

Validation of a combined residual risk score for healthy unaffected women presenting to breast cancer screening centers

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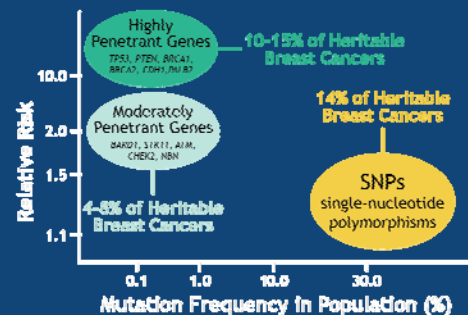
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Hereditary Breast Cancer Risk

- Fewer than 10% of unaffected women with a family history of breast cancer carry a monogenic mutation in known moderate- or high-penetrance breast cancer-risk genes.
- Some missing breast cancer genetic risk is explained by common variants (SNPs).
- SNPs *individually* confer a modest breast cancer risk, but are clinically meaningful when *combined* in a polygenic risk score.



Adapted from Foulkes et al. *N Engl J Med.* 2008;13:2143-53

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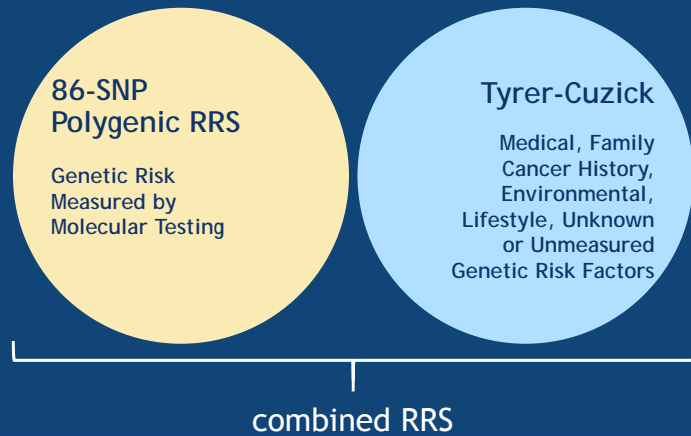
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Combined Residual Risk Score (cRRS)

- A combined residual risk score (cRRS) was developed to capture:

- Genetic risk factors:
86-SNP polygenic residual risk score (RRS)
- Family history risk:
Tyrer-Cuzick



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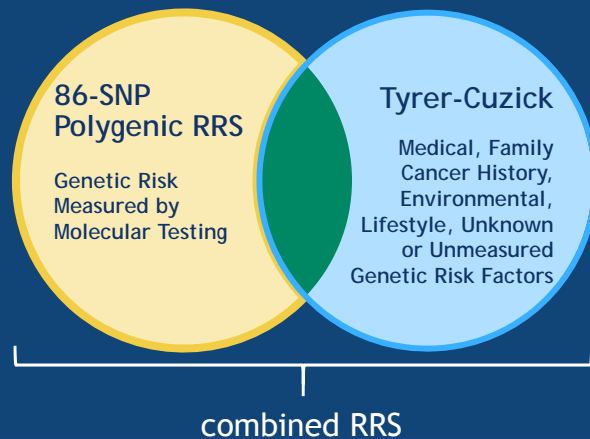
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Combined Residual Risk Score (cRRS)

- There is some overlap between genetic and family history risk factors.
- This was accounted for by adjusting the 86-SNP polygenic RRS for family history to determine an *independent* genetic risk.



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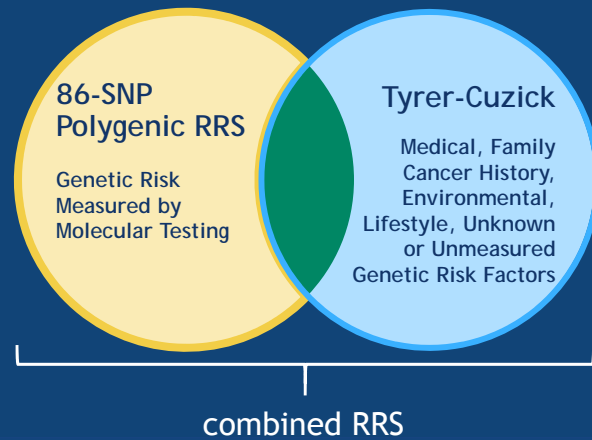
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Combined Residual Risk Score (cRRS)

- cRRS was developed and validated in independent, retrospective cohorts of women (European descent) who had multi-gene panel testing and were negative for mutations in breast cancer-risk genes.
- cRRS has been validated as a significant predictor of breast cancer risk independent of Tyrer-Cuzick.*

*Presented at SABCS 2017 (Poster Discussion PD1-08)



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Objective

- The aim of this study was to independently validate cRRS in a prospective, general population cohort.

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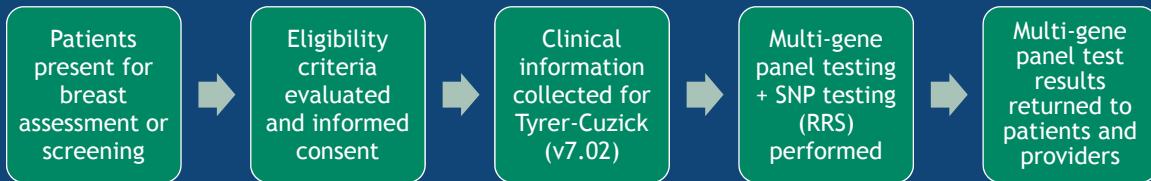
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Study Design and Cohort



- Consecutive series of patient who presented to four different imaging centers for breast assessment or screening
- Female patients age 18-84 of self-reported European ancestry
- Case-control study design

Study Design and Cohort

- Cases: Pathologically confirmed invasive breast cancer diagnosed within 12 months of office visit
- Controls: No personal history of breast cancer
- 531 patients enrolled (116-151 patients enrolled at each site)
 - 13 patients excluded due to pathogenic mutations in breast cancer-risk genes
- 518 patients in final cohort

Characteristic	Cases N=256	Controls N=262
Age, Median (Range)	64 (37-84)	56 (19-84)
Age ≤50 years, N (%)	31 (12%)	100 (38%)

Analysis Methods

- Age-adjusted weighted logistic regression used to examine the association of cRRS and Tyrer-Cuzick with invasive breast cancer (dependent variable).
- Primary analysis
 - Evaluate cRRS and Tyrer-Cuzick independently (bivariate analysis)
- Secondary analysis
 - Evaluate models including both risk measures (multivariate analysis)

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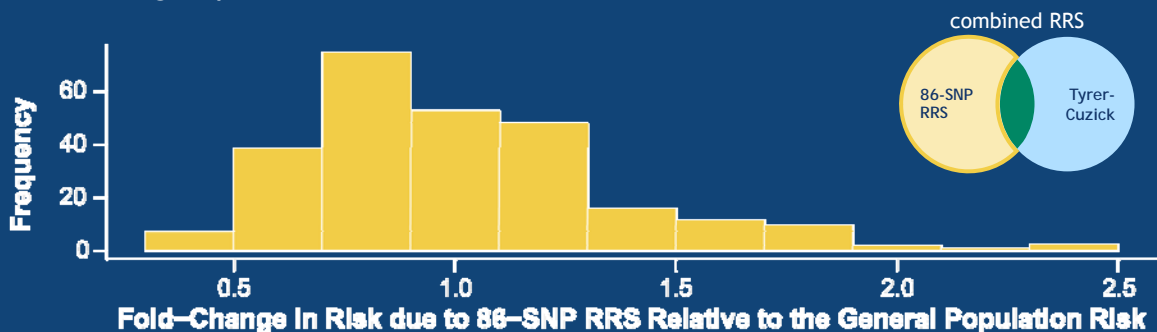
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Genetic Breast Cancer Risk

- There was a range of genetic breast cancer risk among the unaffected control group based on the 86-SNP RRS alone.



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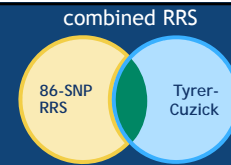
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Bivariate Analysis (Primary)



- Each breast cancer risk prediction model was highly significantly associated with breast cancer.
- cRRS was more strongly associated with breast cancer than Tyrer-Cuzick.

Remaining Lifetime Risk of Breast Cancer

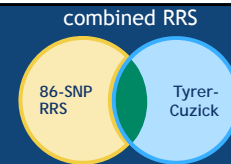
Risk Prediction Model	Odds Ratio* (95% CI)	p-value
Tyrer-Cuzick	2.09 (1.51, 2.88)	3.2×10^{-6}
cRRS	2.73 (2.02, 3.68)	2.5×10^{-12}

5-Year Risk of Breast Cancer

Risk Prediction Model	Odds Ratio* (95% CI)	p-value
Tyrer-Cuzick	2.15 (1.54, 3.01)	3.5×10^{-6}
cRRS	2.81 (2.06, 3.83)	2.6×10^{-12}

*Odds ratios and Wald Confidence Interval (CI) are reported per weighted standard deviation of log odds of breast cancer risk prediction models in unaffected controls.

Multivariate Analysis (Secondary)



- cRRS added significant breast cancer risk discrimination independent of that captured by Tyrer Cuzick.

Remaining Lifetime Risk of Breast Cancer

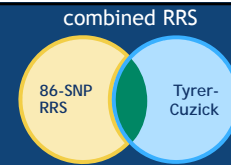
Risk Prediction Model	Odds Ratio* (95% CI)	p-value
Tyrer-Cuzick	0.57 (0.33, 1.01)	0.052
cRRS	4.11 (2.44, 6.91)	2.4×10^{-8}

5-Year Risk of Breast Cancer

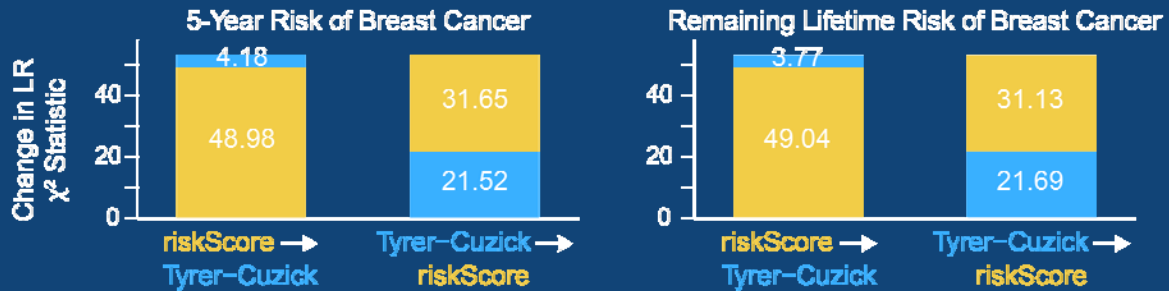
Risk Prediction Model	Odds Ratio* (95% CI)	p-value
Tyrer-Cuzick	0.54 (0.30, 0.98)	0.041
cRRS	4.41 (2.56, 7.58)	1.9×10^{-8}

*Odds ratios and Wald Confidence Interval (CI) are reported per weighted standard deviation of log odds of breast cancer risk prediction models in unaffected controls.

Multivariate Analysis (Secondary)



- cRRS added significant breast cancer risk discrimination independent of that captured by Tyrer Cuzick.



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Conclusions

- The cRRS offers superior risk stratification compared to Tyrer-Cuzick alone in a prospective, general population cohort.
- cRRS may therefore improve prevention and screening strategies for unaffected women testing negative for monogenic mutations in breast cancer-risk genes.

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