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Which Risk Model to Use? Clinical Implications of the ACS MRI Screening Guidelines

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Abstract

The American Cancer Society (ACS) guidelines define the appropriate use of MRI as an adjunct to mammography for breast cancer screening. Three risk assessment models are recommended to determine if women are at sufficient risk to warrant the use of this expensive screening tool, however, the real-world application of these models has not been explored. We sought to understand how these models behave in a community setting for women undergoing mammography screening. We conducted a retrospective analysis of 5,894 women, who received mammography screening at a community hospital and assessed their eligibility for MRI according to the ACS guidelines. Of the 5,894 women, 342 (5.8%) were eligible for MRI, but we found significant differences in the number of eligible women identified by each model. Our results indicate that these models identify very different populations, implying that the ACS guidelines deserve further development and consideration. Cancer Epidemiol Biomarkers Prev; 22(1); 146–9. ©2012 AACR.

Introduction

MRI is the most sensitive breast-cancer screening tool available. However, due to its high cost and relatively low specificity, its use needs to be limited to the highest risk individuals. The American Cancer Society (ACS) published guidelines in 2007 for the use of MRI as an adjunct to mammography screening (1). The guidelines recommend, in addition to other scenarios, the use of MRI for women whose lifetime risk of breast cancer is estimated to be 20% to 25% or greater by a risk assessment model that is heavily reliant on family history. The guidelines specifically recommend using the BRCAPRO, Claus, and Tyrer-Cuzick models, and warn against using models that include only limited family history, such as the Gail model. In the 2012 review of current cancer screening guidelines, the ACS further rationalized the choice of these models, highlighting the importance of including both maternal and paternal first- and second-degree relatives (2).

While each of the 3 recommended models takes into account significant family history, they are fundamentally very different models: each derived using different methods and populations, each using different risk factors, and each predicting different outcomes (3–5).

The BRCAPRO model requires a family pedigree as the only input, including age of the individual, ages of relatives, age of onset for particular cancers, and ethnic heritage. This model is designed to predict who is a BRCA-1 or BRCA-2 gene mutation carrier and who is at the risk of developing breast and ovarian cancer. The BRCAPRO model is based on a Mendelian approach that assumes an autosomal dominant pattern of inheritance.

In contrast, the Tyrer-Cuzick model includes family history and a number of other inputs: the individual’s age, family history of breast and ovarian cancer, age at menarche, parity, age at first childbirth, age at menopause, use of hormone replacement therapy (HRT), Ashkenazi Jewish heritage, history of breast biopsy and atypical hyperplasia, lobular carcinoma in situ (LCIS), height, and body mass index. The model is a statistical model based on the Mayo Clinic Benign Breast Disease cohort, which is made up of 9,376 women, age 18 to 85 years, who had an open breast biopsy between 1967 and 1991.

Finally, the Claus model includes the number of first- and second-degree relatives with breast cancer and the age of cancer onset. The Claus model was developed from the cancer and steroid hormone (CASH) population-based, case–control study involving 4,730 patients with histologically documented breast cancer and 4,688 matched controls. This model is based on the premise that breast cancer risk is transmitted as an autosomal-dominant trait and bases the statistical calculation on the genetic relationships between the affected relatives and the woman in question.
In terms of outcomes, the lifetime risk of breast cancer estimated by the Tyrer-Cuzick and Claus models includes the risk of both invasive breast cancer and ductal carcinoma in situ (DCIS), where BRCAPRO predicts only the risk of invasive breast cancer.

Considering these differences, it is to be expected that these models behave differently and will have varying impact in real-world settings. To understand the economic and health impact the ACS guidelines may have, it is important to determine how these models operate when implemented in community settings. Using a large community-based population, we compared the performance of the 3 recommended models with respect to the ACS guidelines for MRI screening.

Materials and Methods

Under Institutional Review Board’s approval, we conducted a retrospective analysis of 10,000 women, who received mammography screening at a community hospital from April 1, 2006 to September 17, 2007. We estimated their lifetime risk of developing breast cancer using the BRCAPRO, Claus, and Tyrer-Cuzick models.

Of the 10,000 consecutive women, 2,279 were excluded because they had HRT. HRT use was an exclusion criterion as Tyrer-Cuzick required information about hormone use that was not contained in our dataset. Of the remaining 7,821 women, 5,894 had sufficient risk information to run all 3 models. To facilitate the data collection within the clinical setting, a modified BRCAPRO was used that calculated risk based on the ages of diagnosis of breast and ovarian cancer in relatives, without complete data on the ages and vital status of each relative (6). To approximate the additional risk of DCIS that is not included in the BRCAPRO model, we used BRCAPRO as is, and also multiplied the BRCAPRO result by 1.25. We used each model as described in the ACS guidelines where the dataset is allowed. For the Claus model, we used the model suggested by ACS, and while a modification of this model exists that includes ovarian cancer, we did not use that model and instead used the model put forth in the ACS guidelines (4). Pathologic data were not available for this population.

Results

Our analyses found that of the 5,894 women in this study, 342 (5.8%) were eligible for MRI by at least one of the models. There were large differences in the number of eligible women by each model. Most notably, the Tyrer-Cuzick model identified 330 (5.6%) of the study population to be eligible, whereas the BRCAPRO and Claus models identified many fewer eligible women (25, 0.4% and 54, 0.9%, respectively; Fig. 1). Surprisingly, only 13 women (0.2%) were identified to be eligible by all 3 risk models. When the BRCAPRO model results were adjusted to approximate the additional risk of DCIS, we found that these results changed slightly (Fig. 2). This adjustment identified more than twice as many women (61 women, 1% of the study population). Yet, the overlap between the models changed very little with only 18 individuals (0.3%) identified by all 3 models.

Discussion

Our results indicate that these models identify different subpopulations of women eligible for MRI screening. This is not an entirely surprising result in that these models rely on very different risk factors. However, when considering that the purpose and intent of this guideline was to identify a group of high-risk women eligible for MRI, the discrepancies between the models pose a clinical challenge. Without knowing which of these women will develop breast cancer, a reasonable decision would be to screen them all. This is likely to result in the outcome of screening too many women, incurring false positives and unnecessary resource usage. Although if only one model were relied on for this screening decision, it is clear that some models would screen many fewer women than others, possibly missing many who would benefit.

In considering these results, one must recognize the intention of risk assessment models in light of their limitations. Risk assessment models are designed to estimate risk to help develop personalized management strategies.

![Diagram 1](Lifetime breast cancer risk 20% or greater by model)

Tyrer-Cuzick = 330
BRCAPRO = 25
Claus = 54

![Diagram 2](Adjusted BRCAPRO)

Tyrer-Cuzick = 330
Adjusted BRCAPRO = 61
They are a means to quantify our intuition and experience, and help predict future outcomes. Models, however, at best, will only be an approximation to reality and will always have limitations. As was recently shown by Boughey and colleagues, Tyrer-Cuzick did not predict well for women with either atypical hyperplasia or LCIS (7). Furthermore, there has been limited validation of these models. Tyrer-Cuzick and BRCAPRO were validated among high-risk women, (8, 9), but Claus has not been previously validated. None of the models have been validated in a general screening population, which is the population used for this study (10). While none of these models have been validated for the general population, it is likely that they will perform similarly to the high-risk populations, although clearly this is an area that needs further research.

However, identifying weaknesses in models is not a reason to jettison them but rather to recalibrate them. As evidence-based medicine becomes more dependent on clinical decision support, accurate risk prediction models are becoming critical components of quality health care.

This study shows that while 3 models were chosen by the ACS to act as the basis for deciding who is eligible for MRI screening, there are tremendous differences in both the model inputs and the predicted outcomes by each model. Our results reinforce a key finding from a recent review of breast cancer risk assessment models: "some models are able to predict both mutation carriage risks and breast cancer risk; however, to date, all are limited by only moderate discriminatory accuracy" (11). Our results are also limited by our inability to assess the models' accuracy within our population, and some of the limitations of our data (i.e., excluding women with HRT).

When considering the differences in these 3 models, it is not surprising that they identify different patients. The widely used version of the Claus model uses family history of only female breast cancer in up to 2 relatives. While a modification of the Claus model includes ovarian cancer, we did not use that model and instead used the BRCAPRO. The widely used version of the Claus model uses family history of only female breast cancer in up to 2 relatives. While a modification of the Claus model includes ovarian cancer, whereas BRCAPRO estimates the risk of invasive breast cancer only. Despite their differences, these models have been chosen for the same purpose, and result in identifying very different populations deemed eligible for MRI screening.

Given the cost of MRI, care must be taken in implementing this guideline. In fact, the data suggest that the tools we use require refinement. When we achieve our goal to identify women at risk for hereditary cancer, then our clinical approach should include risk assessment, genetic counseling, and testing, and appropriate screening and risk reduction interventions for both the breasts and ovaries, in addition to the recommendation for MRI screening (6). Designing guidelines for MRI should take into account the larger clinical picture.

Disclosure of Potential Conflicts of Interest

K.S. Hughes has commercial research grant from Myriad, honoraria from Speakers Bureau of Myriad, and has ownership interest (including patents) in HughesRiskApps.Net. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Ozanne, P. Bosinoff, K.S. Hughes
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