

Poster #769: Incorporating a Cross-Ancestry Polygenic Risk Score into a Clinical Model Improved Breast Cancer Risk Prediction in Women with Pathogenic Variants



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BACKGROUND

- The integration of polygenic scores (PRSs) into breast cancer risk assessment models has enhanced risk stratification.
- Limited research has explored the impact of PRSs on risk modification for carriers of pathogenic variants in breast cancer susceptibility genes.
- In prior research, we successfully devised and validated a cross-ancestry polygenic risk score (caPRS) tailored to forecast the likelihood of breast cancer (BC) occurrence in women devoid of pathogenic variants (PVs) within BC susceptibility genes.

OBJECTIVE

- Build upon the foundation of the caPRS by integrating it with the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model.
- Assess the impact of genetic and clinical factors on individuals carrying PVs in BRCA1, BRCA2, PALB2, CHEK2, and ATM genes.

METHODS

Cross-ancestry Polygenic Risk Score (caPRS)

- We define the caPRS as a linear combination of the best performing PRS model for each ancestry group weighted by fractional ancestry:

$$caPRS = \sum_{i=1}^5 f_i \beta_i PRS_i$$

where i corresponds to one of 5 continental ancestry groups (European, African, East Asian, South Asian, Admixed American).

Absolute Risks to Age 80

- The estimated absolute risks of developing breast cancer by age 80 for unaffected women were determined by integrating the risk derived from the caPRS with gene-specific clinical risk estimates from the BOADICEA model, using baseline incidences specific to the United States.

Cohorts

- Data on both genetics and clinical information were gathered from two cohorts, including the UK Biobank (UKB) and the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA).
- The study participants comprised 12,525 women who carried pathogenic variants (PVs) in the BRCA1, BRCA2, CHEK2, ATM, and PALB2 genes.

Combining PRS with the BOADICEA clinical risk model significantly improved the breast cancer risk prediction for women who carry pathogenic variants.

Statistical Analysis

- We used a logistic regression model adjusted for age, first-degree BC family history (FHx) and cohort for BRCA1 and BRCA2 to examine the association of the caPRS with BC.
- The effect sizes were expressed as standardized odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

- The caPRS was significantly associated with BC risk across all PV carrier groups (Table 1).
- Using the BOADICEA model alone, the estimated absolute BC risk by age 80 for an average unaffected 20-year-old female in the U.S. with an unknown FHx ranged from 23.8% for CHEK2 carriers to 79.4% for BRCA2 carriers (Table 2 and Figure 1).
- Incorporating caPRS into BOADICEA, the estimated BC risk by age 80 for an average unaffected 20-year-old female in the U.S. with an unknown family history yielded a distribution of risks for each gene. Average values ranged from 27.1% for ATM carriers to 78.7% for BRCA2 carriers (Figure 1).

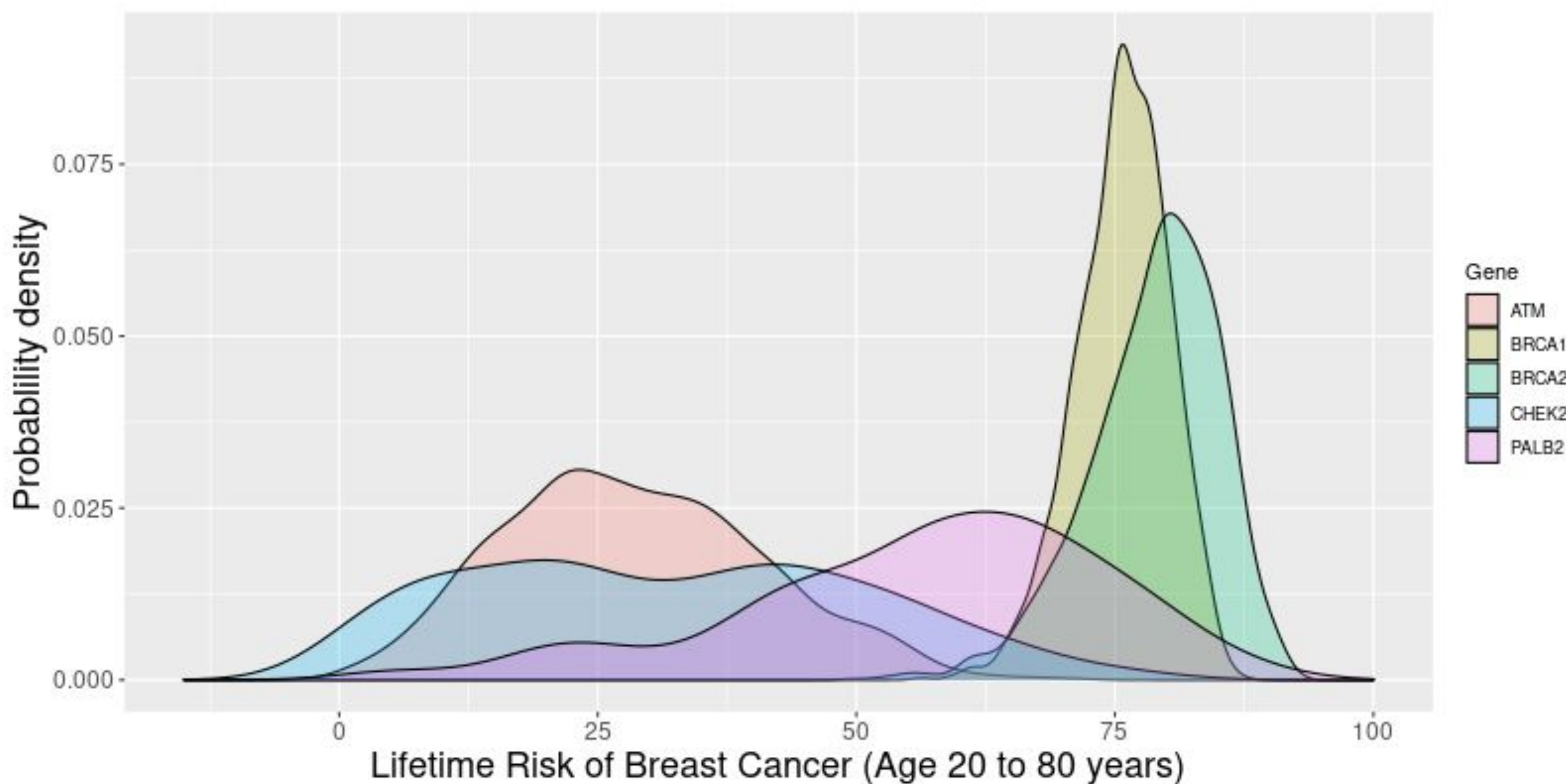
Table 1. Association of caPRS with Breast Cancer Risk in Carriers of Pathogenic Variants

Gene	Cases/N	OR per SD (95% CI)	P-value
ATM	179/2037	1.46 (1.25 - 1.71)	1.5 x 10 ⁻⁶
BRCA1	2755/5794	1.24 (1.17 - 1.31)	1.8 x 10 ⁻¹⁵
BRCA2	1899/4017	1.40 (1.31 - 1.49)	9.8 x 10 ⁻²⁵
CHEK2	53/372	1.88 (1.41 - 2.55)	1.1 x 10 ⁻⁵
PALB2	75/304	1.81 (1.37 - 2.43)	2.0 x 10 ⁻⁵

Table 2. Estimated Lifetime Breast Cancer Risk Up to Age 80.

Gene	Baseline Risk (%)	Integrated Risk (BOADICEA + PRS)	
		Median (%)	Range (%)
ATM	24.9	27.6	0.1 - 70.5
BRCA1	76.1	69.4	56.1 - 87.6
BRCA2	79.4	79.6	49.8 - 89.1
CHEK2	23.8	31.4	0.0 - 78.4
PALB2	53.9	59.0	2.8 - 90.9

Figure 1. Estimated Lifetime Breast Cancer Risk for an Average Unaffected 20-Year-Old Female in the United States with an Unknown Family History.



CONCLUSIONS AND FUTURE DIRECTION

- The caPRS significantly modified risk for carriers of BRCA1, BRCA2, CHEK2, ATM and PALB2 pathogenic variants confirming previous research.
- Prediction models that incorporate the effects of PRSs specifically tailored for women carrying PVs could be instrumental in tailoring guidelines for individuals with PVs in moderate penetrance genes such as ATM and CHEK2.
- Additional data is required to enhance confidence in the risk modification estimates associated with these genes and expand the reach of risk assessment in diverse populations.