mutation carriers, we identified those who had <20% lifetime risk of breast cancer—the ACS MRI screening threshold—yet had a risk ≥10% of carrying a *BRCA* mutation—a common genetic testing threshold.

MATERIALS AND METHODS

With institutional review board approval, we performed a retrospective analysis of data obtained from women who presented for screening mammography to the Massachusetts General Hospital Avon Comprehensive Breast Evaluation Center from May 2003 to July 2005. Patients completed a self-administered questionnaire to ascertain baseline demographic characteristics and risk factor profile information using 1 of 2 methods: an optical scan form or a computer-assisted, self-interview, Tablet PC-based system (available at: http:////www.hughesriskapps.com accessed on April 21, 2008). Prior diagnoses of atypical hyperplasia, lobular carcinoma in situ, and invasive breast cancer were obtained from patient records and the institutional tumor registry in compliance with all provisions of the Health Insurance Portability and Accountability Act of 1996. Over the course of the study period, 41,056 questionnaires were completed by 31,183 women. For women who presented multiple times during the course of the study, data collected from the earliest visit were used. There were 4132 reports that were excluded on the basis of a prior history of breast or ovarian cancer. Another 5735 reports were removed from the study because they were associated with a diagnostic rather than screening mammography. An additional 2409 patients were removed because they had an unidentified ethnic background. Our goal was to identify the percentage of women in the screened population who required MRI or genetic testing. Women aged <40 years were excluded: We assumed that they were preselected for screening because they were at higher risk. Including these patients would have resulted in a spuriously high percentage of those who needed MRI or genetic testing. Excluding women aged <40 years resulted in the removal of 717 records. The final study population size was 18,190 patients.

Patients were stratified as Jewish and non-Jewish based on self-reported data. Analysis of hereditary cancer risk was undertaken using data from the self-administered questionnaires input into BRCAPRO using the software package CaGene (David Euhus; University of Texas Southwestern Medical Center, Dallas, Tex). The data used included the family members with breast or ovarian cancer and the ages of diagnosis. Current ages and vital status of relatives were not available. For each patient, BRCAPRO was used to determine the lifetime risk of breast cancer and the risk of carrying a *BRCA1* or *BRCA2* mutation. Patients who had a lifetime risk ≥20% of developing breast cancer and/or a risk ≥10% of carrying a *BRCA1* or *BRCA2* mutation were identified. We assumed that the number of mutation carriers was predicted correctly by BRCAPRO.

TABLE 1
Lifetime Risk of Cancer and *BRCA1* or *BRCA2* Mutation in a Breast Cancer Screening Population

Risk of Mutation, %	Lifetime Risk of Breast Cancer, %*	No. of Patients (%)	Mean Probability of Mutation*	Projected No. of Mutation Carriers*
≥10	≥20%	78 (0.43)	.34	27
≥10	<20%	374 (2.06)	.17	62
Any	Any	18,190 (100)	.01	183

*Estimated by using the breast cancer risk-assessment model BRCAPRO.

TABLE 2
Lifetime Risk of Breast Cancer and *BRCA1* or *BRCA2* Mutation in a Jewish and Caucasian Non-Jewish Breast Cancer Screening Population

Risk of Mutation, %	Lifetime Risk of Breast Cancer, %*	No. of Patients (%)		Mean Probability of Mutation*		Mutation Carriers*	
		Jewish	Non-Jewish	Jewish	Non-Jewish	Jewish	Non-Jewish
≥10	≥20	23 (2.22)	48 (0.31)	.34	.34	8	16
≥10	<20%	96 (9.28)	267 (1.73)	.17	.16	16	44
Any	Any	1035 (100)	15,543 (100)	.05	.01	48	127

*Estimated by using the breast cancer risk-assessment model BRCAPRO.

RESULTS

Risk Stratification

Based on BRCAPRO analysis, 78 of 18,190 women (0.43%) had ≥20% lifetime risk of breast cancer, all of whom had ≥10% risk of carrying a *BRCA1* or *BRCA2* mutation (Table 1). An additional 374 (2.06%) women had a risk ≥10% of carrying a *BRCA1* or *BRCA2* mutation but a lifetime risk <20% of developing breast cancer.

Women predicted to test positive for BRCA1 or BRCA2

The BRCAPRO model predicted that 183 patients would be mutation carriers in the entire screening population. Of 78 women who had a lifetime risk ≥20% of developing breast cancer, BRCAPRO predicted that 27 women would carry a *BRCA1* or *BRCA2* mutation. Of 374 women who had a lifetime risk <20% of developing breast cancer but a risk >10% of carrying a *BRCA1* or *BRCA2* mutation, BRCAPRO predicted that 62 women would carry a mutation (Table 1). BRCAPRO predicted that 93 patients would carry a mutation and also would have a risk <10% of carrying a mutation.

Risk estimates in a known high-risk population

Of 1035 self-reported Jewish patients who underwent screening mammography, 23 patients (2.22%) had a lifetime risk ≥20% of developing breast cancer, including 8 patients who were predicted to carry a *BRCA1* or *BRCA2* mutation (Table 2). There were 96

Jewish patients who had a lifetime risk <20% of developing breast cancer but a risk >10% of mutation, including 16 patients who were predicted to carry a mutation.

DISCUSSION

It has been established that breast MRI screening of *BRCA1* and *BRCA2* mutation carriers will detect breast cancer earlier and more frequently than mammography.[6-8] However, to our knowledge, none of the randomized, controlled trials of mammography screening stratified women by risk; and, to date, no randomized, controlled trial has proven that earlier detection among high-risk women using MRI actually will result in lives saved. However, this may be a reasonable conclusion, and earlier detection also may have the added benefit of fewer patients requiring chemotherapy as part of their treatment. In addition, in this high-risk patient population, the sensitivity of mammography is considerably lower than in the general screening population.[9] Therefore, it seems prudent to offer these women MRI screening, because they have few options and a high lifetime risk. For this reason, and because resources are limited, the best approach would be to try to identify *BRCA* mutation carriers as accurately as possible so that they will be included in those being screened.

Because the current ages and vital status were not available in this dataset for relatives, this infor-

mation was not used in the BRCAPRO calculation of lifetime risk and risk of mutation. Although the current results, thus, may be slight overestimates of absolute lifetime risk and risk of mutation, it is unlikely that the absence of these data would have changed the status of individual patients relative to the thresholds used. That is, although the ages and vital status of relatives may slightly decrease the risk of mutation for an individual patient, it is unlikely that this information would change that patient from ≥10% risk of mutation to <10% risk or from ≥20% greater lifetime risk of breast cancer to <20% lifetime risk.

Because the mutation status of the vast majority of patients undergoing breast cancer screening is unknown, the estimated lifetime risk of breast cancer may function as a surrogate for mutation status in the majority of screening patients. Thus, when we applied the ACS screening guideline of 20% lifetime risk to our population, we observed that 0.43% of our population (78 of 18,190 patients) met MRI screening criteria, whereas we observed that 1.01% of our population (183 of 18,190 patients) was made up of predicted mutation carriers. If we consider the total number of predicted mutation carriers, only 14.75% (27 of 183 patients) would be eligible for MRI screening based on the ACS lifetime risk cutoff of 20%. Furthermore, we identified an additional 374 patients in our population who did not meet ACS screening criteria yet would be considered by many appropriate for mutation testing based on >10% risk of mutation.

This effect is magnified in a known high-risk population. In Jewish patients, 2.22% (23 of 1035 women) qualified for MRI based on ACS criteria, whereas an additional 96 women were eligible for genetic testing based on a 10% risk of gene mutation. By comparison, in non-Jewish patients, 48 of 15,543 women (3.09%) met MRI criteria, and an additional 267 women were eligible for genetic testing. Therefore, a higher percentage (9.3%) of Jewish patients are at risk of carrying a mutation and not receiving intensive screening compared with non-Jewish patients (1.7%). Consequently, we estimate that 40% of mutation carriers in our Jewish population may go without intensive surveillance.

What are other management approaches for women who have ≥20% lifetime breast cancer risk? One option may be to perform genetic testing on this group and limit risk-minimizing strategies to those with mutations. However, this approach extends risk management strategies to only 15% of all mutation carriers. Conversely, all women in this risk group could be managed as though they are mutation carriers. Although this represents <1% of our population, extending prophylactic surgery and chemoprevention to the 66% of women in this group who are not mutation carriers could cause unnecessary physical and psychological harm. Another approach may be to expand the MRI target population to include all those with ≥10% mutation risk. Although this may result in earlier detection of cancer in some patients, the unidentified mutation carriers would not be able to benefit from referral for counseling about other risk-reduction strategies. It has been demonstrated that prophylactic salpingo-oophrectomy, prophylactic mastectomy, and chemoprevention have significant life expectancy gains in this high-risk population.[10,11] In addition, this strategy likely would cost the most over the lifetime of a patient.

Like all screening programs, the best way to optimize the benefits of screening is to screen those who benefit the most from intervention. In breast cancer, this target population is *BRCA* mutation carriers. Greater awareness should focus on identifying patients with ≥10% risk of mutation and encouraging those patients to undergo genetic counseling and testing. The identified mutation carriers can then undergo annual breast MRI screening in addition to benefiting from discussion of prophylactic surgery and chemoprevention.

Although *BRCA* mutation carriers are at the highest risk of developing breast cancer, women with increased familial risk of breast cancer who are not *BRCA* mutation carriers may harbor breast cancer susceptibility genes that have yet to be characterized. In these high-risk women, breast MRI is highly sensitive and can detect breast cancers that are not observed on mammography.[12] If breast cancer susceptibility genes or gene profiles eventually are identified in these patients, then genetic testing and focused MRI screening may be applied more easily to this additional high-risk group.

The current study raises concern that, if the ACS guidelines are applied to a broad screening population, then a large number of women who are at the highest risk genetically for breast cancer may be excluded from MRI screening. A more effective approach may be to encourage genetic testing on women who are identified as high-risk, thus providing a better definition of the MRI target population. This would benefit both patients and the healthcare system; money would be used appropriately for women who have proven benefit from screening.

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