

# 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.

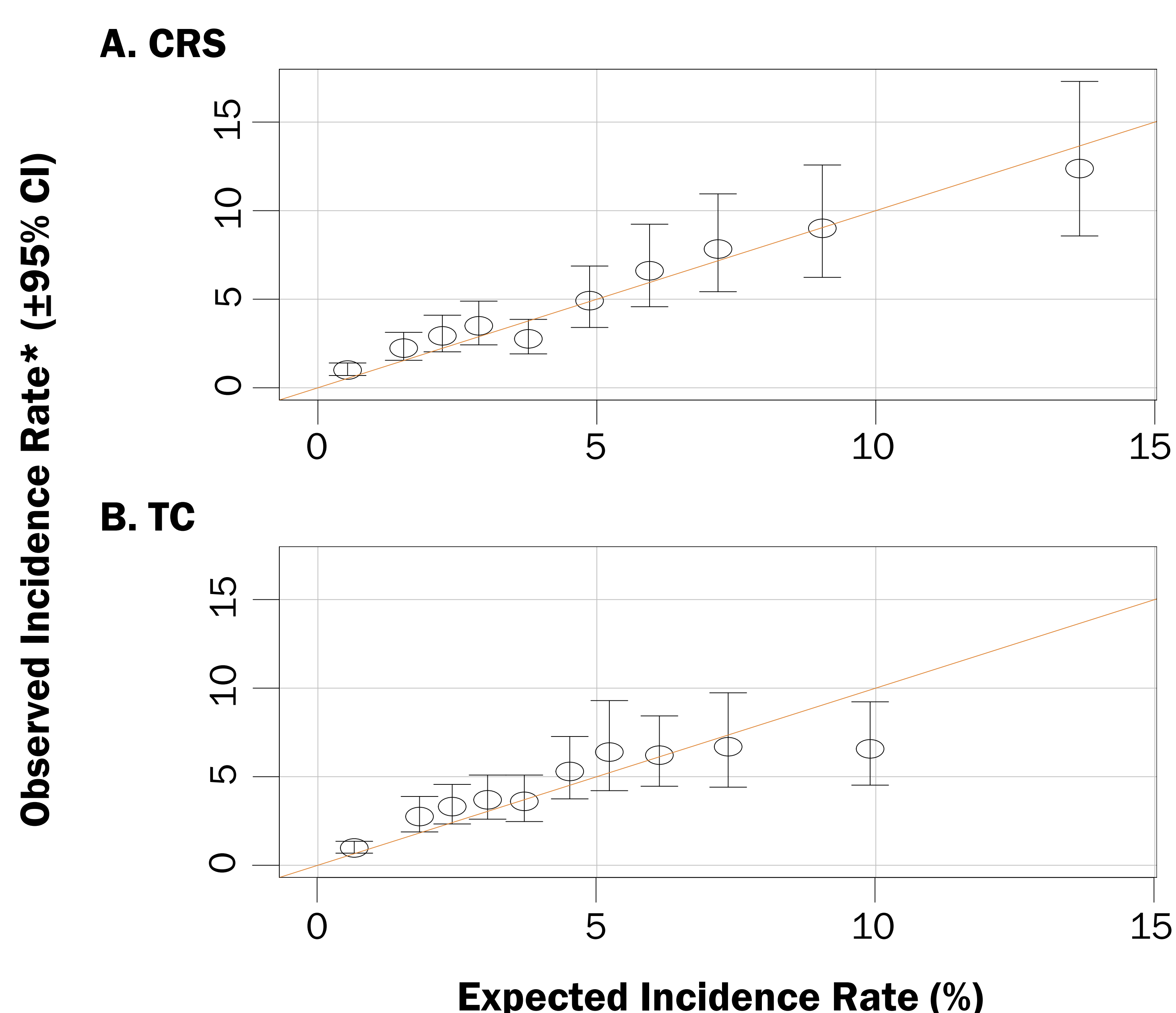
### Statistical Analysis

- 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).

Figure 1. Calibration Plots by Decile of (A) CRS and (B) TC



\*per 1,000 person years

- 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,  $p=2.55 \times 10^{-13}$ ); the HR/SD was 1.43 (95% CI=1.29-1.59,  $p=1.61 \times 10^{-11}$ ) 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,  $p=1.20 \times 10^{-11}$ ), 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).

Figure 2. Discriminatory Accuracy of CRS, TC, and PRS

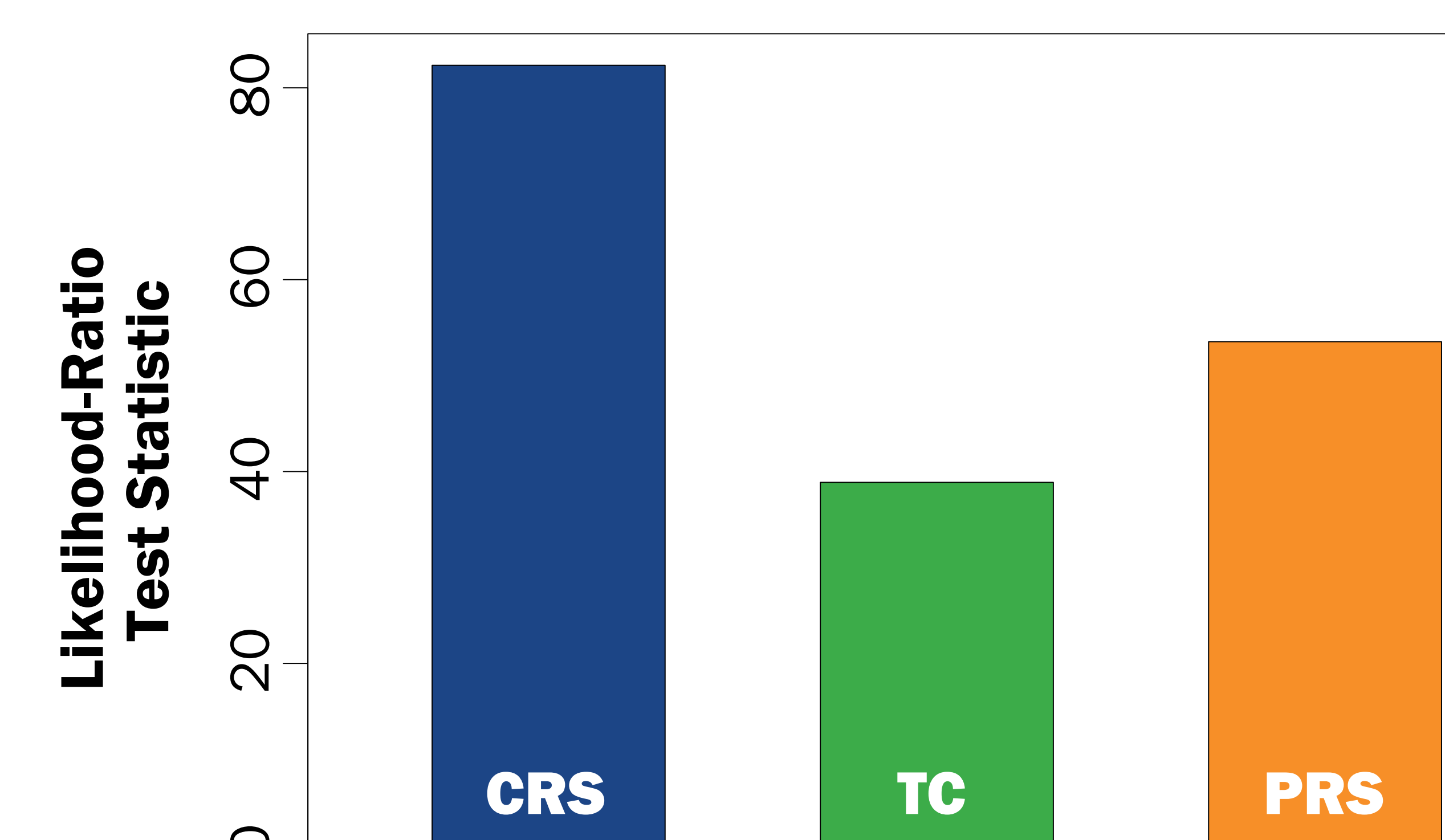
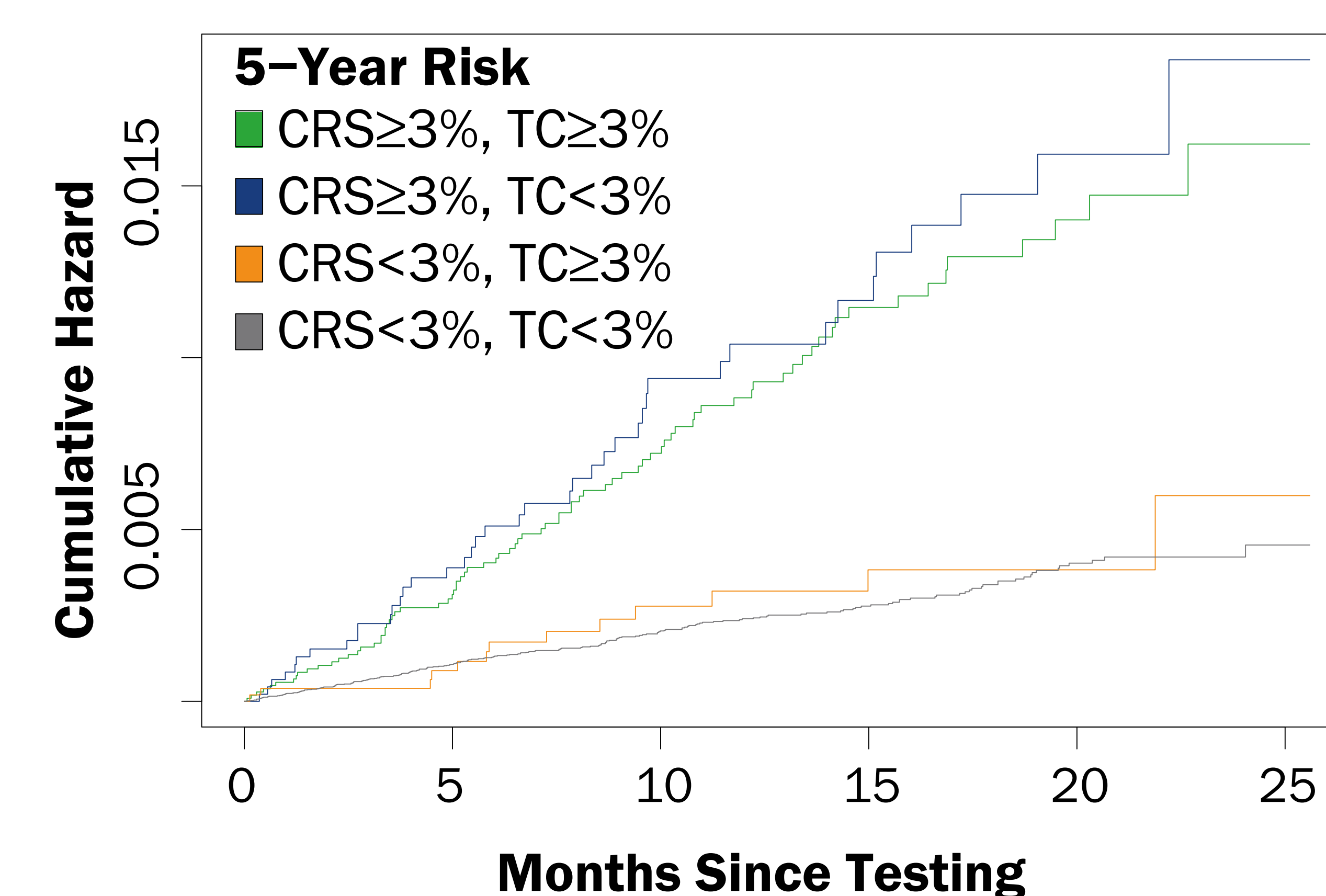


Figure 3. Cumulative BC Incidence by Risk Category



## 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.