

Integrating Clinical and Polygenic Factors to Predict Breast Cancer Risk in Women Undergoing Genetic Testing

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PURPOSE Screening and prevention decisions for women at increased risk of developing breast cancer depend on genetic and clinical factors to estimate risk and select appropriate interventions. Integration of polygenic risk into clinical breast cancer risk estimators can improve discrimination. However, correlated genetic effects must be incorporated carefully to avoid overestimation of risk.

MATERIALS AND METHODS A novel Fixed-Stratified method was developed that accounts for confounding when adding a new factor to an established risk model. A combined risk score (CRS) of an 86–single-nucleotide polymorphism polygenic risk score and the Tyrer-Cuzick v7.02 clinical risk estimator was generated with attenuation for confounding by family history. Calibration and discriminatory accuracy of the CRS were evaluated in two independent validation cohorts of women of European ancestry (N = 1,615 and N = 518). Discrimination for remaining lifetime risk was examined by age-adjusted logistic regression. Risk stratification with a 20% risk threshold was compared between CRS and Tyrer-Cuzick in an independent clinical cohort (N = 32,576).

RESULTS Simulation studies confirmed that the Fixed-Stratified method produced accurate risk estimation across patients with different family history. In both validation studies, CRS and Tyrer-Cuzick were significantly associated with breast cancer. In an analysis with both CRS and Tyrer-Cuzick as predictors of breast cancer, CRS added significant discrimination independent of that captured by Tyrer-Cuzick ($P < 10^{-11}$ in validation 1; $P < 10^{-7}$ in validation 2). In an independent cohort, 18% of women shifted breast cancer risk categories from their Tyrer-Cuzick–based risk compared with risk estimates by CRS.

CONCLUSION Integrating clinical and polygenic factors into a risk model offers more effective risk stratification and supports a personalized genomic approach to breast cancer screening and prevention.

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INTRODUCTION

Mammography and adjuvant treatment of early-stage disease are widely used for the mitigation of morbidity and mortality in invasive breast cancer.¹ Effective prevention requires the identification of higher-risk individuals, which has typically involved family history evaluation, assessment of clinical and lifestyle factors, and testing for the presence of pathogenic variants (PVs) in a limited number of high- or moderate-risk breast cancer genes.² Although guidelines for PV carriers have long recommended enhanced screening and discussion of surgical prevention measures, they do not adequately address the increased risk for unaffected PV-negative women with a strong family history of breast cancer. This clinical need has prompted recent proposals for more risk-adapted screening.^{3,4}

Higher-risk women rely on risk prediction tools using clinical and demographic factors, such as the Tyrer-Cuzick model and others, for management guidance.⁵⁻¹⁰

The overall discriminatory accuracy of such prediction models, however, leaves room for improvement.^{11,12} Addition of single-nucleotide polymorphism (SNP)–based risk, aggregated into polygenic risk scores (PRSs), has been shown to enhance the discriminatory power of the Gail,¹³⁻¹⁶ BOADICEA,¹⁷⁻²⁰ BRCAPRO,²¹ iCARE,²²⁻²⁴ and Tyrer-Cuzick models.^{21,25-28} In many of these studies, PRS-based risk is assumed to be independent of clinical risk, despite evidence for a genetic component in many of the conventional clinical risk factors.^{29,30} Family history in particular shows evidence for a partial overlap with polygenic risk, as addition of a 77-SNP score attenuated the odds ratio (OR) for family history by 12%–13% and attenuation increased to 21% for a 313-SNP score.^{31,32} In a separate report, a 75-SNP PRS was significantly associated with family history.²⁰ Accurate risk prediction from a combined clinical and genetic risk model thus requires adjustment for shared risk contribution from genetic and clinical factors.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Recently, single-nucleotide polymorphisms (SNPs) at multiple genomic locations have been shown to affect breast cancer risk. Polygenic risk scores that aggregate SNP-based risks explain considerable genetic breast cancer susceptibility. We examined confounding and interaction between an 86-SNP polygenic risk score and each clinical factor in the Tyrer-Cuzick model to inform the development of a combined clinical and polygenic risk score. The combined risk score was evaluated in two independent prespecified validation studies.

Knowledge Generated

The combined risk score showed improved stratification compared with the Tyrer-Cuzick model alone. This included downgrading and upgrading across risk categories.

Relevance

Professional societies recommend increased screening for women with a > 20% lifetime risk of developing breast cancer. Improved risk stratification from the combined risk score can help target the use of more intense screening strategies for unaffected women with truly elevated risk based on clinical and genetic factors.

Here, we describe the development and validation of a strategy for integrating a SNP score with a validated clinical risk model, with attenuation for correlated effects. We used a previously validated 86-SNP PRS³³ and the Tyrer-Cuzick clinical risk estimator to create a combined risk model adjusted for the shared genetic component related to family history.

MATERIALS AND METHODS

Study Populations

These studies are based on two sample cohorts: a consecutive clinical testing cohort of patients submitted for hereditary cancer predisposition between June 1, 2017 and June 11, 2019 divided into sets for development and validation and one prospectively collected case-control validation study (validation 2). Clinical testing cohort data were subdivided according to successive time intervals to ensure the independence of development and validation activities (Fig 1); this included two development sets (development 1 and 2), one validation set (validation 1), and one clinical performance population. Genetic testing for all patients was performed at a Clinical Laboratory Improvement Amendments-approved and College of American Pathology-approved laboratory (Myriad Genetics, Inc., Salt Lake City, UT) by next-generation sequencing.³⁴ Hybridization probes for the 86 SNPs in the PRS were included in the sequencing panel.³³

Women were eligible if they were of age 18-84 years, of European ancestry (Ashkenazi and non-Ashkenazi; self-reported), and negative for likely PVs or PVs in 11 breast cancer-related genes (*BRCA1*, *BRCA2*, *TP53*, *PTEN*, *STK11*, *CDH1*, *PALB2*, *CHEK2*, *ATM*, *NBN*, and *BARD1*). Patients were excluded as unaffected controls if they reported a history of ductal carcinoma in situ, lobular carcinoma in situ, hyperplasia, or unspecified breast disease. Women were excluded from the clinical testing cohort if

they were submitted from states that disallow the research use of samples after completion of genetic testing. All studies were conducted with institutional review board (IRB) oversight (Quorum Review IRB #31713, 32556, 32608).

Development 1 included women from the clinical testing cohort unaffected by cancer of any type accrued between June 1, 2017 and August 11, 2017 (N = 5,489). Development 2 (N = 141,160) included 112,232 women unaffected by breast cancer and 28,928 breast cancer cases from the clinical testing cohort accrued between August 11, 2017 and January 11, 2019. Clinical characteristics of this set were previously reported.³³

Validation 1 consisted of women in the clinical testing cohort accrued between June 1, 2017 and August 10, 2017 (N = 1,615). Cases included women with invasive breast cancer submitted for genetic testing within 1 year of diagnosis because of potential hereditary breast and ovarian cancer syndrome. Controls included unaffected women submitted for genetic testing because of possible hereditary nonpolyposis colorectal cancer syndrome as these patients have a breast cancer family history consistent with that of general population controls.

For validation 2, a consecutive series of women who presented to four breast cancer screening centers (Elizabeth Wende Breast Care, The Breast Center of NWA, Bethesda Health, and Cuda Women's Health Center/Cape Cod Healthcare) were prospectively recruited between February 6, 2017 and November 11, 2017 (N = 518). Cases included women with a pathologically confirmed first diagnosis of invasive breast cancer ≤ 12 months preenrollment or an incident breast cancer ≤ 6 months postenrollment. Unaffected controls had no history of breast disease through the end of study enrollment.

An independent set of clinical testing patients unaffected by breast cancer accrued between January 12, 2019 and

	Cohort Description		Accrual	Findings	
	Inclusion	Exclusion			
Development of a Fixed-Stratified Model for Combined Risk	Development 1 N = 5,489	Clinical testing cohort: 18-84 years old, European ancestry, PV-negative, from states that allow research use of data or samples post-testing	History of breast cancer, DCIS, LCIS, hyperplasia, or unspecified breast disease; eligible for validation set 1	6/1/2017 to 8/11/2017	The PRS was significantly associated with family history but no other Tyrer-Cuzick clinical factor
	Development 2* N = 141,160	Clinical testing cohort: same inclusion criteria as development set 1	Controls could not have a history of DCIS, LCIS, hyperplasia, or unspecified breast disease	8/11/2017 to 1/11/2019	β and C_k were established
Clinical Validation of the CRS	Validation 1 N = 1,615	Clinical testing cohort: same basic inclusion or exclusion criteria as development set 2 Cases: breast cancer diagnosis, submitted for testing due to suspicion of HBOC within 1 year of diagnosis Controls: unaffected women submitted for testing due to suspicion of HNPCC		6/17/2017 to 8/10/2017	Risk estimates from the CRS and Tyrer-Cuzick models were significantly associated with breast cancer.
	Validation 2 N = 518	Prospectively acquired case-control study enrolled from imaging centers Cases: pathologically confirmed first diagnosis of invasive breast cancer ≤ 12 mos. preenrollment or incident breast cancer ≤ 6 mos. postenrollment Controls: unaffected, no history of breast disease through the end of study enrollment		2/6/2017 to 11/11/2017	The CRS added significant discrimination independent of that captured by the Tyrer-Cuzick risk model.
Assessment of Clinical Performance	Clinical Performance Population N = 32,576	Clinical testing cohort: same inclusion criteria as development set 1	History of breast cancer, DCIS, LCIS, hyperplasia, or unspecified breast disease	1/12/2019 to 6/11/2019	Addition of the 86-SNP PRS to Tyrer-Cuzick shifted risk categorization for 18% of women, including upgrades (8%) and downgrades (10.5%)

FIG 1. Summary of independent study cohorts. *Development 2 was previously published by Hughes et al.³³ CRS, combined risk score; DCIS, ductal carcinoma in situ; HBOC, hereditary breast and ovarian cancer; HNPCC, hereditary nonpolyposis colon cancer; LCIS, lobular carcinoma in situ; PRS, polygenic risk score; SNP, single-nucleotide polymorphism.

June 11, 2019 (clinical performance population; N = 32,576) was used to assess risk stratification of the combined score.

86-SNP PRS

The PRS was calculated as a linear combination of centered genotype calls for 86 confirmed breast cancer-associated SNPs (Data Supplement). Score composition information has been previously published.³³

Clinical Data and Tyrer-Cuzick Risk Calculation

Family history of breast and ovarian cancer and personal risk factor data (Data Supplement) were retrieved from test request forms for clinical testing samples or from completed questionnaires collected as part of the prospective study. Absolute 5-year and remaining lifetime risk (RLR) estimates by Tyrer-Cuzick were calculated according to version 7.02.

Statistical Methods

Associations between the 86-SNP PRS and Tyrer-Cuzick variables. We examined association between PRS and each clinical factor in the Tyrer-Cuzick model in development 1 (N = 5,489). For each factor, we conducted a simple linear regression with PRS as the dependent variable and the clinical factor as the independent variable. From these models, we examined regression coefficients, P values based on F-statistics, and Pearson correlation coefficients.

Design of the combined risk score. To calculate absolute risk incorporating Tyrer-Cuzick and PRS, we developed a Fixed-Stratified method (Data Supplement) to attenuate PRS after fixing the effects of confounded factors from the Tyrer-Cuzick model and to constrain risk separately within strata of the confounders. Briefly, women were stratified on the basis of breast cancer family history. Absolute risk for a woman in strata k was calculated as follows:

$$1 - (1 - \text{TC})^{\exp\{\beta \times \text{PRS} + C_k\}}, \quad (1)$$

where β represents the per-unit log(OR) of the PRS from a multivariable logistic regression model with the effect of breast cancer family history fixed. The calibration constant C_k was calculated such that the average relative risk due to PRS was 1 within unaffected women from strata k . β and C_k were determined using development 2 (N = 141,160).

Simulation studies. Simulation studies compared risks calculated by the Fixed-Stratified method with those from multivariable co-estimation and from univariable estimation of the effects of family history and PRS (Data Supplement).³²

Clinical validations. The combined risk score (CRS) was validated in two independent studies (Table 1): a clinical testing set (validation 1; N = 1,615) and the prospective case-control cohort (validation 2; N = 518). Validations were conducted according to prespecified statistical analysis plans using R version 3.5.3.³⁵ P values were

TABLE 1. Clinical Characteristics of Study Patients in the Validations

Characteristic	Variable	Validation 1			Validation 2		
		All Patients	Breast Cancer Cases	Controls	All Patients	Breast Cancer Cases	Controls
Patients	N (%)	1,615 (100)	988 (61)	627 (39)	518 (100)	256 (49)	262 (51)
Age (years) ^a	Range	18-84	18-84	18-73	19-84	37-84	19-84
	Median	48	50	44	61	65	56
	% ≤ 50	58	52	67	25	12	38
Ancestry; N (%)	Ashkenazi Jewish	14 (1)	4 (<1)	10 (2)	36 (7)	16 (6)	20 (8)
	White/non-Hispanic	1,581 (98)	975 (99)	606 (97)	458 (88)	233 (91)	225 (86)
	Ashkenazi Jewish and White/non-Hispanic	20 (1)	9 (1)	11 (2)	24 (5)	7 (3)	17 (6)
≥ 1 First-degree relative with invasive breast cancer	N (%)	362 (22)	303 (31)	59 (9)	152 (29)	62 (24)	90 (34)
≥ 1 Second-degree relative with invasive breast cancer	N (%)	620 (38)	465 (47)	155 (25)	204 (39)	85 (33)	119 (45)
≥ 1 First-degree relative and/or ≥ 1 second-degree relative with invasive breast cancer	N (%)	816 (51)	618 (63)	198 (32)	295 (57)	126 (49)	169 (64)

^aAge at diagnosis for women with breast cancer and age at testing for unaffected women.

calculated from likelihood ratio chi-squared test statistics and reported as two-sided.

Primary analyses tested the CRS and Tyrer-Cuzick individually for association with breast cancer in age-adjusted logistic regression models (Data Supplement). Secondary analyses tested the incremental improvement of the CRS over Tyrer-Cuzick by including both risk estimators in the same age-adjusted model. Exploratory analyses tested calibration of the CRS by comparing average absolute risk estimates with those from the Tyrer-Cuzick model; with proper calibration, we expected to observe the same average risk for Tyrer-Cuzick as for the CRS among unaffected controls. These analyses were conducted separately for RLR and 5-year risk of developing breast cancer. Weighted logistic regression was used with weights for unaffected controls calculated such that average Tyrer-Cuzick RLR matched general population rates (Data Supplement).

Performance of the 86-SNP PRS. Effect sizes of the 86-SNP PRS in validations 1 and 2 were calculated as ORs per standard deviation from multivariable logistic regression models adjusted for age, personal and family cancer history, and Ashkenazi ancestry and compared with those published previously.³³ We tested for interaction between PRS and each clinical factor in Tyrer-Cuzick by constructing models with age, clinical factor, PRS, and an interaction term as predictor variables.

Clinical performance of the CRS. The clinical performance population (N = 32,576) was used to assess risk stratification using the CRS. RLR of breast cancer was calculated according to both the Tyrer-Cuzick model and the CRS, and classifications (increased [$> 20\%$] or low [$\leq 20\%$] risk) from both were compared.

RESULTS

Associations Between PRS and Tyrer-Cuzick Variables

We examined associations between the 86-SNP PRS and Tyrer-Cuzick model clinical factors in development 1 using linear regression models (Data Supplement). The 86-SNP PRS was significantly associated with family history, measured as either an affected first-degree relative ($P = 2.0 \times 10^{-9}$) or as a weighted count of affected relatives ($P = 6.9 \times 10^{-16}$). A marginal association with hormonal replacement therapy use was not significant after adjustment for multiple testing. The 86-SNP PRS was not correlated with any other Tyrer-Cuzick model clinical factor.

Simulation Studies

We evaluated the performance of the Fixed-Stratified method in a simulation study on the basis of previously published parameters for a 77-SNP PRS and family history.³² In the simulation, we matched published univariable and bivariable ORs for the 77-SNP PRS and family history and visually matched the published figure of cumulative absolute risk (Data Supplement). For women without family history, risk estimates based on the combined effects of the 77-SNP PRS and family history were accurate regardless of adjustment for confounding (Data Supplement). In contrast, for women with family history, the Fixed-Stratified method matched risks from multivariable co-estimation, whereas the unadjusted model overestimated risk (Data Supplement).

Clinical Validations

Validation 1 included 988 (61%) breast cancer cases and 627 (39%) unaffected controls (Table 1). Median age of hereditary cancer testing was 48 years [IQR 40 to 57].

TABLE 2. Results From the Prespecified Validation Analyses

Analysis	Breast Cancer Risk Model	Validation 1 (N = 1,615)		Validation 2 (N = 518)	
		Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Primary analysis	CRS RLR	2.08 (1.83 to 2.37)	8.1×10^{-34}	2.44 (1.89 to 3.19)	9.3×10^{-13}
	Tyrer-Cuzick RLR	1.84 (1.63 to 2.09)	8.5×10^{-24}	1.91 (1.45 to 2.54)	3.3×10^{-06}
	CRS 5-year risk	4.58 (3.57 to 5.90)	7.5×10^{-38}	2.46 (1.90 to 3.21)	3.8×10^{-13}
	Tyrer-Cuzick 5-year risk	5.14 (3.79 to 7.02)	3.7×10^{-28}	1.96 (1.48 to 2.63)	1.4×10^{-06}
Secondary multivariable analysis	CRS RLR	1.88 (1.57 to 2.26)	4.1×10^{-12}	3.21 (2.12 to 4.95)	1.5×10^{-08}
	Tyrer-Cuzick RLR	1.15 (0.96 to 1.38)	.13	0.68 (0.43 to 1.07)	.096
	CRS 5-year risk	3.49 (2.44 to 5.03)	3.5×10^{-12}	3.26 (2.14 to 5.05)	1.3×10^{-08}
	Tyrer-Cuzick 5-year risk	1.59 (1.01 to 2.49)	.044	0.67 (0.42 to 1.07)	.095

Abbreviations: CRS, combined risk score; RLR, remaining lifetime risk.

Women with breast cancer tended to be older than unaffected controls. Overall, 362 (22%) patients reported breast cancer in ≥ 1 first-degree relative and 620 (38%) in ≥ 1 second-degree relative.

The prospectively collected case-control validation 2 included 256 (49%) breast cancer cases and 262 (51%) unaffected controls (Table 1). Median age at enrollment was 61 years (IQR 50-70). Nearly one third (29%) of patients reported breast cancer in a first-degree relative and 204 (39%) patients in ≥ 1 second-degree relative.

In both validations, RLR and 5-year risk estimates of the CRS and Tyrer-Cuzick were significantly associated with breast cancer (Table 2 and Fig 2). In a model with both risk predictors, the CRS added significant discrimination independent of that captured by Tyrer-Cuzick for both RLR ($P < 10^{-11}$ in validation 1; $P < 10^{-7}$ in validation 2) and 5-year risk ($P < 10^{-11}$ in validation 1; $P < 10^{-7}$ in validation 2; Data Supplement).

Although all patients in validation 2 provided complete Tyrer-Cuzick risk factor questionnaires, data on Tyrer-Cuzick variables were incomplete for some patients in validation 1. Analyses were repeated in the subset of patients with complete information for all Tyrer-Cuzick risk factors with results similar to those from the full data set (Data Supplement).

Calibration of the CRS was examined by comparing average risk estimates with those from Tyrer-Cuzick in the control samples from either validation. The average RLR and 5-year risk estimates matched exactly in both validations (RLR 12.6%; 5-year 0.96%). Estimates were also consistent for patients grouped according to 5-year age bins (Fig 3). Concordance of mean CRS and Tyrer-Cuzick risk estimates indicates that the CRS was properly calibrated.

Effect sizes of the 86-SNP PRS calculated as ORs per standard deviation from multivariable logistic regression models were similar to previously published³³ results in

FIG 2. Discriminatory accuracy of CRS over Tyrer-Cuzick or PRS alone in validation 1 (A) and validation 2 (B). CRS, Tyrer-Cuzick, and PRS were evaluated separately in terms of likelihood ratio chi-squared test statistics from age-adjusted logistic regression models. In both validation studies, the CRS performed significantly better than either Tyrer-Cuzick or PRS at discriminating between women with and without invasive breast cancer. CRS, combined risk score; PRS, polygenic risk score.

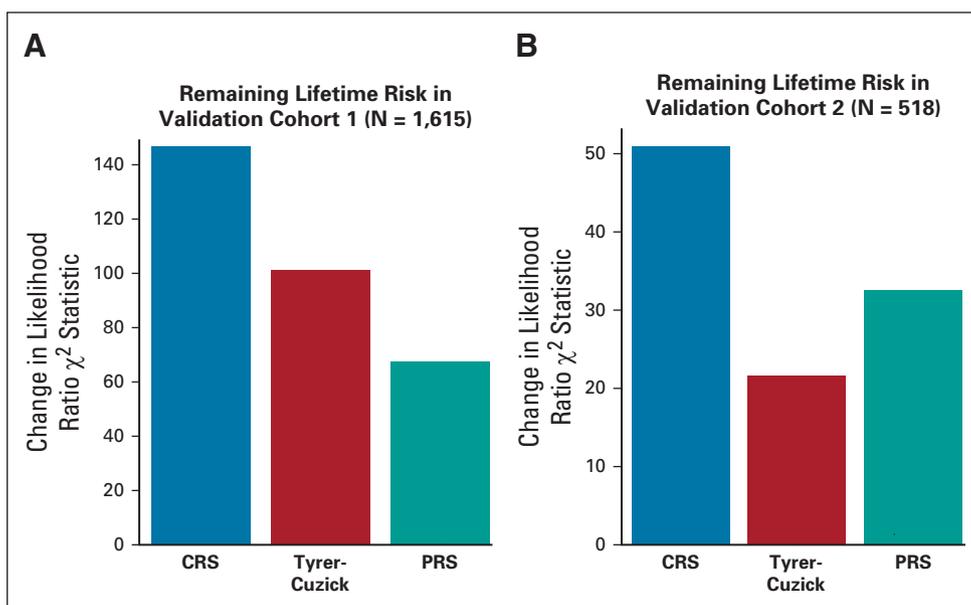
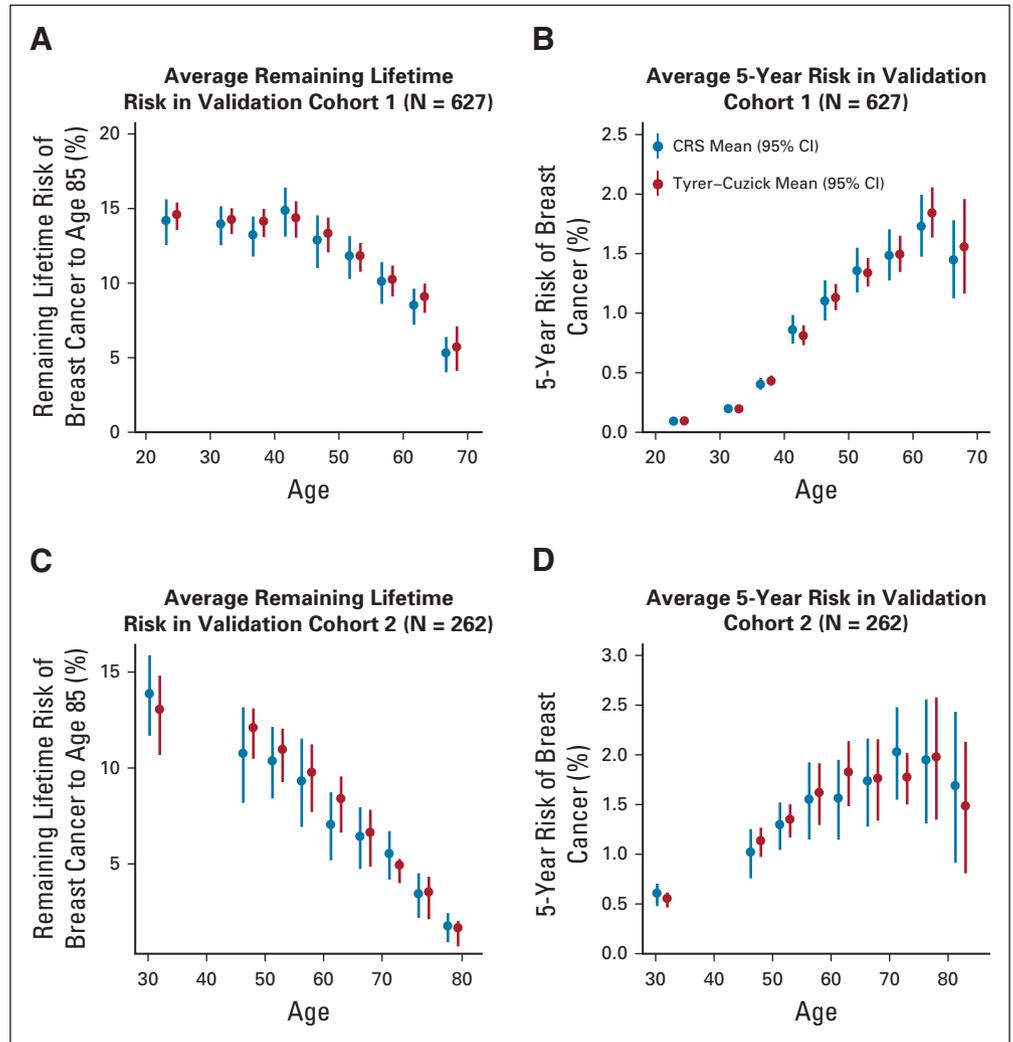


FIG 3. Evaluation of concordance between CRS (blue) and Tyrer-Cuzick (red). Estimates for average remaining lifetime (A and C) and 5-year risk (B and D) for unaffected controls in validation 1 (A-B) and validation 2 (C-D). Patients were grouped into 5-year age bins, and average risks were evaluated according to CRS and Tyrer-Cuzick. 95% CIs are also reported. CRS, combined risk score.



validation 1 (OR 1.57, 95% CI, 1.33 to 1.86) and validation 2 (OR 1.65, 95% CI, 1.37 to 2.00; Data Supplement). No evidence of interaction between the 86-SNP PRS and clinical factors in the Tyrer-Cuzick model in either of the two validations was observed (Data Supplement).

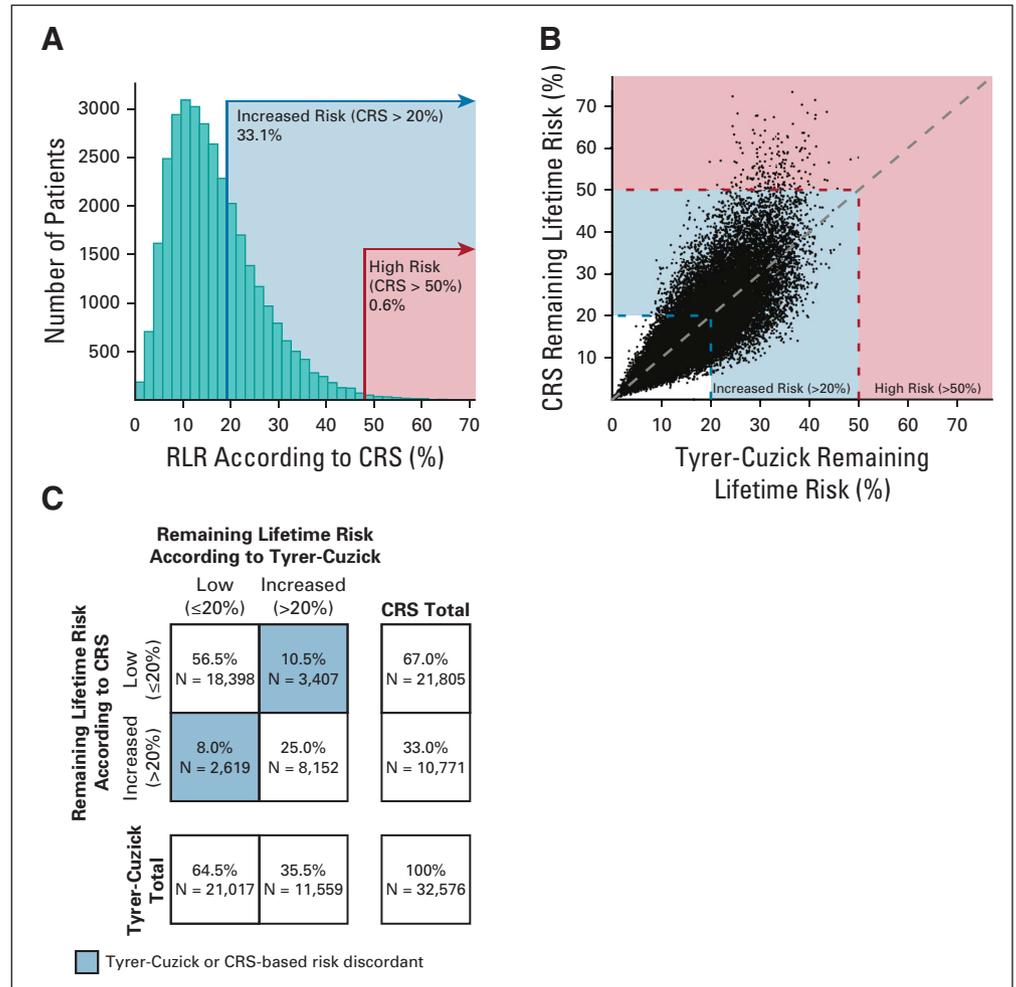
Clinical Performance of the CRS

To illustrate how application of the CRS changes RLR estimates compared with Tyrer-Cuzick alone, we calculated RLR using Tyrer-Cuzick or CRS for an independent set of 32,576 unaffected women (clinical performance population). RLR estimates in this cohort using the CRS ranged from 0.01% to 74.0% (Fig 4A). This was a greater range than for RLR estimates from the Tyrer-Cuzick model for the same population (Fig 4B). Although Tyrer-Cuzick and CRS identified 35.5% and 33.0% of women as having > 20% RLR, respectively (Fig 4C), inclusion of SNP-based risk shifted risk categories for 18% of women. Of those with RLR > 20% by Tyrer-Cuzick alone, 29% were downgraded to ≤ 20% RLR by the CRS. Conversely, 12% of women with RLR ≤ 20% by Tyrer-Cuzick were upgraded to RLR > 20% by the CRS.

DISCUSSION

Clinical and epidemiologic risk factors have primarily been used to assess breast cancer risk in PV-negative women. Integration of these factors with SNP-based risk necessitates examination of both confounding effects and interactions between SNP-based and clinical risk. Here, we propose a novel Fixed-Stratified method that accounts for the confounding effect of family history. We applied this method to combine an 86-SNP PRS with the Tyrer-Cuzick risk model and tested the resulting CRS in two independent cohorts. Addition of the 86-SNP score significantly improved discrimination relative to the Tyrer-Cuzick model for predicting risk of breast cancer, and the CRS model showed excellent calibration across age groups. American Cancer Society guidelines recommend magnetic resonance imaging screening for women with > 20%-25% lifetime risk of breast cancer to improve early-stage cancer detection.³⁶ In a clinical testing population, we showed that for 33% of PV-negative women, the CRS-estimated risk was > 20% and these women would qualify for consideration of enhanced surveillance. This includes 2,619

FIG 4. Distribution of CRS risk estimates in unaffected women. (A) Remaining lifetime risk (RLR) in a population of unaffected women (clinical performance population, N = 32,576; excluded women with ductal carcinoma in situ, lobular carcinoma in situ, hyperplasia, or unspecified breast disease) according to CRS with thresholds at 20% (increased) and 50% (high) RLR. (B) Scatterplot of RLR based on the Tyrer-Cuzick and CRS risk models for patients within the clinical performance population. (C) Distribution of patients above and below the 20% RLR threshold in the clinical performance population according to both the Tyrer-Cuzick and CRS models. Blue squares indicate patients with discordance between the scores (eg, the Tyrer-Cuzick model produced a score that indicated a patient had low RLR, but the same patient was determined to have increased RLR by the CRS model). CRS, combined risk score.



women (8%) who would have been categorized as < 20% using Tyrer-Cuzick–estimated risk alone.

Combinations of PRSs with the Tyrer-Cuzick model have been presented previously, generally without attenuation for confounding. An 88-SNP score was added to Tyrer-Cuzick under the assumption of independence in a nested case-control study.²⁵ Although the SNP score added discrimination to the Tyrer-Cuzick prediction, it had poor calibration. In a larger data set, an 18-SNP PRS showed a small but significant correlation with the Tyrer-Cuzick model; however, its effect size for predicting risk was only marginally affected by adjustment with the Tyrer-Cuzick model.²⁶ More recently, a 143-SNP PRS added to the Tyrer-Cuzick model attenuated the PRS effect, indicating an overlap between Tyrer-Cuzick and PRS.²⁷ Combined risk associations of a 313-SNP PRS and classical breast cancer risk factors have also recently been evaluated, although these combined risks have yet to be validated.³⁷ These examples highlight two issues. First, previous examinations of confounding often evaluated the correlations between a PRS and a model rather than individual clinical factors.^{21,25,26} This approach might have obscured associations between PRS and clinical factors

with a stronger genetic component. Second, genetic overlap is more likely with a larger PRS since casting a wider net for cancer-associated SNPs is more likely to also capture a larger fraction of the genetic component of clinical risk. Here, we focused on correlations between the PRS and individual Tyrer-Cuzick variables rather than the Tyrer-Cuzick model as a whole. We identified confounding between PRS and family history and adjusted for the genetic overlap with family history. Others have examined the question of interaction between PRS and clinical factors and confirmed the appropriateness of a multiplicative model.³⁷

Attenuation of shared PRS and family history risk has been described for the addition of a 313-SNP PRS to BOADICEA and the iCARE model.^{17,24,37} Segregation analysis was used to incorporate the PRS into BOADICEA. One limitation of that approach is approximating the distribution of the polygenic component with a binomial distribution; it is not clear how important this limitation is. The iCARE model is based on reducing the family history contribution by subtracting half of the PRS variance from the log(OR) for family history. However, the family history within this approach was binary (presence or absence of a first-degree

relative with breast cancer). This limitation does not allow for optimal utilization of family history for patients with > 1 first-degree relative or those with second-degree relatives. Limitations of the present study include a potential ascertainment bias in the clinical testing population cohorts. Qualification for genetic testing is often based on family history. It has been previously shown that this potential bias can be avoided by accounting for family history in a multivariable model.^{38,39} Consequently, all analyses presented here were conducted by multivariable co-estimation. In support of this approach, results from validation 1 (clinical testing samples) were similar to results obtained in validation 2, for which participants were prospectively collected and were unaffected by potential bias due to selection for hereditary cancer testing. Evaluation of the CRS in a prospectively collected, unselected population-based sample is being pursued.⁴⁰ Future work to expand assessment tools such as Tyrer-Cuzick and the PRS for non-European ancestries will be required to apply these tools to other ancestry populations. Finally, information for Tyrer-Cuzick for the clinical testing populations was obtained from provider-completed test request forms. As such, the accuracy and/or completeness of this information cannot be verified and missing information could not be

obtained retrospectively. However, subanalysis of validation 1 in women with complete Tyrer-Cuzick information showed similar results as the whole data set, indicating that missing information did not substantially affect the analysis.

This CRS model is suitable for reporting age-specific risk of developing breast cancer for unaffected women of European descent with or without significant family history. It is currently the only Tyrer-Cuzick–based model fully adjusted for the shared risk between SNPs and family history and is therefore less likely to overestimate risk in women with a family history of breast cancer. A CRS containing the 86-SNP PRS is commercially available for PV-negative women of European ancestry (Myriad Genetics, Salt Lake City, UT). Additional studies are needed to explore informative SNPs for non-European ancestries. Future evaluation of the CRS model with additional variables such as breast density (ie, Tyrer-Cuzick v8), lifestyle, and dietary factors is desirable. Combined clinical and genetic risk models improve breast cancer risk prediction and may result in better allocation of cancer risk–reduction resources, such as chemoprevention and enhanced imaging techniques, to women with the highest combined risk.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](http://OpenPayments)).

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