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Breast Cancer Risk Prediction and Mammography Biopsy Decisions:

A Model-Based Study

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Abstract

Background—Controversy continues about screening mammography, in part because of the risk of false-negative and false-positive mammograms. Pre-test breast cancer risk factors may improve the positive and negative predictive value of screening.

Purpose—To create a model that estimates the potential impact of pre-test risk prediction using clinical and genomic information on the reclassification of women with abnormal mammograms (BI-RADS3 and BI-RADS4 [Breast Imaging-Reporting and Data System]) above and below the threshold for breast biopsy.

Methods—The current study modeled 1-year breast cancer risk in women with abnormal screening mammograms using existing data on breast cancer risk factors, 12 validated breast cancer single nucleotide polymorphisms (SNPs), and probability of cancer given the BI-RADS category. Examination was made of reclassification of women above and below biopsy thresholds of 1%, 2%, and 3% risk. The Breast Cancer Surveillance Consortium data were collected from 1996 to 2002. Data analysis was conducted in 2010 and 2011.

Results—Using a biopsy risk threshold of 2% and the standard risk factor model, 5% of women with a BI-RADS3 mammogram had a risk above the threshold, and 3% of women with BIRADS4A mammograms had a risk below the threshold. The addition of 12 SNPs in the model resulted in 8% of women with a BI-RADS3 mammogram above the threshold for biopsy and 7% of women with BI-RADS4A mammograms below the threshold.

Conclusions—The incorporation of pre-test breast cancer risk factors could change biopsy decisions for a small proportion of women with abnormal mammograms. The greatest impact comes from standard breast cancer risk factors.

Background

Screening mammography is an important but imperfect tool for reducing breast cancer mortality. Multiple trials have established that screening results in a 15%–22% reduction in

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breast cancer mortality among women aged 40–75 years. Further, this reduction comes at some "cost,"[1] including a 20%–40% risk of an abnormal mammogram (in the absence of cancer) after 10 years of annual screening.[1–11] Concern about the risk of false-positive tests and the limited mortality benefit was a key factor in the recent recommendation by the U.S. Preventive Services Task Force that women in their 40s discuss the risks and benefits of screening with their doctor.[12] Despite the controversy generated by this recommendation, all agree that fewer false-positive test results would be good. Similarly, all agree that fewer missed cancers would be good. The challenge is how to get there.

The performance of any screening test is defined by positive and negative predictive value (PPV and NPV) and is tied to the sensitivity and specificity of the test itself. Thus, most attempts to improve the performance of screening mammography have focused on improving the test itself through addressing issues of image quality and image interpretation.[13–17] Given a fixed sensitivity and specificity, knowing pre-test probability can dramatically change post-test probability.

However, the determination of pre-test probability also has a substantial impact on the performance of a screening test, but it has received considerably less attention in breast cancer screening. For example, assuming a test specificity of 80% and sensitivity of 90%, a positive test will be a true positive 19% of the time among individuals with a 5% pre-test probability of disease but 53% of the time among individuals with a 20% pre-test probability of disease. Multiple breast cancer risk factors have been identified including family history, reproductive history, race/ethnicity and breast density. Risk prediction models including these factors have been found to have fair discriminatory ability (area under the ROC: 0.58–0.68) , similar to the Framingham model for heart disease.[18–24]

More recently, multiple single nucleotide polymorphisms (SNPs) have been found to be associated with breast cancer risk and have been validated in multiple studies.[25–34] These SNPs appear to be independent of traditional breast cancer risk factors, and to have a small impact on the discrimination of breast cancer risk prediction when added to clinical risk factors (increase in AUC from 0.607 to 0.632).[35,36] No SNP panel for breast cancer risk prediction is approved by the U.S. Food and Drug Administration (FDA), but several breast cancer SNP panels are now commercially available.[37,38]

The current article examines the impact of pre-test breast cancer risk prediction on the reclassification of women with an abnormal mammogram above or below the risk threshold for biopsy. Currently, the biopsy threshold is linked to the Breast Imaging-Reporting and Data System (BI-RADS) classification of screening mammograms and falls between the BI-RADS 3 and 4 categories. Women with BI-RADS3 mammograms have a 1-year probability of breast cancer less than 2% and undergo 6-month follow-up rather than biopsy, whereas women with BI-RADS4 mammograms have a 1-year probability of breast cancer of 15%–30% and are referred for biopsy.[39–47] Recently, the American College of Radiology has subdivided the BIRADS4 category into 4A, 4B and 4C, with breast cancer probability ranging from 6% to 13% in BI-RADS 4A mammograms to 15%–36% and 48%–79% for 4B and 4C, respectively.[43,48,49] However, biopsy continues to be recommended for all the subgroups.

Thus, for the current study, the authors sought to determine the degree to which the inclusion of pre-mammogram predicted breast cancer risk factors would reclassify women with BI-RADS 3 mammograms above the risk threshold for biopsy and reclassify women with BI-RADS 4 mammograms below the risk threshold for biopsy. A biopsy risk threshold of 2% was used in the base case based on the existing practice of recommending biopsy for BI-RADS4 but not BIRADS3 lesions, but the biopsy risk thresholds of 1% and 3% were

also examined. Evaluation was also made of the impact of the use of clinical, nongenetic risk factor information and the incremental impact of the inclusion of SNPs in the risk prediction model.

Methods

The authors modeled 1-year breast cancer risk in women undergoing screening mammography using data from the Breast Cancer Surveillance Consortium (BCSC) following the approach of Barlow et al.[50] The BCSC data were collected from 1996 to 2002 and include seven mammography registries, 2,392,998 screening mammograms, and information on 11 breast cancer risk factors (age in 5-year increments, race, Hispanic ethnicity, BMI, age at birth of first child, prior breast biopsy, first-degree relatives with history of breast cancer, current hormone therapy use, surgical menopause, previous mammographic outcome, and breast density using a BI-RADS measure).

The inclusion of multiple mammograms on a subset of women in the BCSC data has been previously shown to have minimal impact on breast cancer risk prediction using the BCSC data.[50] Both invasive and non-invasive (i.e., ductal and lobular carcinoma in situ) cancers were included in the breast cancer risk estimate, as these outcomes are often combined in the available data on mammography outcomes and breast cancer risk prediction. Data analysis was conducted in 2010 and 2011.

A model was constructed of the relative risk conferred by various combinations of breast cancer SNPs using established methods[35] (see Appendixes A–D for specific models, available online at www.ajpmonline.org). The base case included seven SNPs with validated associations with breast cancer, the same ones included in the prior Gail analysis. In a second model, the current study included an additional five SNPs that have been added to create a 12-SNP risk panel by deCODE (Table 1).

Estimates were made of the probability that a woman had cancer given the baseline level of nongenetic risk factors using a logistic regression model based on BCSC data and the probability that a woman had cancer given the baseline level of nongenetic risk factors and lowest-risk genotypes by including published genotype risk ratios and frequencies. The authors assumed that women with baseline clinical, nongenetic risk factors had the same genotype frequencies and effects as those in the general population. Estimates were then made of the 1-year risk of breast cancer for all possible combinations of genotypes and nongenetic risk factors. Because of the large number of possible combinations with the 12 SNP panel,[37] the approach was simplified by using genotype risk ratios for larger risk strata. These risk ratios were standardized to the general population using the risk ratios and frequencies from the deCODE data, which are based on more than 30,000 cases and controls. [37]

To determine the post-test probability of breast cancer diagnosis with a given set of risk factors and a specific mammography result, a weighted average approach derived from Bayes' formula was used.[51] This approach assumes that, given cancer status, mammography results are independent of risk factors, and it does not require the probability of a specific set of mammographic findings or the probability of mammographic findings given cancer. Using data from the New Hampshire mammography registry, it was assumed that the average probability of malignancy following a BI-RADS3 result was 1.0%, and following a BI-RADS4 result was 18.6%.[39] These rates are very similar to other published estimates.[42–44] Probabilities following BI-RADS 4A, 4B, and 4C results were assumed to be 6%, 15%, and 53%, respectively.[43]

To determine the value of pre-test breast cancer risk prediction in a screening population, calculation was made of the probability of each set of risk factors, and the post-test probability of malignancy by pre-test risk percentile was determined for a theoretic screening mammography population. Examination was then made of the reclassification of women with various mammography results above and below various thresholds of risk.

Results

Pre-Mammography Breast Cancer Risk Classification

Using clinical, nongenetic risk factors alone, the probabilities of being diagnosed with breast cancer in the next year ranged from 0.0003 to 0.0392. Across risk deciles, average pre-test probability ranged from 0.0017 in the lower-risk decile to 0.0102 in the highest-risk decile. (Table 2). Including the seven-SNP panel slightly increased the differentiation between high- and low-risk groups. The inclusion of the 12-SNP panel marginally increased the differentiation compared to the seven-SNP panel.

Post-mammography Breast Cancer Risk Classification

The incorporation of pre-test breast cancer risk prediction influenced the estimated probabilities of malignancy among women with BI-RADS3 and BI-RADS4 mammograms (Table 3). For women with BI-RADS3 mammograms, the use of clinical, nongenetic risk factors resulted in women in the lowest 5% of pre-test risk having a 1-year breast cancer risk <0.29% (i.e., <2.9/1000), whereas women in the highest 5% of pre-test risk had a 1-year breast cancer risk >3.0% (i.e., >30/1000). The inclusion of SNPs in the model had a relatively small effect on risk classification, leading to women in the lowest 5% of pre-test risk having a 1-year breast cancer risk <0.24% (i.e., <2.4/1000) and women in the highest 5% of pre-test risk having a 1-year breast cancer risk >4.0% (i.e., >40/1,000).

For women with BI-RADS4 mammograms, the use of clinical, nongenetic risk factors resulted in only women in the lowest 5% of pre-test risk having a 1-year breast cancer risk of 6.2% compared to a 35.2% risk for women in the highest 5% of pre-test risk. Again, the addition of SNPs to the breast cancer risk prediction model had a small effect, resulting in women in the lowest 5% of pre-test risk having a 1-year breast cancer risk of 4.9% compared to a 39.8% risk for women in the highest 5% of pre-test risk. Incorporating extra information from the mammogram using the subclassifications of BI-RADS 4A, 4B and 4C increases the risk discrimination within the population, including the proportion of women who are reclassified below the risk threshold for biopsy. A woman in the lowest 1% of pre-test risk with a BI-RADS 4A would have a 0.9% probability of malignancy, whereas a woman in the highest 1% pre-test risk with a BI-RADS 4C would have a 79.1% probability of malignancy.

Table 4 reports the effect of breast cancer risk prediction across the various models on the reclassification of women across the threshold for biopsy using biopsy risk thresholds from 1% to 3%. The greatest level of reclassification occurred with the risk prediction model that included clinical, nongenetic risk factors and SNPs, although the incremental impact is relatively small. Using a biopsy risk threshold of 2% and the standard risk factor model, 5% of women with a BI-RADS3 mammogram had a post-test risk above the threshold for biopsy, and 3% of women with BI-RADS4A mammograms had a post-test risk below the threshold. With the same biopsy threshold and adding 12 SNPs to the risk prediction model, 8% of women with a BI-RADS3 mammogram had a post-test risk above the threshold for biopsy, and 7% of women with BIRADS4A mammograms had a post-test risk below the threshold.

Given an estimated 39 million women who undergo a screening mammogram each year in the U.S., over 800,000 women will have a BI-RADS3 mammogram and over 200,000 will have a BI-RADS4A mammogram in the U.S. each year.[44,52] The use of the standard risk prediction model would reclassify nearly 45,000 women with a BI-RADS3 mammogram above threshold for biopsy and 6000 women with a BI-RADS 4A mammogram above the threshold for biopsy in the U.S. each year. These numbers would increase to 72,000 and 14,000, respectively, with the inclusion of 12 SNPs in the risk prediction model.

Discussion

Despite the controversy over recommendations about screening mammography, there is little disagreement that reducing the rate of false-positive and false-negative tests would be beneficial. These results demonstrate that the incorporation of the pre-test probability of breast cancer into the prediction of breast cancer risk after an abnormal mammogram leads to a wide range of posttest probabilities of breast cancer, some of which cross risk thresholds that are currently used for clinical management recommendations. These results have several implications.

First, the results of this model suggest that the incorporation of breast cancer risk factors into mammography recommendations could improve mammography outcomes by increasing the proportion of cancers diagnosed at an early stage, reducing biopsies among women who do not have cancer, and potentially even reducing the number of missed cancers. Based on a prediction model using clinical, nongenetic risk factors alone, 5% of women who currently undergo 6- month follow-up have a post-test probability of cancer of more than 2%.

This proportion could increase to 8% if 12 breast cancer associated SNPs are added to the prediction model. Referring these women for biopsy might lead to earlier cancer diagnosis and perhaps even reduce the number of missed cancers, given that almost one third of patients do not adhere to short-term follow-up recommendations.[53] In addition, a small proportion of women who currently undergo biopsy have a sufficiently low pre-test risk of breast cancer that their probability of being diagnosed with breast cancer in the next year is less than 2%. Changing the management recommendation for these women from immediate biopsy to short-term follow-up might reduce the number of women without cancer undergoing biopsy.

Of course, both of these changes would come with some “costs.” Recommending biopsy in high-risk women who previously underwent short-term follow-up would increase the number of biopsies, many of which would occur among women who did not have cancer. Changing to a short-term follow-up recommendation for very-low-risk women who previously underwent biopsy would lead to delay in cancer diagnosis for some women. Although clinical, nongenomic risk factors are often collected at the time of screening, SNP testing is not available at the point of care and is unlikely to have been completed prior to screening.

To a great extent, the eventual decision about whether to include pre-test risk information in the recommendations for biopsy depends on the balance of these costs and benefits. Prospective studies incorporating the full range of possible risk factor information and examining various risk thresholds for biopsy are needed to determine the actual impact of the inclusion of pre-test risk information on the overall burden of false-positive and false-negative tests. Of note, these studies should include information about mammographic findings (e.g. type of mass, mass margin, type of calcifications), which are associated with the probability of breast cancer within BI-RADS categories and may improve the discrimination of risk prediction models in this population.[16,43,47,54]

Second, these results contribute to the growing literature about the impact of breast cancer risk prediction on clinical decision making, particularly around the incremental impact of the inclusion of genetic polymorphisms in breast cancer risk prediction.[18–24,35,36,55–59] Prior models have demonstrated that the addition of currently identified breast cancer–associated SNPs offers a relatively minor improvement on the ability to discriminate between high- and low-risk women.[35,36,56,59,60] However, the inclusion of this individualized risk prediction in screening programs has been linked to improvements in program efficiency in several of these models.[57,58]

The current results echo these prior studies demonstrating minor improvement in discrimination from the inclusion of SNPs but some effect on reclassification around biopsy risk thresholds. Although the increase from a seven-SNP panel to a 12-SNP panel had relatively little impact on reclassification in this model, the incremental cost of testing for an additional SNP is small, and it is likely that these tests will be disseminated as panels of multiple SNPs. Further, prior models have suggested that discrimination could increase with the inclusion of a greater number of genetic-susceptibility alleles, particularly if the SNPs have relatively strong associations with breast cancer risk (i.e., per-allele OR of 1.3 to 1.5).[61,62] The effect of the inclusion of SNPs in the model was small, and multiple issues need to be addressed before the use of SNP panels for breast cancer risk prediction is incorporated into the management of screening mammograms, including the rapidity at which new genomic information is identified.

Limitations

The current analysis has several important limitations. The data were modeled from various sources rather than from both clinical and genomic data on a single population. Although it is reasonable to assume that the published SNP relative risks are generalizable to the BCSC cohort, confirmation of these results in a cohort with clinical, genomic and imaging data is needed. Further, new genomic markers are being identified and validated rapidly and may increase the impact of risk stratification on mammography decisions. The deCODE assay has recently been expanded to include 16 markers. [37]

No distinction was made between the probability of invasive and in-situ cancers in the current models, as much of the available data collapse these outcomes. However, the implications of an in-situ cancer are different than those of invasive cancer, and biopsy decisions may be improved by the ability to predict the risk of these varying outcomes separately. The current model assumed that clinical and genomic risk factors predicted cancer risk rather than BI-RADS score, which makes clinical sense but has not been proven in existing data sets to our knowledge.

Thresholds for biopsy decisions in the current study were set to be between 1% and 3%, in order to encompass the current practice; however the optimal threshold for maximizing overall patient outcomes is not known.[63] Demonstrating the impact of risk prediction on post-mammography breast cancer probability does not ensure that providers or patients would adhere to risk-based follow-up recommendations. However, the uncertainty generated by the current discordance in screening recommendations has created an opportunity for improving decision making in this area.

Conclusion

Although breast cancer risk prediction using clinical and genomic information has the potential to change decisions about management of abnormal mammograms for a minority of women, the public health impact could be substantial given the incidence of abnormal mammograms among U.S. women. Improvement in risk prediction through the inclusion of

additional clinical or genomic risk factors or imaging information may lead to a greater role for breast cancer risk prediction in the management of abnormal screening mammograms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

SNP panels

Locus	Chromosome	SNP	High-risk allele frequency	OR	7-SNP Panel	12-SNP Panel
TNRC9/TOX3	16	rs3803662	0.269	1.28	x	x
MAP3K1	5	rs889312	0.28	1.13	x	x
8q24	8	rs13281615	0.4	1.08	x	x
LSP1	11	rs3817198	0.3	1.07	x	x
MRPS30	5	rs4415084	0.372	1.15		x
2q35	2	rs13387042	0.497	1.20	x	x
CASP8	2	rs1045485	0.87	1.13	x	x
NEK10	3	rs4973768	0.46	1.11		x
1p11	1	rs11249433	0.39	1.15		x
RAD51L1	14	rs999737	0.76	1.13		x
COX11	17	rs6504950	0.72	1.05		x
FGFR2	10	rs2981582	0.38	1.26	x	x

SNP, single-nucleotide polymorphism

Table 2

Predicted pre-test probability of breast cancer in the next year

Risk deciles	Standard risk factors only	12-SNP panel only	Standard risk factors + 7-SNP panel	Standard risk factors + 12-SNP panel
1	0.0017	0.0026	0.0014	0.0014
2	0.0024	0.0032	0.0022	0.0021
3	0.0029	0.0036	0.0027	0.0026
4	0.0035	0.0040	0.0033	0.0032
5	0.0041	0.0043	0.0039	0.0038
6	0.0047	0.0047	0.0045	0.0045
7	0.0055	0.0051	0.0053	0.0053
8	0.0063	0.0057	0.0063	0.0063
9	0.0075	0.0065	0.0078	0.0078
10	0.0103	0.0084	0.0116	0.0121

Table 3

Average post-test probability of breast cancer for low- and high- pre-test risk groups

BI-RADS3 (Average risk = 0.010)				
	Standard risk factors only	12-SNP panel only	Standard risk factors + 7-SNP panel	Standard risk factors + 12-SNP panel
Lowest-risk 1%	0.0020	0.0042	0.0016	0.0015
Lowest-risk 5%	0.0029	0.0049	0.0023	0.0024
Highest-risk 5%	0.0237	0.0192	0.0289	0.0274
Highest-risk 1%	0.0303	0.0235	0.0370	0.0397
BI-RADS4 (Average risk = 0.186)				
	Standard risk factors only	12-SNP panel only	Standard risk factors + 7-SNP panel	Standard risk factors + 12-SNP panel
Lowest-risk 1%	0.0430	0.0864	0.0359	0.0332
Lowest-risk 5%	0.0616	0.1007	0.0523	0.0488
Highest-risk 5%	0.3524	0.3062	0.3862	0.3983
Highest-risk 1%	0.4141	0.3521	0.4650	0.4830
BI-RADS4A (Average risk = 0.06)				
	Standard risk factors only	12-SNP panel only	Standard risk factors + 7 SNP panel	Standard risk factors + 12-SNP panel
Lowest-risk 1%	0.0124	0.0257	0.0103	0.0095
Lowest-risk 5%	0.0180	0.0304	0.0152	0.0142
Highest-risk 5%	0.1326	0.1100	0.1506	0.1574
Highest-risk 1%	0.1649	0.1318	0.1953	0.2070
BI-RADS4B (Average risk = 0.15)				
	Standard risk factors only	12 SNP panel only	Standard risk factors + 7 SNP panel	Standard risk factors + 12 SNP panel
Lowest-risk 1%	0.0336	0.0681	0.0279	0.0258
Lowest-risk 5%	0.0483	0.0796	0.0409	0.0382
Highest-risk 5%	0.2962	0.2543	0.3275	0.3388
Highest-risk 1%	0.3531	0.2956	0.4016	0.4191
BI-RADS4C (Average risk = 0.53)				
	Standard risk factors only	12 SNP panel only	Standard risk factors + 7 SNP panel	Standard risk factors + 12 SNP panel
Lowest-risk 1%	0.1816	0.3183	0.1551	0.1448
Lowest-risk 5%	0.2436	0.3555	0.2129	0.2012
Highest-risk 5%	0.7271	0.6841	0.7542	0.7632
Highest-risk 1%	0.7772	0.7284	0.8109	0.8218

BI-RADS, Breast Imaging-Reporting and Data System

Table 4

Proportion of women reclassified across biopsy risk threshold according to risk prediction model, %

		Risk prediction model			
Biopsy risk threshold, %		**Standard risk factors**	**Standard risks + 7 SNPs**	**Standard risks + 12 SNPs**	**12-SNP panel**
2	BI-RADS3 above threshold	5	7	8	1
	BIRADS4As below threshold	3	6	7	0
1	BI-RADS3 above threshold	43	40	39	43
	BIRADS4As below threshold	0	0	1	0
3	BI-RADS3 above threshold	1	1	2	0
	BIRADS4As below threshold	15	19	20	2