# Associations between Clinical Factors in v7.02 of the Tyrer-Cuzick Model and a SNP-Based European Ancestry Residual Risk Score

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## BACKGROUND

- Genome-wide association studies (GWAS) have identified common variants, primarily single-nucleotide polymorphisms (SNPs), that individually confer modest risk but together explain a significant proportion of genetic breast cancer (BC) predisposition.
- GWAS have also demonstrated that SNPs cannot replace family history evaluation, as familial BC assessment captures a large magnitude of risk information that is not captured by SNPs. Thus, combining SNP markers with family history assessment can improve BC risk stratification.
- However, to avoid double-counting shared risk information, familial and/or SNP-based risks must be adjusted for confounding.
- Tyrer-Cuzick (TC) V7.02 is a well-validated and widely used comprehensive model for estimating BC risk based on family history, clinical and biological factors. TC also incorporates information about height, weight, BMI, age of menarche, parity and age of first childbirth, menopausal status and age of onset, and use of hormonal replacement therapy (HRT).
- Confounding of SNPs with these factors is not well understood.
- Here we present an analysis of associations between an 86-SNP Residual Risk Score (RRS) and factors included in TC V7.02.
- This analysis informed development methodology for the combined Residual Risk Score (cRRS), which provides comprehensive risk assessment incorporating RRS and TC V7.02.

## METHODS

### COHORT

- De-identified clinical records and genotypes were collected from a consecutive series of patients referred for hereditary cancer testing with a multigene panel.
- Study subjects included unaffected women age 18-84 who reported European ancestry and tested negative for mutations in 11 genes associated with BC (*BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1*).

### STATISTICAL ANALYSIS

- For each risk factor, we constructed a univariate linear regression model with RRS 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.
- Scatterplots and boxplots were used to visually assess associations.
- All analyses were conducted using R version 3.4.4. P-values were reported as two-sided with no corrections for multiple testing.

## RESULTS

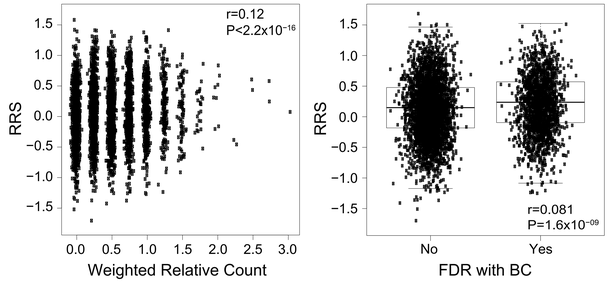
- A summary of clinical factors can be found in Table 1.
- The RRS was significantly associated with familial BC (Figure 1).
- We observed marginal evidence of association between the RRS and HRT use (p=0.04). However, this association would not survive a multiple testing correction, and was not significant after multivariate adjustment for family cancer history.

***Table 1. Summary of Clinical Factors and Associations***

| Clinical Factor | N | Median (IQR) | Regression Coefficient (95% CI) | P Value |
|---|---|---|---|---|
| **Family History of BC** | | | | |
| WRC | 5,489 | 0.5 (0.0 – 0.8) | 0.13 (0.096, 0.16) | $6.9\times10^{-16}$ |
| FDR with BC | 5,489 | - | - | $2.0\times10^{-09}$ |
| Yes | 1,819 | - | 0.078 (0.053, 0.10) | |
| No | 3,670 | - | *Reference* | |
| **Height** (inches) | 5,349 | 65.0 (63.0 – 67.0) | -0.001 (-0.0055, 0.0034) | 0.64 |
| **Weight** (lbs) | 5,313 | 163.0 (140.0 – 198.0) | $-6.1\times10^{-05}$ (-0.00033, 0.00021) | 0.66 |
| **BMI** | 5,289 | 27.2 (23.4 – 32.8) | -0.00029 (-0.0020, 0.0014) | 0.74 |
| **Age of Menarche** (years) | 5,020 | 13.0 (12.0 – 14.0) | -0.0015 (-0.0093, 0.0063) | 0.70 |
| **Age of Menopause** (years) | 965 | 49.0 (45.0 – 52.0) | $8\times10^{-04}$ (-0.0035, 0.0051) | 0.72 |
| **Duration of Menarche** (years) | 908 | 36.0 (31.0 – 39.0) | 0.0013 (-0.0031, 0.0058) | 0.55 |
| **Parity** | 5,331 | - | - | 0.13 |
| Nulliparous | 1,293 | - | *Reference* | - |
| Parous | 4,038 | - | -0.022 (-0.05, 0.0067) | - |
| **Age of First Live Birth** (years) | 3,644 | 25.0 (21.0 – 29.0) | 0.0013 (-0.0013, 0.0039) | 0.34 |
| **HRT Use** | 5,257 | - | - | 0.038 |
| Yes | 839 | - | -0.035 (-0.069, -0.0019) | - |
| No | 4,418 | - | *Reference* | - |
| **HRT Type** | 633 | - | - | 0.58 |
| Combined | 323 | - | *Reference* | - |
| Estrogen Only | 238 | - | 0.041 (-0.036, 0.12) | 0.30 |
| Progesterone Only | 72 | - | 0.015 (-0.102, 0.133) | 0.80 |
| **HRT Length of Use** (years) | 267 | 6.0 (2.0 – 12.0) | 0.0041 (-0.0031, 0.011) | 0.27 |

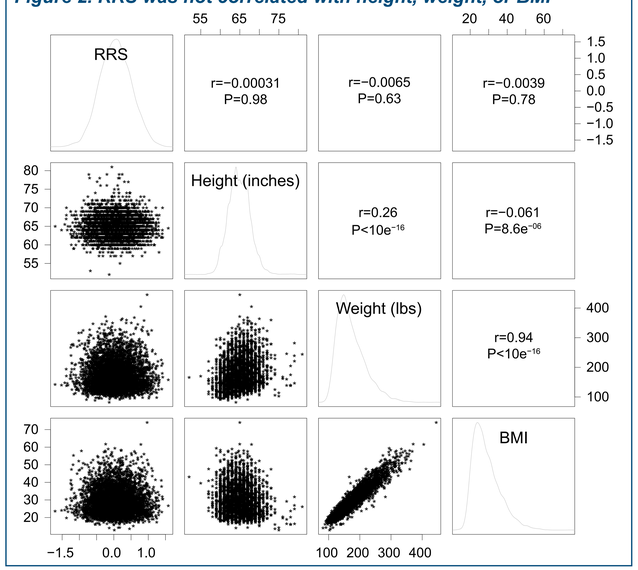
WRC, Weighted Relative Count; FDR, First Degree Relative

***Figure 1. RRS was significantly associated with familial breast cancer***



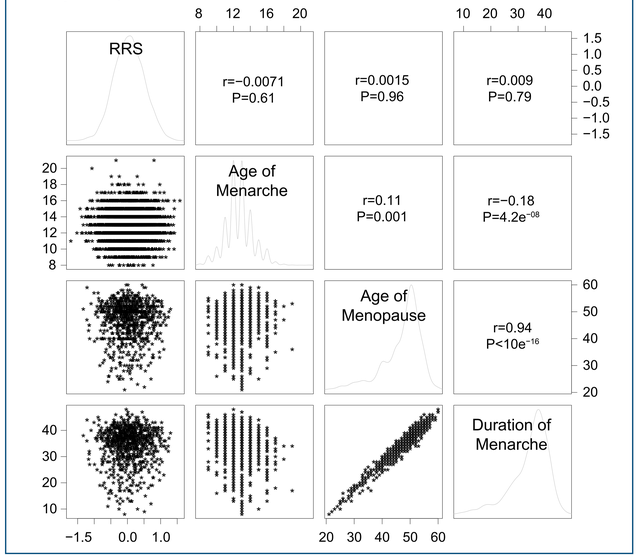

FDR, First Degree Relative

***Figure 2. RRS was not correlated with height, weight, or BMI***




- We found no evidence for association of the RRS with height, weight, BMI, menopausal stage, age of menarche, age of menopause, duration of menarche, parity, age of first live birth, HRT type, or HRT length of use (Figures 2 & 3).

***Figure 3. RRS was not correlated with age of menarche, age of menopause, or duration of menarche***




## CONCLUSIONS

- RRS is not correlated with the non-familial risk factors in TC V7.02, indicating that combining the RRS with these elements of the model is not subject to confounding.
- RRS is significantly correlated with family history ($p<2.2\times10^{-16}$). However, the magnitude of correlation is modest (r=0.12).
- Risk assessment methods that fail to account for correlation between SNPs and family history will double-count a small fraction of familial risk.
- The cRRS is the only method for BC risk assessment that accounts for correlation between SNPs and family history.

***ACKNOWLEDGMENT:*** The authors would like to thank Mark Robson for his contributions.

Presented at SABCS on December 7, 2018