

PB3447: Improved Breast Cancer Risk Stratification by Integration of a Cross-ancestry Polygenic Model with Clinical Risk Factors

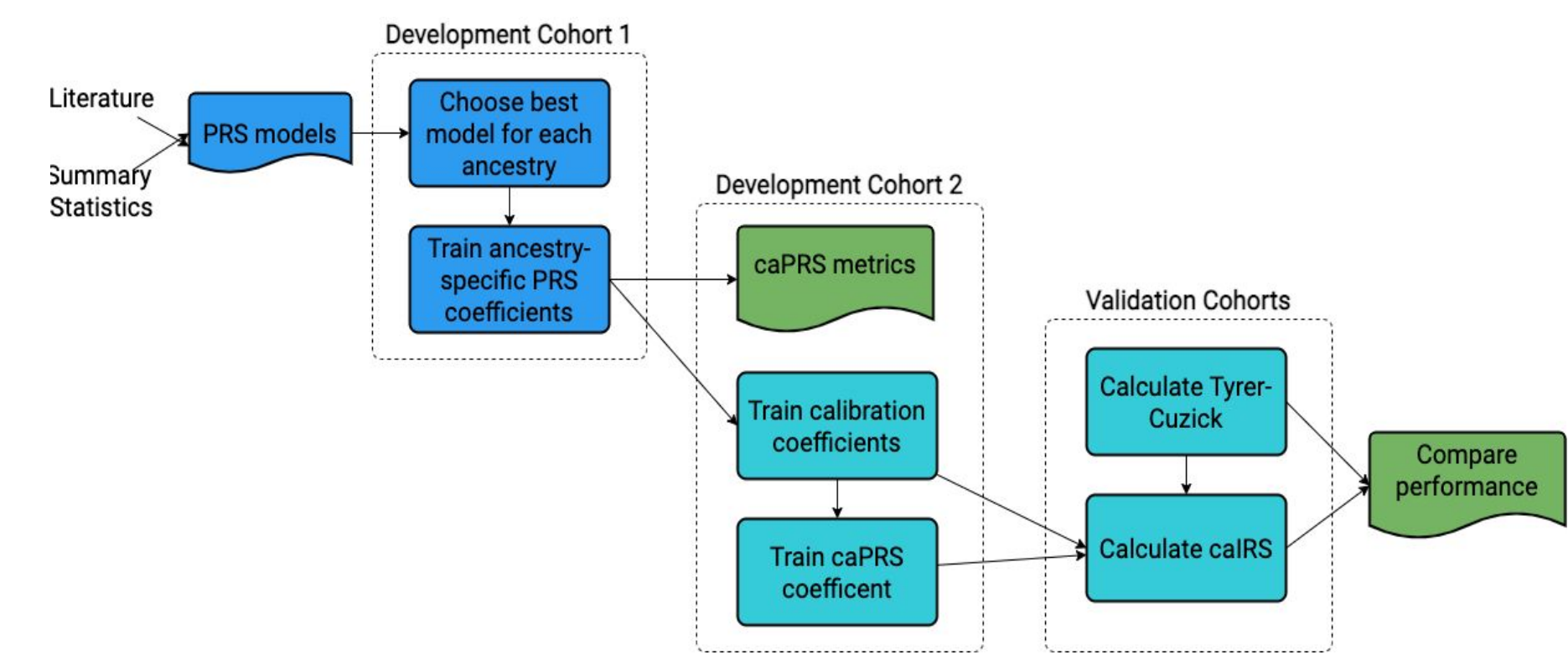
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BACKGROUND

- Polygenic risk scores (PRS) weight many variants with small effects sizes based on genome-wide association studies and aggregate them into a single measure.
- Only 5 -10% of breast cancer (BC) is thought to be caused by single gene mutations of high effect size, therefore PRS has the potential to influence risk for a majority of women.
- Clinical risk assessment tools are not well calibrated for women of certain ancestries.

METHODS

Figure 1: Schematic of development and validation workflow



- The schematic of development and validation of the cross-ancestry integrated risk score (caIRS) is shown in Figure 1.
- We defined the cross-ancestry polygenic risk score (caPRS) as a linear combination of the best performing PRS model for each ancestry group weighted by fractional ancestry:
$$caPRS = \sum f_i \cdot \beta_i \cdot PRS_i$$
where i is one of the five continental ancestries.
- The cross-ancestry integrated risk score (caIRS) combines caPRS and version 8.0 of the Tyrer-Cuzick (T-C) model using the fixed-stratified method.
- We calculated the 5-year risk and remaining lifetime risk based on the T-C clinical model and caIRS.
- Associations with BC risk were evaluated in terms of p-values and OR per SD from multivariate logistic regression models adjusted for age in two independent validation cohorts consisting of more than 130, 000 women; the Women’s Health Initiative (WHI) and the UK Biobank (UKB).

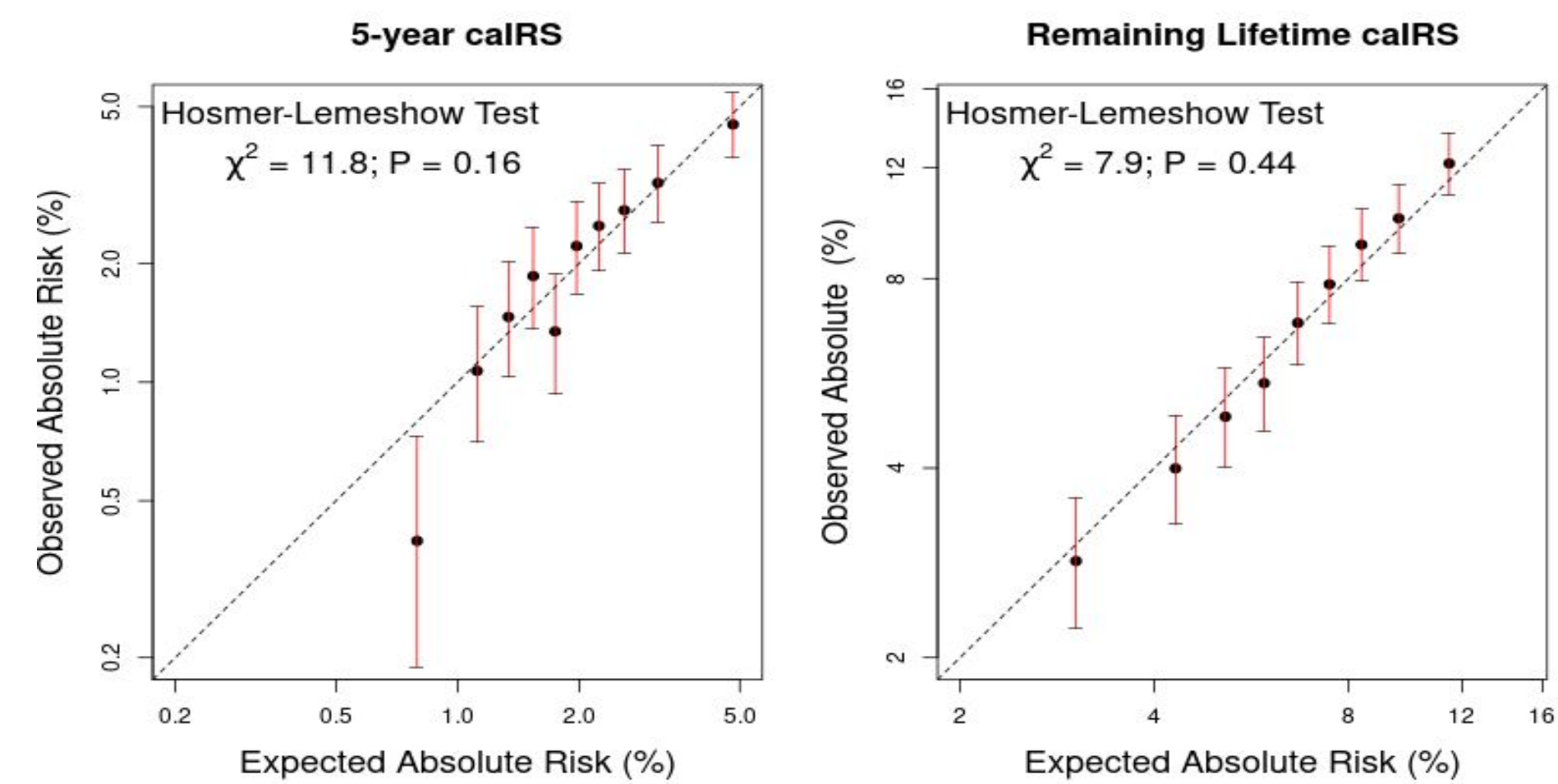
Table 1: Performance of T-C and caIRS for predicting Risk of Breast Cancer

Self-reported Ancestry	Cohort	N _{total}	Model	OR per SD (95% CI)	p-value	AUC
Caucasian/ White	WHI	14426	T-C	1.40 (1.30 - 1.51)	7.7×10 ⁻¹⁹	0.59 (0.57 - 0.61)
			caIRS	1.91 (1.79 - 2.04)	5.2×10 ⁻⁸⁸	0.67 (0.66 - 0.69)
	UKB	104661	T-C	1.29 (1.25 - 1.33)	2.1×10 ⁻⁶⁹	0.57 (0.56 - 0.58)
			caIRS	1.78 (1.74 - 1.82)	<10 ⁻³²⁴	0.66 (0.65 - 0.68)
African American/ Black	WHI	7650	T-C	1.20 (1.08 - 1.33)	4.4×10 ⁻⁴	0.56 (0.53 - 0.58)
			caIRS	1.39 (1.27 - 1.53)	8×10 ⁻¹²	0.59 (0.57 - 0.62)
	UKB	1239	T-C	1.43 (1.04 - 1.93)	0.03	0.60 (0.52 - 0.68)
			caIRS	1.70 (1.27 - 2.26)	4×10 ⁻⁴	0.64 (0.56 - 0.72)
Hispanic/ Latino	WHI	3208	T-C	1.31 (1.10 - 1.54)	2.5×10 ⁻³	0.58 (0.53 - 0.62)
			caIRS	1.88 (1.62 - 2.19)	3.6×10 ⁻¹⁶	0.68 (0.63 - 0.72)
East Asian	UKB	468	T-C	1.18 (0.62 - 2.12)	0.60	0.68 (0.53 - 0.83)
			caIRS	2.00 (1.15 -3.54)	0.014	0.74 (0.59 - 0.88)
South Asian	UKB	1327	T-C	1.20 (0.90 - 1.56)	0.21	0.64 (0.57 - 0.71)
			caIRS	1.67 (1.31 - 2.13)	3.9×10 ⁻⁵	0.69 (0.62 - 0.76)

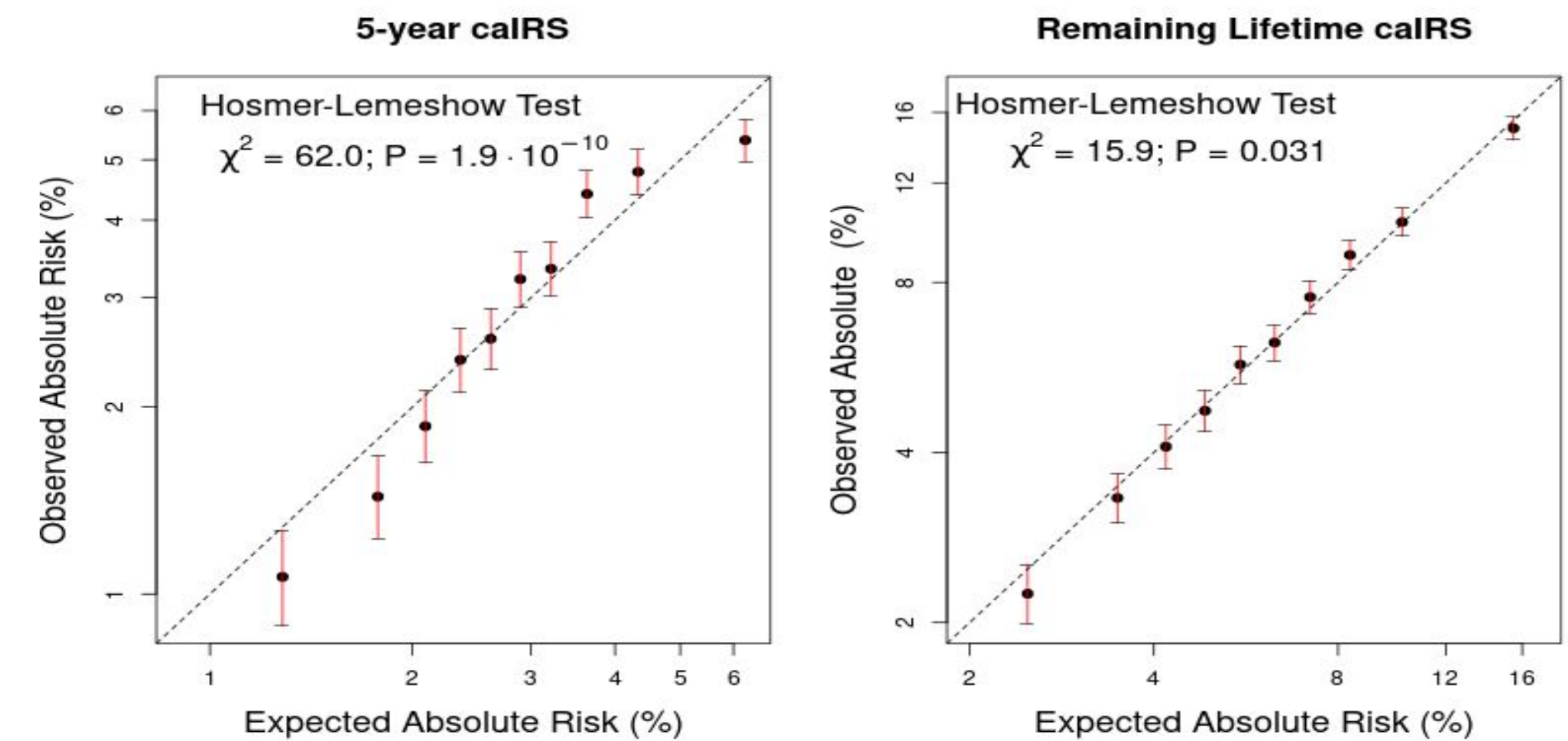
A cross-ancestry polygenic risk score integrated with the Tyrer-Cuzick model improved breast cancer risk stratification and may help identify women at higher risk of developing breast cancer across multiple population groups

Figure 2: Calibration of caIRS predictions of Breast Cancer in WHI and UKB

WHI



UKB



RESULTS

- caIRS outperformed T-C alone for all populations tested (Table 1).
- The largest improvement in remaining lifetime BC risk was observed in Hispanic women in WHI; 44% increase in the OR per sd (increase from 1.31 [1.10 - 1.54] to 1.88 [1.62 - 2.19]).
- Overall, caIRS was well calibrated across all deciles. In WHI, the p-values associated with the Hosmer-Lemeshow test statistic were 0.16 and 0.44 for 5-year and remaining lifetime BC risk, respectively (Figure 2).

CONCLUSIONS/FUTURE DIRECTIONS:

- Adding a caPRS to the T-C model improved BC risk stratification for women of multiple ancestries.
- Use caIRS to refine risk stratification for women with mutations in BC predisposition genes.
- Validate caIRS in larger non-European cohorts.