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

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Background

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

• 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 January 2021 and September 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 statistics2 together with reference data3 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.3

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).

• After adjusting for age, personal/family cancer history, and ancestry, the odds ratio per standard deviation (OR/SD) of MA-PRS 383 in the full cohort was 1.56 (95% CI 1.53, 1.58, \(p=2\times10^{-671}\)) (Figure 1).

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

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

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

• A comparison between the 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).

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

Figure 3. MA-PRS 383 calibration (observed vs expected)

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.

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.

*Included patients identifying as Black.