Validation of a Combined Residual Risk Score to Predict Breast Cancer Risk

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BACKGROUND

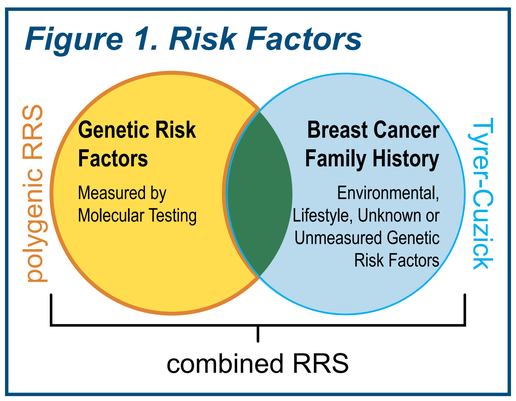
- While there are several well-known breast cancer risk genes, <10% of unaffected women with a strong family history of breast cancer test positive for clinically actionable, monogenic mutations in these genes.
- Several models have been developed to evaluate breast cancer risk based on family cancer history and other genetic and non-genetic factors; and, large-scale genotyping studies have identified common variants that individually confer modest breast cancer risk, but together partially explain genetic susceptibility in many women without monogenic mutations.
- Here we describe the validation of a combined polygenic residual risk score (cRRS) that accounts for genetic and non-genetic breast cancer risk factors.

METHODS

Residual Risk Score (RRS) and Combined RRS (cRRS)

- A polygenic RRS was developed and corrected for family history to determine breast cancer risk conferred by common genetic variants[1-3] independent of family history risk factors (Figure 1).
- The cRRS was developed to account for genetic and family history risk factors by combining the RRS with the Tyrer-Cuzick model[4] (Figure 1).

Figure 1. Risk Factors



Cohorts

- All patients had genetic testing for hereditary cancer risk and clinical information was obtained from provider-completed test request forms.
- Independent RRS training (N=24,259) and validation (N=10,575) cohorts were composed of women of European descent who had multi-gene panel testing and were negative for mutations in breast cancer risk genes (*BRCA1*, *BRCA2*, *TP53*, *PTEN*, *STK11*, *CDH1*, *PALB2*, *CHEK2*, *ATM*, *NBN*, *BARD1*).
  - 14 (1%) patients were Ashkenazi Jewish, 4 (<0.1%) of whom had breast cancer.
- The cRRS was validated in an independent case-control cohort (N=1,617).
  - Breast cancer cases had a first diagnosis of pathologically confirmed ductal invasive breast cancer within 1 year of multi-gene panel testing.
  - Unaffected controls had genetic testing for hereditary non-polyposis colon cancer (HNPCC) and no cancer history of any type.
- The cRRS and Tyrer-Cuzick models were also evaluated in a large clinical cohort of unaffected individuals who had multi-gene panel testing between June 2017 and February 2018 (N=30,891).
- All analyses were done according to a pre-specified statistical analysis plan.

cRRS VALIDATION

Table 1. cRRS Validation Cohort

	All Patients	BC Cases	Unaffected Controls
Total Patients, N (%)	1,617 (100)	990 (61)	627 (39)
Age at Hereditary Cancer Testing, years			
Median (Range)	48 (18-84)	50 (18-84)	44 (18-73)
% Tested ≤ 50	57	52	67
Cancer History in First Degree Relatives, N (%)			
≥ 1 BC	361 (22)	302 (31)	59 (9)

BC, Invasive ductal breast cancer

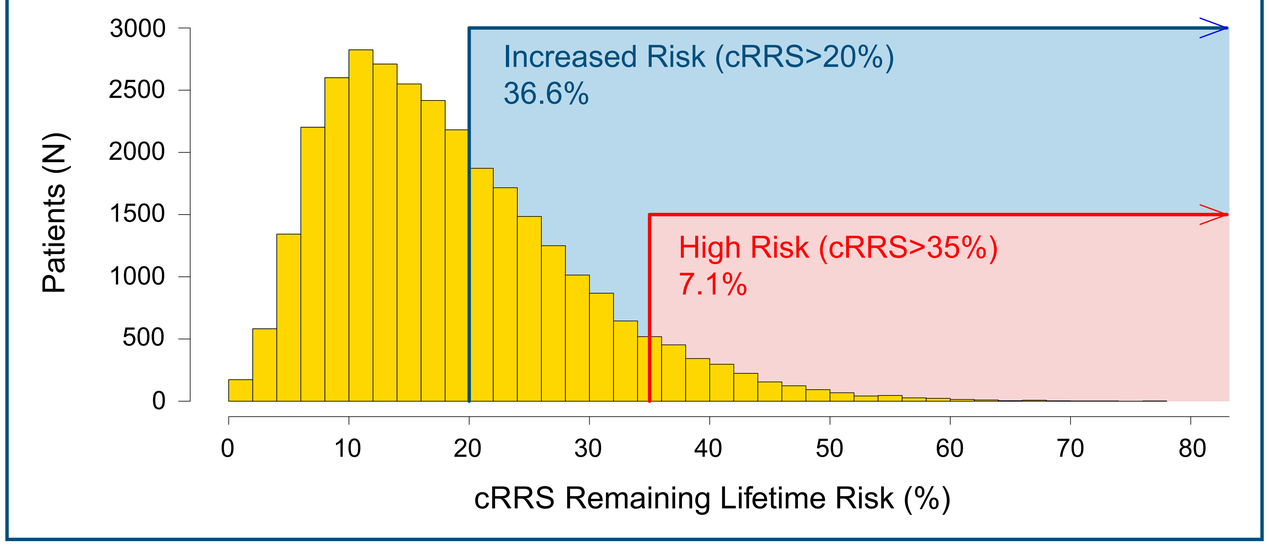
Table 2. Association with Breast Cancer

Breast Cancer Risk	Odds Ratio (95% CI)	p-Value
Multivariate Analysis*		
cRRS Remaining Lifetime Risk	2.00 (1.64, 2.43)	8.3×10^{-13}
cRRS 5-Year Risk	3.91 (2.66, 5.75)	1.0×10^{-12}

*Independent variables were cRRS, Tyrer-Cuzick breast cancer risk, and age.

- Remaining lifetime and 5-year breast cancer risk estimates were modeled on the scale of age-adjusted log odds.
- The remaining lifetime and 5-year breast cancer risk estimates determined by cRRS and Tyrer-Cuzick were highly significant (remaining lifetime: cRRS $p=4.1\times10^{-36}$, Tyrer-Cuzick $p=5.4\times10^{-24}$; 5-year: cRRS $p=5.2\times10^{-39}$, Tyrer-Cuzick $p=3.5\times10^{-28}$).
- cRRS added significant breast cancer risk discrimination independent of that captured by Tyrer-Cuzick for both remaining lifetime risk ($p=8.3\times10^{-13}$) and 5-year risk ($p=1.0\times10^{-12}$) (Table 2).
- The cRRS remaining lifetime risk estimates ranged from 0.2% to 77.1% in the clinical testing cohort (Figure 2).
  - 36.6% of patients had a lifetime risk >20% and 7.1% had a lifetime risk >35%.

Figure 2. Breast Cancer Risk in Clinical Testing Cohort (N=30,891)



CONCLUSIONS

- A residual risk score was developed and is highly predictive of risk of development of future breast cancer in unaffected women with significant family history after testing negative for known high and intermediate risk mutations.
- When combining genetic risk from residual risk score with the Tyrer-Cuzick model, the cRRS was a superior predictor of breast cancer risk compared to Tyrer-Cuzick alone.
- The clinical testing implementation of a combined residual risk score in women at risk for hereditary breast cancer may offer significant potential for the management of >90% of high-risk women who test negative for monogenic mutations in breast cancer susceptability genes.

References: [1]Mavaddat et al. *J Natl Cancer Inst.* 2015; 107:djv036. [2]Michailidou et al. *Nat Genet.* 2013;45:353. [3]Michailidou et al. *Nat Genet*. 2015;47:373. [4]Tyrer et al. *Stat Med*. 2004;23:1111-30.

Presented at Montreal HBOC on May 9, 2018