ORIGINAL REPORT

Model for Individualized Prediction of Breast Cancer Risk After a Benign Breast Biopsy

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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A B S T R A C T

Purpose

Optimal early detection and prevention for breast cancer depend on accurate identification of women at increased risk. We present a risk prediction model that incorporates histologic features of biopsy tissues from women with benign breast disease (BBD) and compare its performance to the Breast Cancer Risk Assessment Tool (BCRAT).

Methods

We estimated the age-specific incidence of breast cancer and death from the Mayo BBD cohort and then combined these estimates with a relative risk model derived from 377 patient cases with breast cancer and 734 matched controls sampled from the Mayo BBD cohort to develop the BBD–to–breast cancer (BBD-BC) risk assessment tool. We validated the model using an independent set of 378 patient cases with breast cancer and 728 matched controls from the Mayo BBD cohort and compared the risk predictions from our model with those from the BCRAT.

Results

The BBD-BC model predicts the probability of breast cancer in women with BBD using tissue-based and other risk factors. The concordance statistic from the BBD-BC model was 0.665 in the model development series and 0.629 in the validation series; these values were higher than those from the BCRAT (0.567 and 0.472, respectively). The BCRAT significantly underpredicted breast cancer risk after benign biopsy ($P = .004$), whereas the BBD-BC predictions were appropriately calibrated to observed cancers ($P = .247$).

Conclusion

We developed a model using both demographic and histologic features to predict breast cancer risk in women with BBD. Our model more accurately classifies a woman's breast cancer risk after a benign biopsy than the BCRAT.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women in the United States, with more than 230,000 invasive breast cancers and an additional 65,000 noninvasive breast cancers expected in 2013.[1] Ideally, women at increased risk for breast cancer should be identified so that appropriate surveillance and prevention strategies can be offered. Unfortunately, currently available risk prediction models do not provide accurate estimates of risk at the individual level. The Breast Cancer Risk Assessment Tool (BCRAT) was designed to identify groups of women at increased risk for entry onto chemoprevention trials.[2,3] However, it is commonly used clinically today to predict risk for individual women, where it has limited accuracy.[4] Other risk prediction models include the International Breast Cancer Intervention Study (IBIS) and Breast Cancer Surveillance Consortium models. The IBIS model focuses primarily on familial breast cancer, and the Breast Cancer Surveillance Consortium model does not incorporate specific histologic findings from benign biopsies.

Annually, one to two million women in the United States undergo breast biopsy to investigate a palpable or mammographic abnormality and have benign findings.[5] These women with so-called benign breast disease (BBD) have an increased risk of breast cancer, stratified by the degree of epithelial abnormality.[6-8] In addition, other histologic features, such as the degree of lobular involution,[9,10] are

strongly associated with breast cancer risk. These observations are consistent with other cancers, where examining the histologic features of the tissue at risk greatly improves risk assessment. To our knowledge, no model for breast cancer risk prediction has incorporated substantial tissue-based information, such as that available from a benign breast biopsy. The BCRAT incorporates number of prior breast biopsies and the presence of atypical hyperplasia. The IBIS model also includes these features and the presence of lobular carcinoma in situ.[11] Using the Mayo BBD cohort, we tested both of these models in women with atypical hyperplasia, a high-risk benign lesion, and found that neither predicted breast cancer risk better than chance alone.[12,13] This underscores the need for improved models for the prediction of breast cancer risk in women with BBD.

Here we present a model that predicts the absolute risk of developing breast cancer at the time of benign biopsy. It uses histologic features assessed from the biopsy, together with other demographic and clinical features. We also compare the performance of this model to that of the BCRAT, the most commonly used tool in women with BBD.

METHODS

Study Population

The Mayo BBD cohort has been previously described.[7,10] This study set comprises 9,854 women age 18 to 85 who had excisional benign breast biopsies

Table 1. Clinical Characteristics of the Women Later Diagnosed With Breast Cancer (patient cases) and Unaffected Women Matched to Those With Breast Cancer (controls) by Model Development and Validation Subgroups

| | Model Development | | | | | Validation | | | | |
| | Patient Cases (n = 377) | | Controls (n = 734) | | | Patient Cases (n = 378) | | Controls (n = 728) | | |
Clinical Characteristic	No.	%	No.	%	P	No.	%	No.	%	P
Follow-up, years					< .001					< .001
Median	11.6		21.8			10.7		22.2		
25th percentile	6.0		16.1			5.5		15.9		
75th percentile	17.1		29.3			15.6		29.8		
Age at benign biopsy, years					.8978					.8678
Median	51.0		51.0			52.0		52.0		
25th percentile	44.0		44.0			45.0		46.0		
75th percentile	60.0		60.0			61.0		61.0		
Histologic impression					< .001					< .001
Nonproliferative	202	53.6	494	67.3		196	51.9	458	62.9	
Proliferative	175	46.4	240	32.7		182	48.1	270	37.1	
No. of atypical foci					< .001					< .001
0	341	90.5	707	96.3		348	92.1	703	96.6	
1	12	3.2	15	2.0		12	3.2	20	2.7	
2	12	3.2	10	1.4		10	2.6	3	0.4	
≥ 3	12	3.2	2	0.3		8	2.1	2	0.3	
Extent of lobular involution					.0232					< .001
Missing	28		33			33		43		
None	72	20.6	117	16.7		78	22.6	108	15.8	
Partial	218	62.5	417	59.5		220	63.8	421	61.5	
Complete	59	16.9	167	23.8		47	13.6	156	22.8	
Radial scars					.0099					.6352
Missing	1		0							
Absent	342	91.0	697	95.0		359	95.0	696	95.6	
Present	34	9.0	37	5.0		19	5.0	32	4.4	
Columnar cell alterations/sclerosing adenosis					.0015					< .001
Missing	2		0			0		4		
No	206	54.9	475	64.7		198	52.4	456	63.0	
Yes	169	45.1	259	35.3		180	47.6	268	37.0	
Family history of breast cancer					.001					.0093
Missing	1		3			1		4		
None	195	51.9	454	62.1		214	56.8	469	64.8	
Any	181	48.1	277	37.9		163	43.2	255	35.2	
Age at first live birth, years/No. of children					.0875					.0091
Missing	37		69			22		53		
≤ 20/1+	55	16.2	143	21.5		69	19.4	141	20.9	
≥ 21/3+	102	30.0	215	32.3		105	29.5	251	37.2	
≥ 21/1-2	120	35.3	195	29.3		105	29.5	185	27.4	
No children	63	18.5	112	16.8		77	21.6	98	14.5	

between 1967 and 1991 at the Mayo Clinic (Rochester, MN). Demographic descriptors and risk factors were identified from medical records and questionnaires.[7,10] Archived hematoxylin and eosin slides of the benign biopsies were reviewed systematically by our breast pathologist (D.W.V.). Over a median of 18.9 years of follow-up, 924 women were diagnosed with breast cancer. The study protocol, including patient contact and follow-up methods, was approved by the Mayo Clinic Institutional Review Board with methods previously described.[7]

From the cohort, we selected two case-control sets, one for the development of a risk prediction model and a second for model validation. For the model development set, we randomly sampled 377 women who developed breast cancer (patient cases). We individually matched 734 controls, up to two per patient case, by age at biopsy and year of biopsy. Similarly, we identified an independent validation set of 378 patient cases and 728 matched controls.

Statistical Approach

To create a tool that predicts the absolute risk of breast cancer at the time of BBD, as a function of age at BBD and time since BBD, we followed the case-registry paradigm used to develop the BCRAT. This required the combination of age-specific hazards of breast cancer (invasive or in situ), age-specific hazards of the competing risk of death, and a relative risk model for individualized risk assessment.[3,14]

We estimated age-dependent hazards of breast cancer and the competing risk of death from our full BBD cohort with more than 180,000 person-years of follow-up. We used incidence density approaches to estimate the baseline risks of death and breast cancer in 5-year age categories by dividing the number of events observed in the age category by the person-years in that category.[15]

The variables considered for inclusion in the relative risk model were clinical characteristics and demographics, including age at menarche, a combined categorization of age at first live birth and number of children, breastfeeding history, menopausal status, height, body mass index, number of biopsies, family history, and indication for biopsy; and histologic variables, including overall impression (proliferative v nonproliferative), number of foci of atypical hyperplasia (if any), lobular involution (none, partial, or complete) as previously defined,[10] radial scars, and the presence of fibroadenoma, calcifications, intraductal papilloma, and sclerosing adenosis/columnar alterations. We modeled the effect of age through the baseline hazard rather than the relative risk model.

We used a multiple-imputation approach to fill in missing values before analysis[16,17] and created five independently imputed data sets. We used a forward stepwise selection approach in conditional logistic regression models to identify candidate features from each of the five data sets. Variables that met a threshold for inclusion of $P < .20$ in any of the five sets were examined in a combined data set, and variables with $P > .05$ were removed in a backward stepwise manner. Each pair of remaining variables was examined in the combined data set for evidence of interaction. Interactions with multivariable $P < .05$ were included in an initial relative risk regression model derived from the discovery case-control set.

We used the case-registry approach to combine the estimates of baseline risk of breast cancer and death with this initial relative risk model[3,14] and incorporated the results into a SAS macro (SAS Institute, Cary, NC) that computes the probability of breast cancer risk at a specified time after BBD. We used this macro to predict breast cancer risk at 5 and 10 years after BBD on both the model development and validation data sets. Similarly, we used the SAS macro available for the BCRAT[3,18] to calculate absolute breast cancer risks. From these projected risk probabilities, we computed concordance statistics (c-statistics) for the model development and model validation series separately.

After validating this initial model, we updated the relative risk estimates by combining data from both our case-control series (both model development and validation) and re-estimated the regression coefficients in the regression model defined from the discovery set alone. This provided updated coefficient estimates for the relative risk model to enhance precision. We combined this updated relative risk model with the age-specific risks of breast cancer and death to devise the final BBD model. This updated relative risk model was combined with estimates of the age-specific hazards of breast cancer and death in an SAS macro that computes the absolute risk of breast cancer after BBD. This updated macro represents our final BBD–to–breast cancer (BBD-BC) risk assessment tool.

To assess calibration, we obtained 10-year absolute risk predictions for all women in the combined case-control series using the final BBD-BC model and

the BCRAT and applied the approach of Mealiffe et al.[19] This method uses a Hosmer-Lemeshow lack of fit test[20] to assess agreement between observed and model-predicted proportions of breast cancer events within groups defined by strata of the absolute risks.[19,21] We next examined the extent to which the BBD-BC reclassified individuals into risk groups used by others for 5-year risk predictions ($< 1\%$, 1% to 1.66%, 1.67% to 2.5%, 2.51% to 4%, and $> 4\%$).[22] We computed components of the net reclassification improvement[23] to compare the improvement offered by the BBD-BC over the BCRAT. The first components of the net reclassification improvement reflect the proportions of patient cases receiving a higher versus lower risk categorization. The second set of components reflects the proportions of controls receiving a lower versus higher risk categorization.[24,25]

To apply the BBD-BC model clinically, we defined a points-based system that calculates an overall risk score for an individual woman by adding together the regression coefficients from the model, after multiplication by a constant, for the specific characteristics of the woman. We then computed the values of this risk score for all possible age and risk factor combinations, binned these values into 20

Table 2. Regression Coefficients of the Final BBD-BC Model From the Pooled Model Development and Validation Case-Control Series

Variable	Odds Ratio	95% CI
Histologic impression		
Nonproliferative	1.00	Reference
Proliferative	1.62	0.97 to 2.71
No. of atypical foci		
Ordinal variable	1.80	1.42 to 2.28
Extent of lobular involution		
Complete	1.00	Reference
Partial	1.41	0.94 to 2.12
None	1.99	1.33 to 2.99
Radial scar		
No	1.00	Reference
Yes	1.17	0.77 to 1.78
Sclerosing adenosis/columnar cell alterations		
No	1.00	Reference
Yes	0.89	0.57 to 1.38
Family history		
No	1.00	Reference
Yes	1.56	1.28 to 1.89
Age at first live birth, years/No. of children		
Nulliparous	1.00	Reference
$\leq 20/1+$	0.66	0.35 to 1.24
$\geq 21/3+$	0.68	0.38 to 1.19
$\geq 21/1-2$	0.75	0.43 to 1.30
Age at first live birth, years/No. of children modified by histologic impression		
Proliferative and nulliparous	1.00	Reference
Proliferative and $\leq 20/1+$	0.88	0.47 to 1.67
Proliferative and $\geq 21/3+$	1.00	0.56 to 1.81
Proliferative and $\geq 21/1-2$	0.63	0.35 to 1.15
Age at first live birth, years/No. of children modified by extent of lobular involution		
Per involution category and nulliparous	1.00	Reference
Per involution category and $\leq 20/1+$	0.94	0.56 to 1.58
Per involution category and $\geq 21/3+$	0.82	0.51 to 1.31
Per involution category and $\geq 21/1-2$	1.27	0.79 to 2.06
Extent of involution modified by sclerosing adenosis and/or columnar cell alterations		
Per involution category and no	1.0	Reference
Per involution category and yes	1.25	0.89 to 1.77

Abbreviation: BBD-BC, benign breast disease–to–breast cancer model.

Table 3. Concordance Statistics Measuring the Ability of the Risk Models to Discriminate Risk on an Individual Level for Risk Predictions Made at 5 and 10 Years After BBD and at Age 90 Years (lifetime risk)

	5-Year Predictions				10-Year Predictions				Age 90 Predictions			
Prediction Model	No. of Patient Cases	No. of Controls	Concordance Statistic	95% CI	No. of Patient Cases	No. of Controls	Concordance Statistic	95% CI	No. of Patient Cases	No. of Controls	Concordance Statistic	95% CI
Model development												
BBD-BC	77	149	0.692	0.62 to 0.77	149	290	0.665	0.61 to 0.72	377	734	0.636	0.60 to 0.67
BCRAT	77	149	0.609	0.53 to 0.69	149	290	0.567	0.51 to 0.62	377	734	0.556	0.52 to 0.59
Validation												
BBD-BC	84	163	0.644	0.57 to 0.72	179	346	0.629	0.58 to 0.68	378	728	0.650	0.62 to 0.68
BCRAT	84	163	0.479	0.40 to 0.56	179	346	0.472	0.42 to 0.53	378	728	0.521	0.48 to 0.56
Combined												
BBD-BC	161	312	0.667	0.61 to 0.72	328	636	0.645	0.61 to 0.68	755	1,462	0.643	0.62 to 0.67
BCRAT	161	312	0.541	0.49 to 0.60	328	636	0.515	0.48 to 0.55	755	1,462	0.538	0.51 to 0.56

Abbreviations: BBD, benign breast disease; BBD-BC, benign breast disease–to–breast cancer model; BCRAT, Breast Cancer Risk Assessment Tool.

risk groups per age decade, and computed the 25th to 75th percentile range for 10-year and lifetime breast cancer risks for each age-specific bin. All analyses were carried out using SAS software (version 9.2; SAS Institute).

RESULTS

The Mayo BBD cohort includes 9,854 women age 18 to 85 years who had a benign biopsy from 1967 to 1991 with a median follow-up of 18.9 years and 187,899 person-years of follow-up. Among questionnaire respondents, 82% reported regular mammographic screening after benign biopsy. Nine hundred twenty-four women developed breast cancer, and 3,012 women are deceased. Appendix Figure 1 (online only) illustrates the age-dependent cumulative incidence of breast cancer (invasive or ductal carcinoma in situ) and death in this cohort.

Variable Selection

Our model development set comprised 377 patient cases and 734 controls matched on age and year of BBD. Of the initial variables considered (see Methods), eight were ultimately included in the initial relative risk model and are listed by case-control status in Table 1. Features individually associated with breast cancer risk included over-

all histologic impression, number of foci of atypical hyperplasia (if present), radial scars, sclerosing adenosis/columnar alterations, family history of breast cancer, extent of lobular involution, and a combined categorization of age at first live birth and number of children. After evaluation of potential interaction effects among these features, the following three pairwise interactions were added to the relative risk prediction model: histologic impression and the combined age at first live birth and number of children measure, lobular involution and the combined age at first live birth and number of children measure, and lobular involution and sclerosing adenosis/columnar alterations.

Model Assessment and Finalization

Using the findings from the model development set, we formed an initial risk prediction tool and computed 5-year, 10-year, and lifetime (age 90 years) risk predictions from the tool and the BCRAT. The c-statistic for the 10-year risk prediction from our model was 0.665 (95% CI, 0.61 to 0.72), which is higher than the c-statistic of 0.567 (95% CI, 0.51 to 0.62) for the BCRAT. We tested this initial model in the independent validation set (Table 1). These 10-year risk predictions resulted in a c-statistic of 0.629 (95% CI, 0.58 to 0.68) from our initial model versus 0.472 (95% CI, 0.42 to 0.53) from the BCRAT.
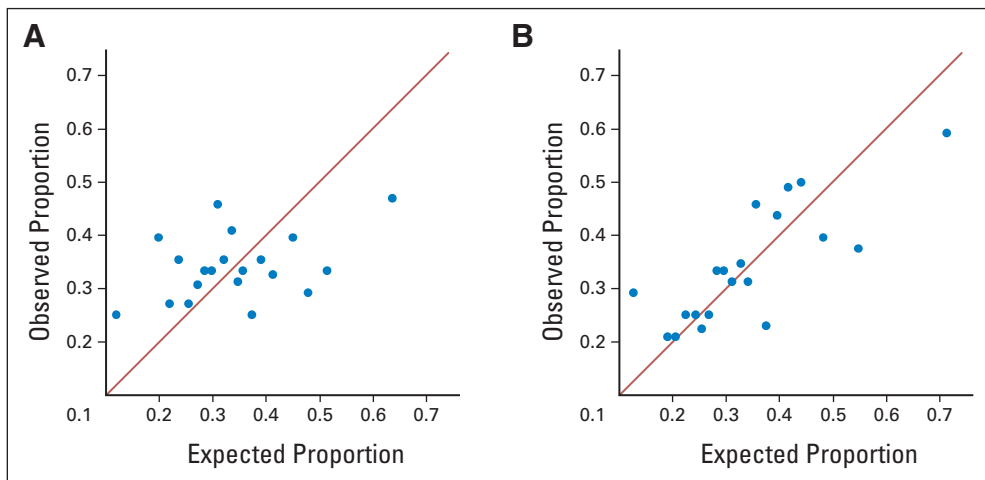
Fig 1. Plots summarizing the calibration of 10-year risk predictions by comparing observed proportion of women with breast cancer to the proportion expected within deciles of predicted risk. If a model is well calibrated, the points should lie along the diagonal line to indicate that the observed proportion of patients in each risk group agrees closely with the proportions predicted from the model. (A) Calibration of the Breast Cancer Risk Assessment Tool. (B) Calibration of the benign breast disease–to–breast cancer model.

After validation, we pooled all patient cases and controls in the model development and validation sets and re-estimated the regression coefficients of the variables. These regression coefficients were used to develop our BBD-BC risk prediction tool (Table 2). We obtained 5-year, 10-year, and lifetime risk predictions from this model and from the BCRAT (Table 3). We also assessed calibration of the 10-year risk predictions while accounting for the case-control design. Figure 1 shows plots comparing the observed versus the predicted proportions of patient cases within 20 risk-based strata for the BCRAT and BBD-BC models. With perfect calibration, the observed and expected numbers would agree, and the points would display a correlation of 1.0 by lying exactly on the diagonal line.

For the BCRAT (Fig 1A), there is significant lack of fit by the Hosmer-Lemeshow test ($P = .004$), and the correlation between observed and predicted breast cancer proportions across the 20 risk strata is weak ($r = 0.283$; $P = .046$). In contrast, the BBD-BC model (Fig 1B) displays stronger correlation between observed and predicted breast cancer proportions ($r = 0.608$; $P < .001$), indicating that the BBD-BC predictions were appropriately calibrated to observed cancers ($P = .247$). The BCRAT predictions tended to be lower than those from the BBD-BC (Appendix Table A1, online only, lists the cutoff values for the 20 risk strata). For 5-year risk predictions, the BBD-BC placed 46.6% more patient cases into higher and 14.8% more patient cases into lower 5-year risk groups than the BCRAT. It placed 23.1% more controls into lower and 34.7% more controls into higher 5-year risk groups than the BCRAT. Importantly, of the 350 patient cases with less than 1.67% 5-year risk via the BCRAT, 49.4% were predicted to have greater than 1.67% 5-year risk via the BBD-BC. For the 405 patient cases with 5-year risk greater than 1.67% via the BCRAT, 13.3% received 5-year predictions less than 1.67% by the BBD-BC (Appendix Table A2, online only).

Given that the BCRAT predicts risk of invasive breast cancer, we excluded patient cases with ductal carcinoma in situ and repeated the analyses on the invasive subgroup only. The 10-year c-statistic for the BBD-BC was 0.642 (95% CI, 0.60 to 0.69), whereas the 10-year c-statistic for the BCRAT was 0.502 (95% CI, 0.46 to 0.55). Calibration for the BCRAT and the BBD-BC models in the invasive subgroup was similar to that described for all women in our primary analyses.

Individualized Risk Prediction

We generated a table-based method for individualized risk assessment using the BBD-BC model. Points for each risk feature (Table 4) are summed to derive a risk score that can be used to obtain individualized 10-year and lifetime breast cancer risks (Table 5). Examples of this model applied to three representative patients are listed in Appendix Table A3 (online only).

DISCUSSION

Using a unique, large cohort of women with BBD, we developed a model that predicts the absolute risk of breast cancer (both invasive and in situ) at 10 years and for lifetime after benign biopsy. To our knowledge, this BBD-BC model is the first breast cancer risk prediction tool that focuses specifically on the sizable pool of women with BBD. Importantly, it incorporates information assessed directly from the breast biopsy, in addition to clinical risk factors. We compared the performance of the BCRAT to that of the BBD-BC and demonstrated that the BBD-BC model has better discrimination and calibration in women with BBD.

Table 4. Model Characteristics and Corresponding Risk Points Assigned	
Characteristic	No. of Points
Main effect characteristics	
Histologic impression	
NP	0
PD	20.5
No. of atypical foci	
0	0
1	24.4
2	48.8
≥ 3	73.2
Extent of lobular involution	
Complete	0
Partial	14.1
None	28.3
Presence of radial scar	
No	0
Yes	6.0
Presence of SA and/or CCA	
Neither	0
SA or CCA or both	−4.7
Family history of breast cancer	
No	0
Yes	18.2
Age at first live birth, years, and No. of children	
Nulliparous	0
≤ 20, ≥ 1	−16.5
≥ 21, ≥ 3	−14.7
≥ 21, 1-2	−11.6
Effect-modifying characteristics	
Age at first live birth, years, and No. of children modified by histologic impression	
Nulliparous or NP*	0
≤ 20, ≥ 1 and PD†	−6.4
≥ 21, ≥ 3 and PD†	−1.0
≥ 21, 1-2 and PD†	−19.8
Age at first live birth, years, and No. of children modified by extent of lobular involution	
Nulliparous or complete involution*	0
≤ 20, ≥ 1 and partial involution†	−2.8
≤ 20, ≥ 1 and no involution†	−5.7
≥ 21, ≥ 3 and partial involution†	−9.6
≥ 21, ≥ 3 and no involution†	−19.2
≥ 21, 1-2 and partial involution†	9.6
≥ 21, 1-2 and no involution†	19.3
Extent of involution modified by SA and/or CCA	
Complete involution or (no SA and no CCA)*	0
Partial involution and either SA or CCA†	9.2
No involution and either SA or CCA†	18.4

NOTE. For a given individual, sum the assigned points for each of the 10 main effect and effect-modifying characteristics to obtain an overall risk score, and see Table 5 for translation into risk estimates.
Abbreviations: CCA, columnar cell alteration; NP, nonproliferative disease; PD, proliferative disease; SA, sclerosing adenosis.
*Use this category if the individual has one or both of the two characteristics.
†Use this category only if the individual has both of the two characteristics.

Discrimination measures the ability of a model to correctly predict patient cases to be at higher risk than controls and is reflected in the c-statistic, where values near 1.0 represent perfect discrimination and values near 0.5 represent no discrimination. In the validation set, the BBD-BC model 10-year c-statistic was 0.63, which is significantly higher than 0.47, the value for the BCRAT. The improved discrimination was also seen at the 5-year and age 90 (lifetime) risk predictions.

Table 5. Translation of BBD-BC Model–Assigned Risk Points (from Table 4) to Average Breast Cancer Risk Estimates

	Age at Initial Biopsy													
	< 30 Years		30-39 Years		40-49 Years		50-59 Years		60-69 Years		70-79 Years		≥ 80 Years	
Sum of Risk Points	10-Year Risk (%)	Lifetime Risk (%)	10-Year Risk (%)	Lifetime Risk (%)	10-Year Risk (%)	Lifetime Risk (%)	10-Year Risk (%)	Lifetime Risk (%)	10-Year Risk (%)	Lifetime Risk (%)	10-Year Risk (%)	Lifetime Risk (%)	10-Year Risk (%)	Lifetime Risk (%)
≤ 0	0.3	11.2	1.0	11.0	1.9	10.3	2.6	8.8	3.5	6.7	3.0	3.8	1.9	1.6
0.1-12.6	0.4	15.5	1.4	15.4	2.8	14.5	3.8	12.4	4.9	9.5	4.3	5.5	2.7	2.3
12.7-18.6	0.5	18.7	1.7	18.5	3.4	17.5	4.6	15.0	6.0	11.6	5.2	6.7	3.3	2.8
18.7-26.9	0.6	21.7	2.0	21.6	4.1	20.5	5.5	17.6	7.1	13.6	6.2	7.9	3.9	3.3
27.0-33.7	0.7	26.0	2.4	25.8	5.0	24.5	6.7	21.2	8.7	16.4	7.6	9.6	4.7	4.0
33.8-38.2	0.8	29.0	2.8	28.9	5.7	27.5	7.6	23.8	9.9	18.6	8.6	10.9	5.4	4.6
38.3-44.2	0.8	31.6	3.1	31.5	6.3	30.0	8.4	26.1	11.0	20.4	9.5	12.0	6.0	5.1
44.3-51.3	1.0	35.7	3.6	35.5	7.3	33.9	9.8	29.6	12.6	23.3	11.0	13.8	6.9	5.9
51.4-57.4	1.3	40.8	4.3	40.6	8.6	38.8	11.5	34.0	14.9	27.0	13.0	16.2	8.2	7.0
57.5-62.1	1.3	44.6	4.8	44.5	9.7	42.6	13.0	37.5	16.7	30.0	14.5	18.1	9.2	7.9
62.2-66.1	1.5	48.1	5.4	47.8	10.7	45.9	14.3	40.6	18.4	32.6	16.0	19.9	10.2	8.7
66.2-71.7	1.7	52.1	6.0	51.9	12.0	49.9	16.0	44.4	20.5	35.9	17.9	22.1	11.4	9.8
71.8-79.2	2.0	57.4	7.1	57.3	14.0	55.3	18.5	49.6	23.6	40.6	20.7	25.4	13.3	11.4
79.3-84.2	2.3	62.7	8.2	62.6	16.1	60.6	21.2	54.8	26.9	45.3	23.6	28.8	15.3	13.1
84.3-88.7	2.6	66.8	9.2	66.7	18.0	64.8	23.6	58.9	29.8	49.2	26.2	31.8	17.0	14.6
88.8-94.5	2.8	70.6	10.3	70.7	20.1	68.9	26.2	63.1	32.9	53.2	29.0	34.9	19.0	16.3
94.6-104.2	3.5	76.1	12.2	76.3	23.6	74.7	30.6	69.2	38.0	59.4	33.6	40.1	22.2	19.2
104.3-111.3	4.2	81.6	14.7	81.8	28.0	80.6	36.0	75.6	44.2	66.2	39.3	46.2	26.3	22.9
111.4-123.5	5.0	86.1	17.9	86.6	33.4	85.7	42.5	81.5	51.3	73.1	45.9	53.0	31.3	27.4
≥ 123.6	7.9	92.6	27.6	93.2	48.2	93.1	58.9	90.7	68.0	85.3	61.9	68.4	44.7	39.9

Abbreviation: BBD-BC, benign breast disease–to–breast cancer model.

Importantly, although both models incorporate age-dependent breast cancer risks, the c-statistics in this study likely underestimate the actual discrimination of both models because we are studying age-matched patient cases and controls. Nevertheless, the c-statistic of the BBD-BC model is 0.63, which compares favorably to estimates reported for the BCRAT in studies not based on age-matched patient cases and controls.[4]

The second measure of model performance, calibration, assesses how accurately a model predicts the level of risk. This is a critical component of an absolute risk prediction model; if a model is not well calibrated, its estimates provide a biased reflection of risk. In calibration, our model offers a real benefit over the BCRAT. The BCRAT demonstrated significant lack of calibration in the Mayo BBD cohort, whereas the BBD-BC predictions were appropriately calibrated to observed cancers in this population. The BCRAT significantly underpredicts breast cancer risk after benign breast biopsy. Therefore, even though the added discrimination provided by our model is modest, the absolute risk estimates from the BBD-BC were better calibrated to observed breast cancer incidence after benign biopsy (Fig 1). Thus, this new BBD-BC model provides improved risk prediction for women with BBD, not only in its discriminatory accuracy, but also in its calibration to observed breast cancer risk after BBD. The lack of calibration of the BCRAT made it difficult to assess the improvement in risk categorization provided by the BBD-BC, because the average risks estimated by the BBD-BC were higher than those of the BCRAT. The BBD-BC model classified a net of 32% of women who developed breast cancer as being in higher risk categories, although BCRAT correctly classified a net of 12% of controls as being in lower risk categories. Although this comparison is most appropriate when made between well-calibrated models, the BBD-BC model was able to correctly change risk categories for a net of 20% of women with BBD when compared with the BCRAT.

To our knowledge, this is also the first report of the performance of the BCRAT in an unselected set of women with BBD who developed breast cancer and matched controls. In this set, the BCRAT displayed poor performance, with low c-statistics and evidence of significant lack of calibration. This suggests that the use of a model developed specifically for women with BBD, such as the BBD-BC model reported here, may provide improved ability to identify women who truly are at increased risk of breast cancer after a benign biopsy.

The BBD-BC model put forward here has a number of strengths. First, it was developed exclusively for women with BBD, an important and large group of women who are understandably concerned about their breast cancer risk. Clinicians routinely use the BCRAT, or the IBIS model, in women with BBD when neither of these models has been expressly validated in this setting. Second, we showed consistent performance in an independent validation set. Finally, the features included in the model are commonly available from the patient's history or from the hematoxylin and eosin slide used for the diagnosis. The only pathologic feature we have incorporated that is not currently reported is the extent of age-related involution of normal breast lobules. For this, we have used a simple three-level measure of no involution versus moderate versus complete involution that could be assessed by a breast pathologist.

We also acknowledge limitations to this work. First, the model is based on data from a cohort of women with BBD at the Mayo Clinic, a largely white population. Unfortunately, the major BBD resources studied to date have all included primarily white women.[7,26,27] Second, we have not yet validated the performance of the model in women with BBD from other study sites. Finally, although better than what has been observed with other models, the discrimination of the model remains suboptimal.

In summary, this new BBD-BC model represents an important step toward individualized breast cancer risk prediction for women with BBD. Our BBD-BC model uses information gained from assessment of the breast tissue at risk, and it improves risk prediction for women with BBD compared with the current standards. More accurate risk prediction sets the stage for more appropriate tailoring of surveillance and risk reduction strategies. We anticipate future work with more sophisticated approaches using molecular markers and genomic assessments to further improve model performance and risk prediction for women with BBD.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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■ ■ ■

GLOSSARY TERMS

calibration: agreement of predicted risks with observed outcomes, for example, mortality rates.

Acknowledgment

Appendix

Table A1. Ten-Year Risk Prediction Cutoffs for the 20 Risk Strata Used to Assess Model Calibration

Stratum	BCRAT 10-Year Risk Range (%)	BBD-BC 10-Year Risk Range (%)
1	< 1.720	< 2.052
2	1.721-2.124	2.052-2.334
3	2.125-2.297	2.335-2.541
4	2.298-2.586	2.542-2.809
5	2.587-2.798	2.810-3.086
6	2.799-3.055	3.087-3.328
7	3.056-3.222	3.329-3.501
8	3.223-3.414	3.502-3.759
9	3.415-3.585	3.760-4.019
10	3.586-3.817	4.020-4.323
11	3.818-4.027	4.324-4.609
12	4.028-4.234	4.610-4.866
13	4.235-4.406	4.867-5.317
14	4.407-4.724	5.318-5.721
15	4.725-5.143	5.722-6.146
16	5.144-5.782	6.147-6.624
17	5.783-6.499	6.625-7.609
18	6.500-7.292	7.610-9.156
19	7.293-8.820	9.157-11.967
20	≥ 8.821	≥ 11.968

Abbreviations: BBD-BC, benign breast disease–to–breast cancer model; BCRAT, Breast Cancer Risk Assessment Tool.

Table A2. Reclassification of the BCRAT With the BBD-BC Model in Categories of 5-Year Breast Cancer Risk

5-Year Risk: BCRAT	5-Year Risk: BBD-BC					Correctly Reclassified (%)	Incorrectly Reclassified (%)
	0% to < 1%	1% to 1.66%	1.67% to 2.5%	2.5% to 4%	> 4%		
Patient Cases							
0% to < 1%	67	33	12	9	2	45.5%	0%
1% to 1.66%	7	70	83	51	16	66.1%	3.1%
1.67% to 2.5%	3	41	69	74	32	48.4%	20.1%
2.5% to 4%	0	9	23	46	40	33.9	27.1%
> 4%	0	1	13	15	39	0%	42.6%
Controls							
0% to < 1%	159	75	27	9	0	0%	41.1%
1% to 1.66%	46	195	152	68	15	9.7%	49.4%
1.67% to 2.5%	7	115	159	103	19	30.3%	30.3%
2.5% to 4%	0	31	78	65	40	50.9%	18.7%
> 4%	0	8	20	32	39	60.6%	0%

Abbreviations: BBD-BC, benign breast disease–to–breast cancer model; BCRAT, Breast Cancer Risk Assessment Tool.

Table A3. Calculation of Risk Scores and Corresponding Translation Into Risk Estimates for Three Hypothetical Women

Risk Calculation and Translation	Example 1 Value	Example 1 Points	Example 2 Value	Example 2 Points	Example 3 Value	Example 3 Points
Part 1: calculation of risk score (see Table 4)						
Main effect characteristic						
(1) Histologic impression	NP	0	PD	20.5	PD	20.5
(2) No. of atypical foci	0	0	0	0	1	24.4
(3) Extent of lobular involution	Complete	0	Partial	14.1	Partial	14.1
(4) Presence of radial scar	No	0	No	0	Yes	6.0
(5) Presence of SA and/or CCA	Neither	0	SA or CCA	−4.7	Neither	0
(6) Family History of Breast Cancer	No	0	Yes	18.2	Yes	18.2
(7) Age at first live birth and No. of children	≥ 21 years, 1-2 children	−11.6	≤ 20 years, ≥ 1 child	−16.5	Nulliparous	0
Effect-modifying characteristic						
(8) Age at first live birth and No. of children, modified by histologic impression	Nullip or NP	0	≤ 20 years, ≥ 1 child, and PD	−6.4	Nullip or NP	0
(9) Age at first live birth and No. of children, modified by extent of lobular involution	Nullip or complete	0	≤ 20 years, ≥ 1 child, and partial	−2.8	Nullip or complete	0
(10) Extent of Involution, modified by SA and/or CCA	Complete or (neither SA nor CCA)	0	Partial and (either SA or CCA)	9.2	Complete or (neither SA nor CCA)	0
Risk score (sum of individuals points)		−11.6		31.6		83.2
Part 2: translation into risk estimate (see Table 5)						
Age at initial biopsy, years		72		65		53
10-year risk, %		3.0		8.7		21.2
Lifetime risk, %		3.8		16.4		54.8

NOTE. Example 1 represents a woman with characteristics reflecting low breast cancer risk. Example 2 represents a woman with characteristics of a moderate risk of breast cancer. Example 3 represents a woman with characteristics reflecting high breast cancer risk. Example 1 (low-risk woman): 72 years of age at initial biopsy, nonproliferative disease (and thus no atypical foci), complete involution, no radial scar, no SA, no CCA, negative family history of breast cancer, two children, and 25 years old at first birth. Example 2 (moderate-risk woman): 65 years of age at first biopsy, proliferative disease, no typical foci, partial involution, no radial scars, no SA, presence of CCA, positive family history of breast cancer, three children, and 19 years old at first birth. Example 3 (high-risk woman): 53 years of age at first biopsy, proliferative disease, one focus of atypia, partial involution, radial scars present, no SA, no CCA, positive family history of breast cancer, and nulliparous.
Abbreviations: CCA, columnar cell alteration; NP, nonproliferative disease; nullip, nulliparous; PD, proliferative disease; SA, sclerosing adenosis.
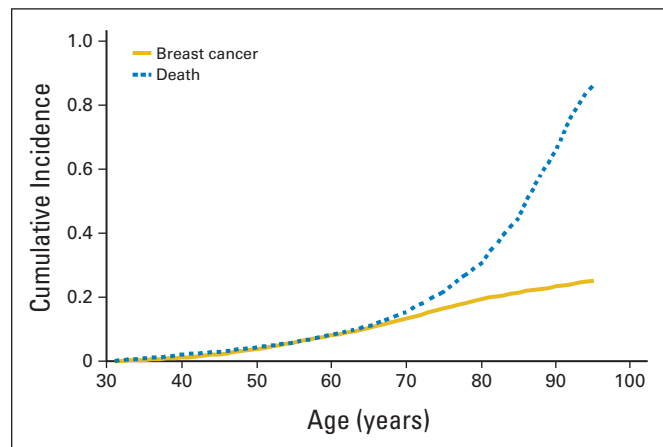
Fig A1. Cumulative incidence of breast cancer and of death among women with benign breast disease (BBD), estimated from the women enrolled onto the Mayo BBD cohort from 1967 to 1991.