A second-generation polygenic risk score (PRS) based on genetic ancestry improves breast cancer (BC) risk prediction for all ancestries

Poster No: P063

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All authors were employed by Myriad Genetics at the time of this study.

Background

- We previously described a multiple-ancestry PRS (MA-PRS 149) based on 56 ancestry-informative and 93 BC-associated SNPs.[1]

OBJECTIVE:

- Here, we aimed to improve the predictive accuracy of MA-PRS 149, particularly for non-Europeans, through the inclusion of additional BC-associated SNPs.

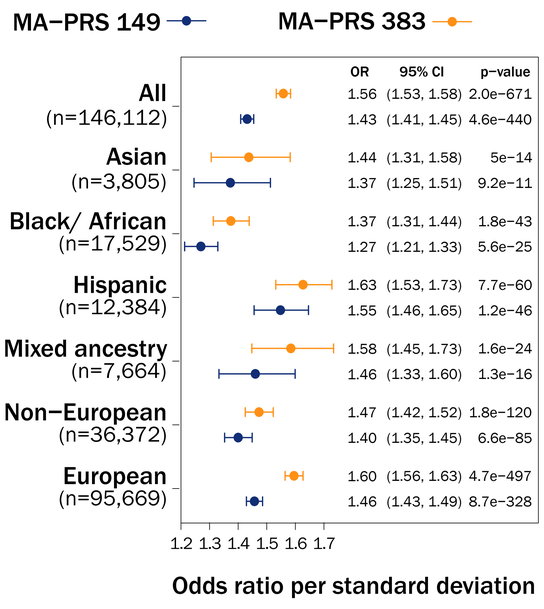
Methods

- Women referred for hereditary cancer testing who were negative for pathogenic variants in BC-associated genes between 1/2021 - 9/2023 were divided into consecutive development and validation study cohorts.
- An optimal set of BC-associated SNPs and European-specific SNP risks were determined using backward elimination from summary statistics[2] together with reference data[3] to account for linkage disequilibrium.
- Ancestry-specific SNP risks were determined from meta-analyses of literature with clinical cohorts of 57,827 Black/ African and 26,992 East Asian women.
- Ancestry-specific PRS were combined into a single MA-PRS based on the development cohort consisting of 157,740 women. The development cohort was used to define a comprehensive risk score (CRS) combining the MA-PRS with the Tyrer-Cuzick risk model. Clinical validation of MA-PRS was conducted in an independent validation cohort.

Results

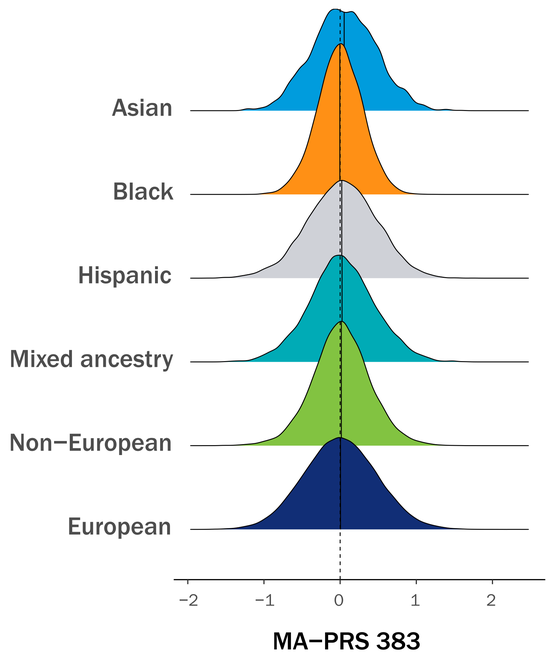
- An optimal set of 383 SNPs (56 ancestry-informative and 327 BC-associated) was included in the final PRS (MA-PRS 383).
- The validation cohort consisted of 146,112 women, 30.2% of whom reported non-European ancestries, and 29.7% of whom had been diagnosed with BC.
- MA-PRS 383 added significant predictive information to clinical factors within each ancestry (Figure 1).

Figure 1. MA-PRS 383 versus MA-PRS 149: Association with breast cancer risk after accounting for clinical factors



- The distribution of MA-PRS 383 in unaffected women was comparable across different ancestries in the validation set (Figure 2).

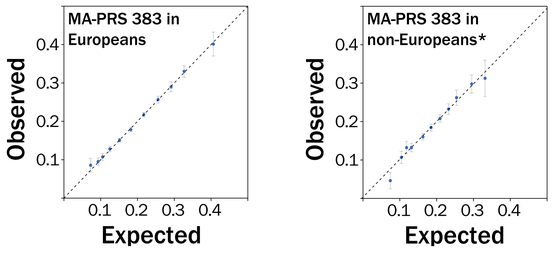
Figure 2. Distribution of MA-PRS 383 in unaffected women of different ancestries (validation set)



- In bivariate analyses, MA-PRS 383 outperformed both MA-PRS 149 and Eur-PRS 383, a PRS obtained by applying European-specific SNP risks to all ancestries.

- Comparison between observed and expected proportions of cases within percentile-based bins of MA-PRS 383 showed that MA-PRS 383 was well-calibrated among both European and non-European women (Figure 3).

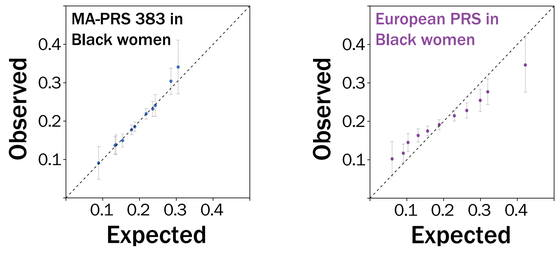
Figure 3. MA-PRS 383 calibration in European and non-European women



*Included patients identifying as Black.

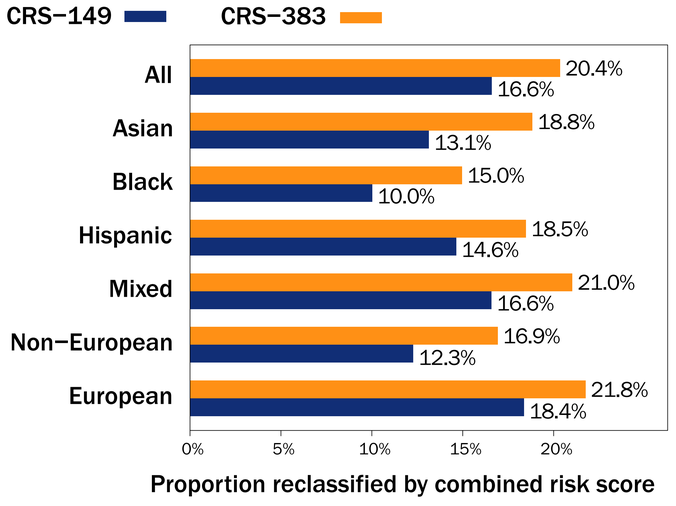
- A similar comparison showed that, while MA-PRS 383 was well-calibrated among Black women, the European PRS was poorly-calibrated in this population (Figure 4).

Figure 4. MA-PRS 383 vs Eur-PRS 383 calibration in Black women



- The combined MA-PRS 383/ Tyrer-Cuzick risk model, CRS-383, reclassified more women from low to high or high to low risk than the combined MA-PRS 149/ Tyrer-Cuzick risk model, CRS-149 (Figure 5).
  - Reclassification rates were similar in different ancestries (Figure 5).
  - Of the 20.4% reclassified by CRS-383 overall, 36.3% were downgraded from the high to the low/moderate risk category.

Figure 5. Patients reclassified by risk model



Conclusions

- MA-PRS 383 was well-calibrated and substantially improved the predictive accuracy of the existing PRS in all tested ancestral populations.
- Incorporation of MA-PRS 383 into BC risk assessment may lead to more accurate identification of women who are most likely to benefit from screening and preventive interventions.

1. Hughes E, et al. JCO Precis Oncol. 2022. 2. Zhang H, et al. Nat Genet. 2020;52:572-581. 3. The 1000 Genomes Project Consortium. Nature. 2015;526:68-74.