Development and Validation of a Combined Residual Risk Score to Predict Breast Cancer Risk in Unaffected Women Negative for Mutations on a Multi-Gene Hereditary Cancer Panel

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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.
- In addition, 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.

OBJECTIVE

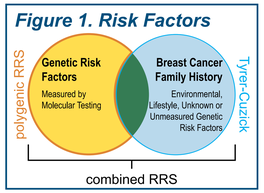
- To describe the development and validation of a combined polygenic residual risk score (cRRS) that accounts for genetic and non-genetic breast cancer risk factors.

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*).
- The cRRS was validated in a 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 July 2017 (N=6,479).

RRS DEVELOPMENT AND VALIDATION

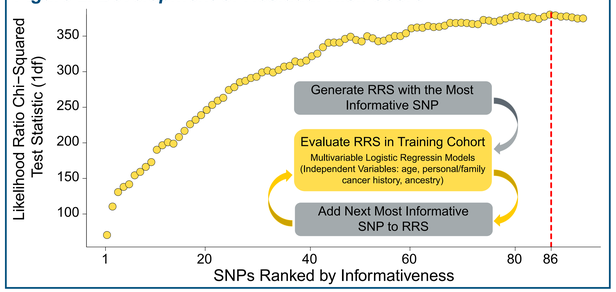
Table 1. RRS Training and Validation Cohorts

	Training Cohort		Validation Cohort	
	All Patients	BC Cases	All Patients	BC Cases
Total Patients, N (%)	24,259 (100)	4,291 (18)	10,575 (100)	1,627 (15)
Age at Hereditary Cancer Testing, years				
Median (Range)	47 (18-84)	54 (22-84)	46 (18-84)	54 (25-84)
Tested ≤ 50	61%	7%	63%	6%
Cancer History in First Degree Relatives, N (%)				
No BC or OC	13,230 (55)	2,800 (65)	5,889 (56)	1,044 (64)
≥ 1 BC	8,725 (36)	1,315 (31)	3,722 (35)	524 (32)

BC, Invasive ductal breast cancer; OC, Invasive epithelial ovarian cancer

- Genotypes were determined with Next Generation Sequencing and validated with Sanger sequencing for 97 variants and single-nucleotide polymorphisms (SNPs) with reported associations with breast cancer risk.[1-3]
  - SNP genotypes were coded as the number of the effect alleles (0, 1, or 2).
- SNP coefficients (β_i) were estimated using weighted averaging of log odds ratios from the training cohort and published studies.[1-3] Weights were inversely proportional to squares of confidence intervals.
  - SNP "informativeness" was defined as $2f_i(1-f_i)\beta_i^2$, where f_i is the effect allele frequency for SNP_i.
- It was determined that the 86 most informative SNPs provided the optimal RRS (Figure 2).
- The RRS was strongly associated with personal history of breast cancer in the validation cohort ($p<10^{-31}$).
  - Odds Ratio per unit standard deviation of the RRS: 1.41 (95% CI = 1.33-1.49).

Figure 2. Development of Residual Risk Score



cRRS VALIDATION

Table 2. 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
Ancestry, N (%)			
White (Non-Hispanic)	1,583 (98)	977 (99)	606 (97)
Ashkenazi Jewish	14 (1)	4 (<0.1)	10 (2)
White (Non-Hispanic) & Ashkenazi Jewish	14 (1)	4 (<0.1)	10 (2)
Cancer History in First Degree Relatives, N (%)			
≥ 1 BC	361 (22)	302 (31)	59 (9)

BC, Invasive ductal breast cancer

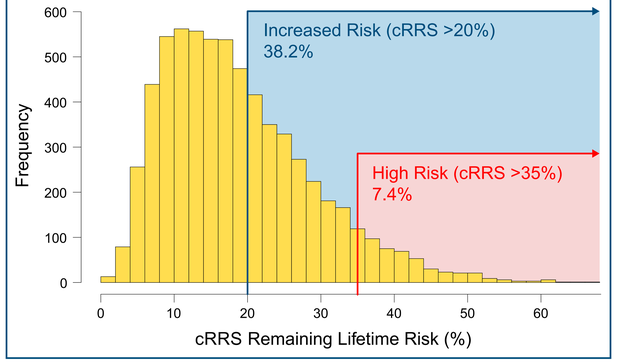
Table 3. Association with Breast Cancer

Breast Cancer Risk	Odds Ratio (95% CI)	p-Value
Bivariate Analysis*		
cRRS Remaining Lifetime Risk	2.10 (1.85, 2.38)	4.1×10^{-35}
Tyrer-Cuzick Remaining Lifetime Risk	1.85 (1.63, 2.09)	5.4×10^{-24}
cRRS 5-Year Risk	4.64 (3.61, 5.95)	5.2×10^{-39}
Tyrer-Cuzick 5-Year Risk	5.14 (3.78, 6.99)	3.5×10^{-28}
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}

*Bivariate logistic regression model to predict case-control status based on the age-adjusted log odds.
**Independent variables were cRRS, Tyrer-Cuzick breast cancer risk, and age.

- The remaining lifetime and 5-year breast cancer risk estimates determined by cRRS and Tyrer-Cuzick were highly significant (Table 3).
  - cRRS (RRS+Tyrer-Cuzick) was more strongly associated with breast cancer than Tyrer-Cuzick alone.
- 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 3).
- Mean cRRS and Tyrer-Cuzick breast cancer risk estimates among unaffected controls were concordant, indicating that the cRRS was properly calibrated.
- The cRRS remaining lifetime risk estimates ranged from 0.88% to 66.4% in the clinical testing cohort (Figure 3).
  - 38.2% of patients had a lifetime risk >20% and 7.4% had a lifetime risk >35%.

Figure 3. Breast Cancer Risk in Clinical Testing Cohort (N=6,479)



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 the genetic risk from the residual risk score was combined with the Tyrer-Cuzick model, the resulting 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 greater than 90% of high-risk women who test negative for monogenic mutations in breast cancer susceptibility 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.

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