Prospective Longitudinal Validation of Breast Cancer Risk Assessment Combining a Polygenic Risk Score for All Ancestries with the Tyrer-Cuzick Model

Brent Mabey, MSc; Elisha Hughes, PhD; Holly J. Pederson, MD; Brooke Hullinger, JD; Susan M. Dornchek, MD; Charis Eng, MD, PhD; Monique Gary, MD; Jennifer R. Klempl, PhD, MPH; Semanti Mukherjee, PhD; Joseph Vijai, PhD; Kenneth Offit, MD; Olufunmilayo Olopade, MD; Sandhya Pruthi, MD; Allison Kurian, MD, MSc; Mark E. Robson, MD; Pat W. Whitworth, MD; FACS, FSSO; Jerry S. Lanchbury, PhD; Thomas P. Slavin, MD; Alexander Gutin, PhD

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).

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).

- In a Cox model adjusted for age at testing, PRS had an HR per standard deviation (SD) of 1.48 (95% CI=1.33-1.64, p=2.55×10^{-13}); the HR/SD was 1.43 (95% CI=1.29-1.59, p=1.61×10^{-11}) after adjusting for family history.
- In a bivariate analysis using both CRS and TC to predict time to BC, CRS added significantly to the model after accounting for TC (HR/SD=2.89, 95% CI=2.12-3.94, p=1.20×10^{-11}), whereas TC did not add significant information after accounting for CRS.
- PRS was more informative than TC for predicting BC risk while CRS was more informative than either PRS or TC (Figure 2).
- 15,986 (12.3%) individuals who classified as high-risk by CRS experienced BC at a nearly 4 times higher rate than those who classified as low-risk (HR=3.75, 95% CI=3.00-4.68).
- 10,248 (7.9%) had discordant classification between CRS and TC models. Among individuals who were classified as high-risk by TC, 32.6% were reclassified as low-risk by CRS; among those classified as low-risk by TC, 4.3% were reclassified as high-risk by CRS.
- In patients with discordant classification between CRS and TC models, BC incidence was consistent with CRS classification but not with TC classification (Figure 3).

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.