**Prospective Longitudinal Validation of a Breast Cancer Risk Prediction Model in a Cohort of 130,058 Individuals**

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**Introduction**

- Accuracy of breast cancer (BC) risk prediction may be improved by combining a polygenic risk score (PRS) with traditional risk factors.
- We recently developed and validated a 149-SNP PRS for individuals (defined as self-reported female sex) of diverse ancestries using ancestry-informative genetic markers and combined this with version 7 of the Tyrer-Cuzick (TC) model to generate a Combined Risk Score (CRS).
- Here, we describe a pre-specified prospective longitudinal clinical validation of CRS as a predictor of BC risk.

**Methods**

**Cohort**

- Individuals who were referred for hereditary cancer testing and negative for pathogenic variants in BC-related genes between January 2017 and February 2019 were matched to medical claims in an anonymized dataset.
- Follow-up began 4 months after testing and extended to the earliest date of BC diagnosis, censoring at the time of BC preventive treatment, or November 1, 2019.
- Incident BC events were determined by an ICD10 code of C50.* and confirmed by relevant treatment codes.

**Statistical Analysis**

- Calibration was evaluated by the ratio of observed (O) to expected (E) incident BCs for the full cohort, and for individuals split into event-based 5-year risk deciles.
- Cox proportional hazards models were used to evaluate discriminatory accuracy in terms of hazard ratios (HR) with 95% confidence intervals (CI).
- Kaplan-Meier analysis was used to examine risk for women split into high- or low-risk groups according to a 3% 5-year risk threshold.

**Results**

- The study cohort consisted of 130,058 individuals with 148,349 total patient years including 6,421 Black individuals/individuals of African ancestry and 5,740 individuals of Hispanic ancestry.
- Over a median follow-up of 12.1 months (range of 4.0-29.5), 340 incident BC events were observed.
- CRS was well calibrated in the overall cohort with an O/E ratio of 1.11 (95% CI=0.99-1.23) and within deciles of predicted risk (Figure 1).
- Importantly, in the highest risk decile, the O/E was 0.91 (95% CI=0.63-1.27) with CRS, but 0.67 (95% CI=0.46-0.94) with TC alone, illustrating the superior calibration of CRS (Figure 1).

**Conclusions**

- The CRS was well-calibrated in predicting BC and significantly improved upon a traditional risk factor model.
- Clinical use of the CRS may lead to improved BC prevention and screening strategies.