

10540: Cross-ancestry Polygenic Risk Score for Breast Cancer Risk Assessment

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BACKGROUND

- Breast cancer (BC) risk is influenced by many common genetic variants with small effect size.
- Polygenic risk scores (PRS) weight these variants based on genome-wide association studies and aggregate them into a single measure.
- Only 5-10% of breast cancer is thought to be caused by single gene mutations of high effect size, therefore PRS has the potential to influence risk for a majority of women.

METHODS

- Performance of multiple breast cancer polygenic models, both published and developed in-house, were evaluated for each of five ancestry groups: European, African, South Asian, East Asian, and Admixed American. The best performing model for each ancestry was included in the cross-ancestry PRS (caPRS).
- Scores were centered using the first four principal components of women without disease and standardized using a population-specific standard deviation. Individuals in the super-populations of the 1000 Genomes Project were used as the reference.
- We define the cross-ancestry polygenic risk score (caPRS) as a linear combination of the best performing PRS model for each ancestry group weighted by fractional ancestry:

$$caPRS = \sum f_i \beta_i PRS_i$$

where i is one of the five continental ancestries.

- Training and validation were performed in >130,000 women across multiple cohorts (Women’s Health Initiative, the Multiethnic Cohort, the ROOT cohort and the UK Biobank).
- Multivariate logistic regression models that included caPRS, age, personal history of ovarian cancer and first-degree family history (FHx) of BC were used to test the association between caPRS and breast cancer risk.

Polygenic risk scores have the potential to improve risk assessment for majority of women across diverse ancestries

Figure 1 : Correlation between adjusted caPRS and odds of breast cancer

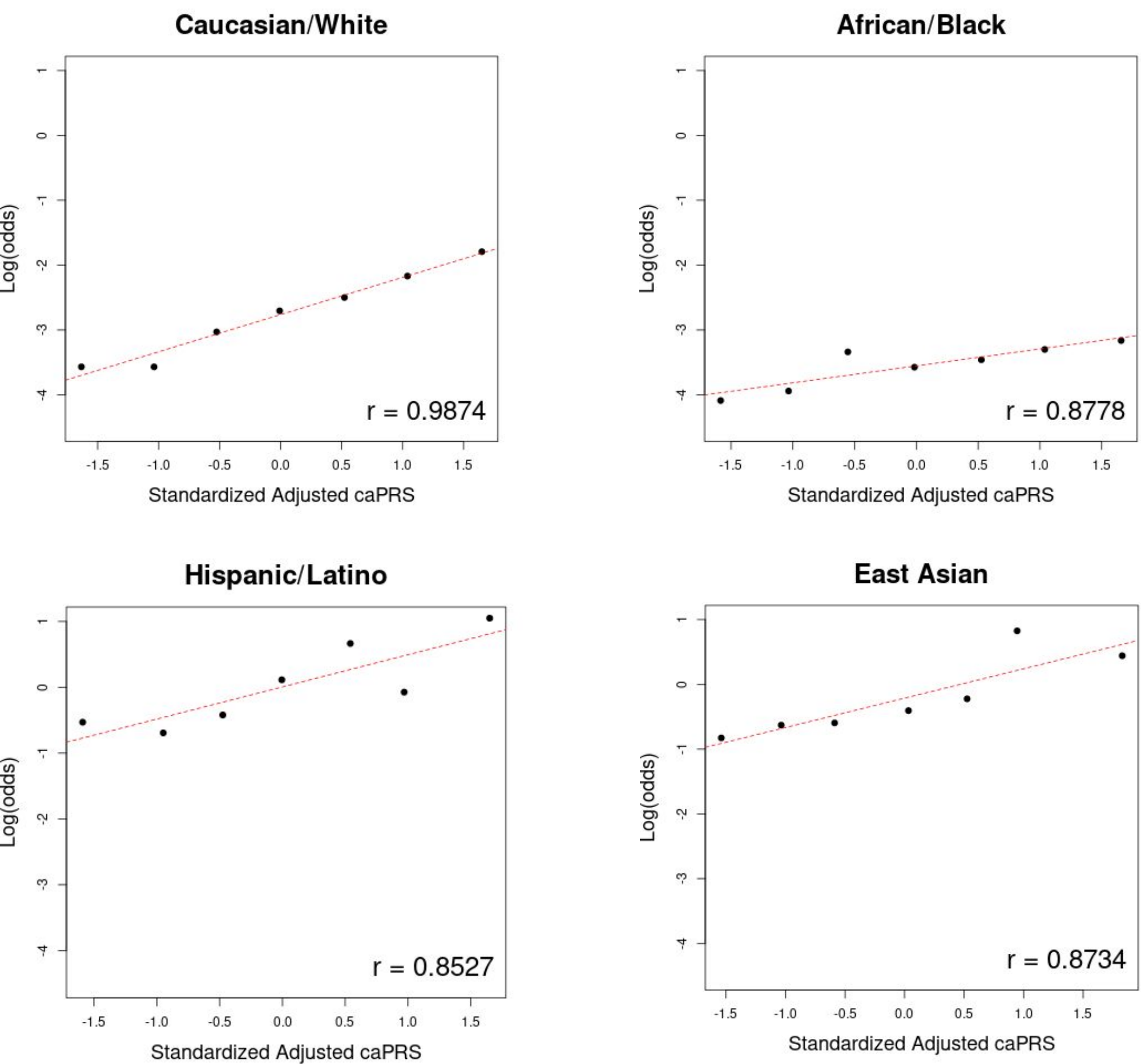


Table 1: Association between caPRS and breast cancer risk

Self-reported	N _{total}	N _{cases}	OR per SD (95% CI)	p-value
Caucasian/White	21,160	1,416	1.68 (1.59 - 1.77)	4.3 x 10 ⁻⁷⁶
African/Black	7,883	233	1.30 (1.15 - 1.48)	6.1 x 10 ⁻⁵
Hispanic/Latino	267	136	1.50 (1.16 - 1.93)	1.3 x 10 ⁻³
East Asian	227	99	1.45 (1.07 - 1.83)	3.8 x 10 ⁻³
South Asian	1,251	46	1.49 (1.10 - 2.03)	9.4 x 10 ⁻³
Other	2,344	120	1.51 (1.26 - 1.82)	9.4x10 ⁻⁶

RESULTS

- The caPRS was significantly associated with personal history of breast cancer in 5 self-reported ancestral groups (Table 1).
- After correction for multiple testing, there was no significant interaction between caPRS and first-degree FHx of BC for each self-reported ancestry.
- caPRS quantile was highly correlated with odds of BC across ancestries (Figure 1, r=0.85 - 0.99). Correlation was not estimated for South Asians due to the low number of cases.
- For African/Black women, caPRS demonstrated a 5% increase in OR per sd (increase from 1.24 [1.08 -1.4]) to 1.30 [1.15 - 1.48]) compared to a widely used 313 SNP European model. Other ancestries also saw a significant increase in OR per sd.

CONCLUSIONS/FUTURE DIRECTIONS:

- caPRS can improve prediction of BC risk in women of diverse ancestries**
- Use caPRS to improve risk stratification over traditional clinical risk factors (ongoing)
- Use caPRS to refine risk for women with mutations in BC predisposition genes (ongoing)
- Validation of caPRS in larger non-European cohorts.

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