Development and Validation of a Polygenic Score to Predict Breast Cancer Risk in Unaffected Hispanic Women Negative for Mutations on a Multi-Gene Hereditary Cancer Panel

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BACKGROUND

- Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer-related death among Hispanic
- For women of European ancestry, genome-wide association studies (GWAS) have identified common variants, primarily single-nucleotide polymorphisms (SNPs), that individually confer modest risk, but together explain a significant proportion of genetic BC predisposition.
- Multiple studies have shown that SNPs discovered through European GWAS may not be appropriate for non-European populations.²⁻⁴
- Here, we present results from an investigation of the ancestry-specific effects of 93 individual SNPs from European and Hispanic GWAS.5-7
- We further describe development and independent pre-specified statistical validation of an Hispanic-specific Residual Risk Score (HRRS).
- Discriminatory accuracy of the HRRS was compared to that of a Residual Risk Score (RRS) previously developed and validated for women of European ancestry.8

OBJECTIVE

- To investigate whether individual SNP breast cancer association odds ratios (ORs) are different for Hispanic versus European women.
- To develop an Hispanic-specific Residual Risk Score (HRRS).
- To validate the improved discriminatory accuracy of HRRS over the European RRS for women of Hispanic ancestry who tested negative for mutations in known breast cancer susceptibility genes.

METHODS

COHORT

- Genotypes and clinical histories were collected from consecutive development and validation cohorts of patients referred for hereditary cancer testing (Table 1).
- Study subjects included women who reported strictly Hispanic or Latin American ancestry, and who tested negative for mutations in 11 genes associated with breast cancer (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1).

ANCESTRY-SPECIFIC SNP ODDS RATIOS

- In the development cohort, we evaluated 93 SNPs from Hispanic and European GWAS.
- For each SNP, we calculated an Hispanic OR and a European OR.
- Hispanic ORs were estimated from meta-analysis of the development cohort and published studies of Hispanic women. 5-6
- European ORs were derived from meta-analysis of European GWAS,⁷ and a previously described study population of women of European ancestry referred for hereditary cancer testing.8

DEVELOPMENT AND VALIDATION

- Based on a development cohort of 5,443 women ascertained from July 2016 through June 2017, we derived an HRRS optimized for women of Hispanic ancestry.
- The HRRS was validated in an independent cohort of 8,519 women ascertained from June 2017 through November 2018.
- Validation included a test for improved discriminatory accuracy of the HRRS over the European RRS.
- Validation analyses were conducted according to a pre-specified statistical analysis plan.

STATISTICAL ANALYSIS

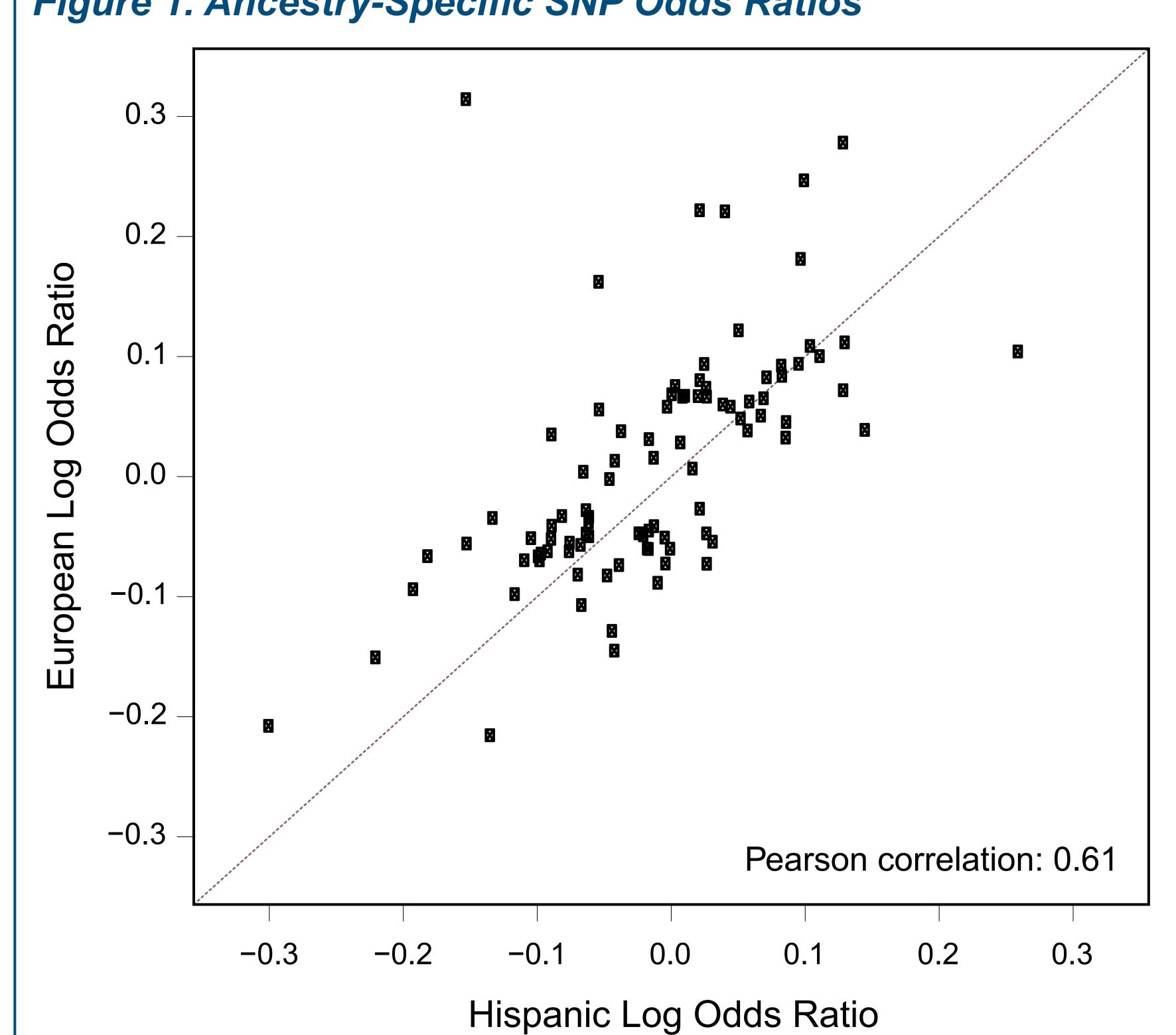
- Z-tests were used to evaluate differences between Hispanic and European ORs for individual SNPs.
- Candidate methods for weighting individual SNPs, and candidate polygenic scores, were evaluated through cross-validation of the development cohort.
- Multivariate logistic regression models were the primary statistical tool for evaluation of individual SNPs, candidate polygenic scores, the HRRS, and the RRS.
- All models included personal/family cancer history and age as independent variables.
- P-values were based on likelihood ratio test statistics and reported as two-sided.

Table 1. Patient Characteristics

	Development Set		Validation Set	
	All Patients	BC Cases	All Patients	BC Cases
Total				
N (%)	5,443 (100)	1,320 (100)	8,519 (100)	1,094 (100)
Age at Hereditary Cancer Testing				
Range	18-82	22-82	18-84	21-81
Median	42.0	47.0	41.0	48.0
≤50	4,107 (75.5)	837 (63.2)	6,550 (76.9)	650 (59.4)
Family History of BC				
No BC	2,073 (38.1)	753 (57.0)	3,113 (36.5)	641 (58.6)
≥1 BC	3,370 (61.9)	567 (43.0)	5,406 (63.5)	453 (41.4)

BC, Breast Cancer



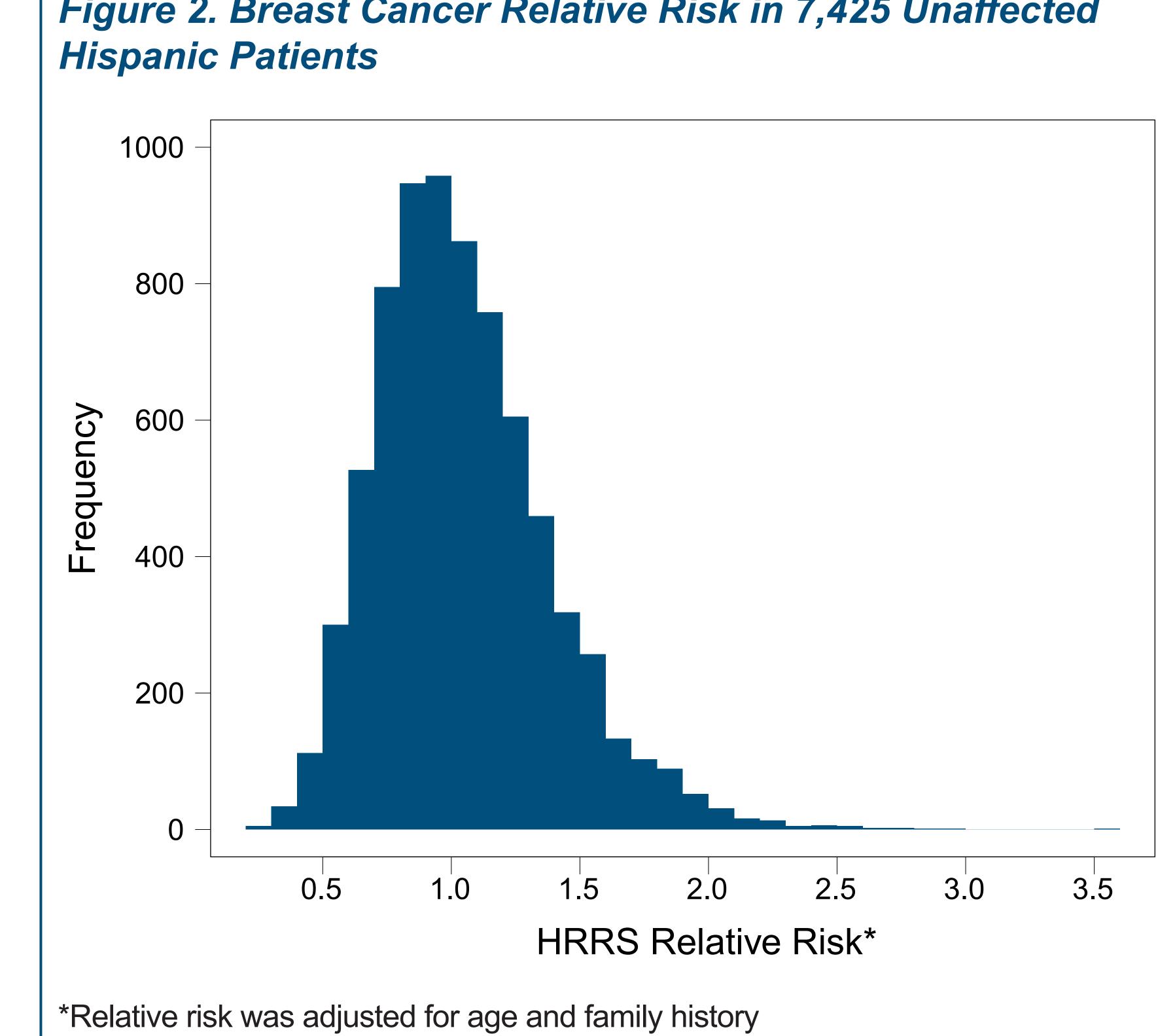


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RESULTS

- Patient characteristics can be found in Table 1.
- The final HRRS included 87 SNPs. SNP weights were based on meta-analysis of Hispanic and European literature and development
- Hispanic and European log ORs of individual SNPs based on metaanalysis of literature and development cohorts are shown in Figure 1.
- Log ORs were modestly correlated between ancestries (Pearson correlation=0.61).
- The HRRS was strongly associated with personal history of breast cancer in the validation cohort (p=7.1x10⁻¹⁹).
- The OR per standard deviation of the HRRS in unaffected controls was 1.38, with 95% confidence interval 1.28-1.48.
- The HRRS showed significantly improved discriminatory accuracy over the European RRS (p=6.0x10⁻⁵).
- HRRS relative risks ranged from 0.26 to 3.6 for unaffected women in the validation cohort (Figure 2).

Figure 2. Breast Cancer Relative Risk in 7,425 Unaffected



CONCLUSIONS

- The HRRS significantly outperformed the European RRS in this population of Hispanic women who were negative for breast cancer predisposition mutations.
- This may have been due to inclusion of Hispanic-specific SNPs and incorporation of Hispanic-specific OR estimates for individual SNPs.
- Clinical implementation of the HRRS may offer improved medical management for high-risk Hispanic women.

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