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Validation of the Breast Cancer Surveillance Consortium Model of Breast Cancer Risk

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Abstract

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Compliance with Ethical Standards

Conflict of Interest: Jeffrey A. Tice, MD declares that he has no conflict of interest. Michael C. S. Bissell declares that he has no conflict of interest. Diana L. Miglioretti, PhD declares that she has no conflict of interest. Charlotte C. Gard, PhD, MBA declares that she has no conflict of interest. Garth H. Rauscher, PhD declares that he has no conflict of interest. Firas M. Dabbous, MS, PhD declares that he has no conflict of interest. Karla Kerlikowske, MD declares that she has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Each registry and the Statistical Coordinating Center received institutional review board approval and a Federal Certificate of Confidentiality and other protection for the identities of the research subjects. All procedures are Health Insurance Portability and Accountability Act (HIPAA) compliant.

Data Availability Statement:
The data that support the findings of this study are available from the Breast Cancer Surveillance Consortium, but restrictions apply to the availability of these data, which were used under a study agreement for this analysis, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the BCSC. Details about the BCSC data are available at http://www.bcsc-research.org/data/index.html.

Purpose: In order to use a breast cancer prediction model in clinical practice to guide screening and prevention, it must be well calibrated and validated in samples independent from the one used for development. We assessed the accuracy of the Breast Cancer Surveillance Consortium (BCSC) model in a racially diverse population followed for up to 10 years.

Methods: The Breast Cancer Surveillance Consortium (BCSC) model combines breast density with other risk factors to estimate a woman's 5 and 10-year risk of invasive breast cancer. We validated the model in an independent cohort of 252,997 women in the Chicago area. We evaluated calibration using the ratio of expected to observed (E/O) invasive breast cancers in the cohort and discrimination using the area under the receiver operating characteristic curve (AUROC).

Results: In an independent cohort of 252,997 women (median age 50 years, 26% non-Hispanic Black), the BCSC model was well calibrated (E/O = 0.94, 95% confidence interval [CI] 0.90–0.98), but underestimated the incidence of invasive breast cancer in younger women and in women with low mammographic density. The AUROC was 0.633, similar to that observed in prior validation studies.

Conclusions: The BCSC model is a well validated risk assessment tool for breast cancer that may be particularly useful when assessing the utility of supplemental screening in women with dense breasts.

Keywords

Breast neoplasms; Risk assessment; Breast density; Breast cancer surveillance consortium; Predictive value of tests; ROC curve

Breast cancer risk is increasingly used to guide recommendations about prevention [1]. The Gail model was one of the earliest breast cancer risk assessment tools [2], but validation of the model highlighted its modest ability to discriminate between women who develop breast cancer and those who do not, which limits its utility for counseling individuals [3]. The Breast Cancer Surveillance Consortium (BCSC) model has greater discrimination than the Gail model, largely through the addition of breast density and benign breast disease [3,4]. The original BCSC model was externally validated in the Mayo Clinic cohort [5]. In this study, we evaluate the performance of the BCSC v2 model in a cohort of women in Chicago.

The Chicago registry collects data on mammography examinations from a large health care delivery organization with facilities throughout metropolitan Chicago [6]. We included women ages 35 to 74 years who had at least one mammogram between 2001 and 2012 who were not diagnosed with breast cancer within 3 months of the index mammogram. Women were excluded if they had a prior DCIS or invasive breast cancer diagnosis, had breast implants, or lacked information on the BCSC model risk factors. Each registry and the Statistical Coordinating Center received institutional review board approval and a Federal Certificate of Confidentiality and other protection for the identities of the research subjects. All procedures are Health Insurance Portability and Accountability Act (HIPAA) compliant.

Age, race/ethnicity, family history of breast cancer, and history of breast biopsies were obtained primarily from self-report at the time of mammography. Community radiologists

classified breast density as part of routine clinical practice using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS®) categories. Community pathologists classified breast biopsy results based on clinical practice. We grouped benign diagnoses as non-proliferative, proliferative without atypia, proliferative with atypia, or lobular carcinoma in situ [7]. We linked to the Illinois Sate Cancer Registry and hospital tumor registry and pathology sources to identify breast cancer diagnoses [6].

We assessed model calibration by calculating the ratio of the expected (E) to observed (O) number of breast cancers and calculated 95% confidence intervals using the Greenwood variance [8]. We used the Kaplan-Meier estimator to calculate the number of cancers observed in each subgroup. An E/O ratio of 1.0 indicates perfect calibration. We assessed model discrimination using the area under the time-dependent receiver operating characteristic curve (AUROC) [9]. An AUC of 0.5 is equivalent to chance and an AUC of 1.0 indicates perfect discrimination. We used identical methods for model development and the recalculation of hazard ratios in the Chicago cohort [7].

Table 1 shows the distribution of the BCSC model risk factors in the Chicago cohort in women with and without breast cancer. Women who developed breast cancer were older and more likely to be white, have a family history of breast cancer and have a history of breast biopsy. The distribution of BI-RADS breast density was similar between those with and without breast cancer.

The BCSC model underestimated breast cancer risk in the Chicago cohort by 6% (Table 2). The underestimation was greatest for younger women (ages 35–44), Hispanic and non-Hispanic black women, and women with almost entirely fat breast density. Calibration was good for women ages 45–74, non-Hispanic white women, and those with the most common scattered fibroglandular and heterogeneously dense breast density.

The AUROC for the model was 0.633. The hazard ratios for the model were similar in the Chicago cohort and the original BCSC development cohort (Table 3) except at older ages for non-Hispanic black women and for women with fatty breasts.

The BCSC v2 model extended the original BCSC model to include benign breast disease. In this external validation, the overall calibration was good (E/O=0.94, 95% CI=0.90–0.98). The underestimation of the BCSC model in the Chicago cohort was nearly identical to that reported for the Gail model in the Nurse’s Health Study (NHS) (E/O=0.94, 95% CI=0.87–0.99) [3]. The discriminatory accuracy of the BCSC v2 model in the Chicago cohort (AUROC=0.633) was similar to that reported using cross-validation in the original cohort for BCSC v2 (AUROC=0.665) [10] and the earlier validation study of the BCSC model (AUROC=0.66) [5], but higher than that of the Gail model in the NHS (AUROC=0.58) [3].

There are several reasons that may explain the modest underestimation of risk by the BCSC v2 model in the Chicago cohort. First, the underlying breast cancer risk in the BCSC model is based on the age and race specific incidence of invasive breast cancer in SEER. Younger women screened for breast cancer prior to most guideline recommendations for screening (ages 35–45) are likely at higher than average risk for breast cancer, so a model based on average risk would be expected to underestimate risk for this younger population. Second,

the prevalence of obese (19%) and morbidly obese women (16%) in the Chicago cohort is high [6]. There is a strong association between body mass index (BMI) and breast density and between BMI and breast cancer incidence. Since the BCSC v2 model does not account for BMI, obesity may represent an important confounder leading to under-estimation of risk, particularly in women with low breast density. This may also explain why low breast density was not as strongly associated with reduced risk in the Chicago cohort than in the BCSC cohort. Finally, the breast cancer risk in non-Hispanic black women in the Chicago cohort appears to be higher than that of the BCSC model, which is based on SEER. Given the high proportion of black women in the Chicago cohort, this may also contribute to the underestimation of risk.

When risks estimated from a breast cancer model are used for counseling individual women about health decisions, it is essential that the model be well calibrated, so that the risk information communicated is accurate. The Gail model has been extensively validated in cohorts women in the United States (US) with the E/O ratio ranging from 0.89 to 1.02 [11,12,3]. The Tyrer-Cuzick model, which was developed in high risk women in the United Kingdom, appears to be less well calibrated in the US (E/O 0.98–1.9) [13,14].

The BCSC risk model has now been externally validated in two US separate cohorts. The BCSC risk model is the only model that includes a clinical measure of BI-RADS density, which increases the clinical utility of the model, and is available for average-risk women of all race/ethnicities. This has important clinical implications as risk-based screening strategies are developed to identify women who may benefit from chemoprevention or supplemental imaging [15].

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Table 1:

Baseline Characteristics of Women in the Chicago Cohort

	No breast cancer (N=248,828)	Breast cancer (N=4,169)
Age group, years		
35–39	24,578 (9.9%)	189 (4.5%)
40–44	55,421 (22.3%)	601 (14.4%)
45–49	44, 407 (17.8%)	650 (15.6%)
50–54	39,034 (15.7%)	674 (16.2%)
55–59	30,088 (12.1%)	646 (15.5%)
60–64	22,373 (9.0%)	563 (13.5%)
65–69	20,386 (8.2%)	532 (12.8%)
70–74	12,541 (5.0%)	314 (7.5%)
Race / ethnicity		
White, non-Hispanic	149,312 (60.0%)	2,648 (63.5%)
Black, non-Hispanic	63,859 (25.7%)	1,136 (27.2%)
Asian	8,507 (3.4%)	128 (3.1%)
American Indian	440 (0.2%)	6 (0.1%)
Hispanic	23,670 (9.5%)	200 (4.8%)
Other/mixed	3,040 (1.2%)	51 (1.2%)
Family history of breast cancer in first degree relative	33,823 (13.6%)	913 (21.9%)
Breast density *		
A: Almost entirely fat	22,099 (8.9%)	374 (9.0%)
B: Scattered fibroglandular densities	89,773 (36.1%)	1,433 (34.4%)
C: Heterogeneously dense	111,107 (44.7%)	1,925 (46.2%)
D: Extremely dense	25,849 (10.4%)	437 (10.5%)
Benign breast disease		
None (no prior biopsy)	212,088 (85.2%)	3,153 (75.6%)
Prior biopsy (unknown diagnosis)	31,353 (12.6%)	883 (21.2%)
Nonproliferative	4,400 (1.8%)	93 (2.2%)
Proliferative without atypia	732 (0.3%)	22 (0.5%)
Proliferative with atypia	81 (0.03%)	5 (0.1%)
Lobular carcinoma in situ	174 (0.07%)	13 (0.3%)

* Using the Breast Imaging Reporting and Data System (BI-RADS) density categories

Table 2.

Calibration of the Breast Cancer Surveillance Consortium Version 2 Model in risk factor subgroups

Risk group				
	Expected 5-year rate (E)	**Observed 5-year rate (O)**	**E/O**	**(95% CI)**
Full cohort	1.13	1.20	0.94	(0.90–0.98)
Age groups, years				
35–39	0.48	0.56	0.86	(0.71–1.04)
40–44	0.69	0.82	0.84	(0.76–0.93)
45–49	1.02	1.03	0.99	(0.90–1.10)
50–54	1.21	1.13	1.07	(0.96–1.18)
55–59	1.44	1.42	1.02	(0.92–1.13)
60–64	1.58	1.86	0.85	(0.77–0.95)
65–69	1.74	2.00	0.87	(0.78–0.96)
70–74	1.86	1.79	1.04	(0.90–1.20)
Race/Ethnicity				
White, non-Hispanic	1.19	1.24	0.96	(0.92–1.01)
Black, non-Hispanic	1.13	1.25	0.91	(0.84–0.98)
Asian	0.89	1.03	0.87	(0.68–1.11)
Hispanic	0.94	1.51	0.62	(0.26–1.52)
American Indian	0.78	0.80	0.98	(0.83–1.16)
Other, mixed	1.13	1.49	0.76	(0.54–1.07)
BI-RADS breast density				
a: Almost entirely fat	0.87	1.33	0.66	(0.58–0.75)
b: Scattered fibroglandular densities	1.10	1.07	1.03	(0.96–1.11)
c: Heterogeneously dense	1.20	1.26	0.95	(0.89–1.01)
d: Extremely dense	1.14	1.33	0.86	(0.76–0.97)
First degree family history of breast cancer				
No	1.03	1.12	0.92	(0.88–0.96)
Yes	1.76	1.74	1.01	(0.93–1.11)
Benign Breast Disease				
None (no prior biopsy)	1.01	1.07	0.94	(0.90–0.99)
Prior biopsy, unknown diagnosis	1.84	1.92	0.96	(0.88–1.05)
Non-proliferative	1.40	1.89	0.74	(0.58–0.96)
Proliferative without atypia	1.81	2.80	0.65	(0.39–1.07)
Proliferative with atypia	3.43	3.41	1.01	(0.25–3.98)

Risk group				
	Expected 5-year rate (E)	**Observed 5-year rate (O)**	**E/O**	**(95% CI)**
Lobular carcinoma in situ	5.51	4.50	1.22	(0.59–2.53)

BCSC: Breast Cancer Surveillance Consortium; E/O: Expected rate divided by the observed rate; 95% CI: 95% confidence interval; BI-RADS: Breast Imaging Reporting and Data System.

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Table 3.

Hazard Ratios from the Cox proportional hazards model demonstrating the interactions of age with other risk factors on breast cancer

	Chicago Cohort				**BCSC Model, Version 2**			
	Age (years)				**Age (years)**			
	40	**50**	**60**	**70**	**40**	**50**	**60**	**70**
Race / Ethnicity								
White, non-Hispanic	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Black, non-Hispanic	1.17	1.05	0.95	0.85	1.20	1.03	0.89	0.76
Asian	1.00	1.03	1.05	1.08	0.99	0.88	0.78	0.70
American Indian	1.38	1.00	0.72	0.52	0.76	0.73	0.69	0.66
Hispanic	0.89	0.75	0.64	0.54	1.02	0.92	0.82	0.74
Other, mixed	0.74	1.09	1.62	2.41	1.10	0.95	0.82	0.71
First degree family history								
No	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Yes	1.72	1.47	1.43	1.60	1.89	1.60	1.47	1.47
BI-RADS density								
a: Almost entirely fat	0.58	0.72	0.88	1.09	0.48	0.54	0.60	0.67
b: Scattered fibroglandular densities	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
c: Heterogeneously dense	1.66	1.49	1.34	1.21	1.62	1.51	1.40	1.31
d: Extremely dense	2.50	1.99	1.59	1.27	1.97	1.81	1.66	1.53
Benign breast disease								
No prior biopsy	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Prior biopsy, unknown diagnosis	1.50	1.40	1.42	1.56	1.50	1.44	1.46	1.57
Non-proliferative	1.07	2.02	2.66	2.45	1.31	1.43	1.56	1.70
Proliferative without atypia	1.90	2.02	2.18	2.40	1.70	1.66	1.76	2.02
Proliferative with atypia	3.92	5.57	3.48	0.96	3.19	2.97	2.77	2.59
Lobular carcinoma in situ	1.53	7.09	4.13	0.30	7.64	3.60	3.29	5.84