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Editorial

EDITORIAL

Polygenic Risk Scores for Breast Cancer Risk Prediction: Lessons Learned and Future Opportunities

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In this issue of the Journal, Shieh et al. report findings from an assessment of performance of a polygenic risk score (PRS) for breast cancer in Latin American women (Latinas) (1). Study participants were either residents of the Western United States whose genetic ancestry was primarily a mix of Indigenous American and European ancestry or residents of Latin American countries (ie, Mexico, Colombia, and Peru). The PRS was developed based on single nucleotide polymorphisms (SNPs) identified from genome-wide association studies (GWASs) conducted in largely European-ancestry populations. The results indicate that a PRS of approximately 180 SNPs had relatively high discriminatory accuracy, with an area under the curve (AUC) of 0.63 (95% confidence interval [CI] = 0.62–0.64). Importantly, this AUC is identical to the AUC derived in the largest such analysis of European-ancestry women (2). That study included more than 100 000 breast cancer cases and 100 000 controls. For a PRS based on 3082 SNPs, the AUC was 0.630 (95% CI = 0.628–0.651). The consistency of the present report with results from the largest study of European-ancestry women suggests that PRS developed based on GWAS findings from European-ancestry women may be equally useful for Latinas. It will not be necessary to wait years until GWASs of tens of thousands of Latinas with breast cancer have been conducted. Instead, the PRS tested by Shieh et al. can be used for Latinas from the Western United States and Latin America just as existing PRS are used for U.S. women of European ancestry. The findings fill a critical knowledge gap and may have immediate public health impact. Latinas constitute a large and rapidly growing population group, yet commercial laboratories currently do not return PRS results to these women. Given that information from a PRS has the potential to improve stratification for breast cancer screening, it is imperative that Latinas have access to the same PRS feedback as women of European ancestry do.

It may not be surprising that a PRS based on SNPs identified in European-ancestry women performs equally well in Latinas, given that the Latinas in this study had a mean proportion of European ancestry of approximately 49%; Indigenous American ancestry accounted for most of the remainder of ancestral proportions, with less than 5% African and 2% Asian ancestry. To date, research on germline genetic variants in relation to breast cancer risk in Latinas has indicated that most SNPs of interest have similar minor allele frequencies in women with Indigenous American and European ancestry, as well as similar magnitudes of association, with a few notable exceptions (3). Nevertheless, demonstration of the performance of a PRS, as was done in the present study, was essential, in part, because the one prior report on PRS for breast cancer risk prediction in Latinas indicated poorer performance (AUC 0.59) (4). The prior study was considerably smaller, with only 147 Latina cases, and the PRS was based on 71 SNPs. A key strength of the present analysis was stratification by quartile of Indigenous American ancestry. The stratum-specific results indicated that the PRS was equally predictive among women with the highest proportions of Indigenous American ancestry as in women with the highest proportions of European ancestry.

It is critical that not all "underrepresented" populations be lumped together in efforts to advance breast cancer risk prediction and prevention. The authors correctly note that their PRS, though likely applicable to Latina populations with similar distributions of genetic ancestry, may not be generalizable to Caribbean Latinas (including women from Puerto Rico and the Dominican Republic), who typically have an appreciable proportion of African ancestry. The two published PRS for breast cancer in African American women (4,5), both of which were based largely on SNPs identified in GWASs of European-ancestry populations, show poor performance compared with PRS in other populations, with AUCs of 0.55 and 0.53. Although one would expect susceptibility loci to be similar across race/ethnicity, the most informative SNPs for each locus may differ and have indeed been shown to differ most often for individuals of African ancestry as compared with all other ancestral populations (6,7).

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Because of the considerably greater genetic diversity in African-ancestry populations and differences in linkage disequilibrium architecture, a well-performing PRS for breast cancer in women of African ancestry will not be possible until large-scale fine mapping of previously identified loci has been carried out, along with statistically powerful GWASs in women of African ancestry for identification of possible novel loci. The necessary data collection required to make such work possible has been a long time coming, but we are finally reaching the point at which a truly African-ancestry-specific PRS may be possible.

Similarly, despite the relative success of the PRS in the present study of Latinas, conducting GWASs of larger samples of Latin American women of high Indigenous American ancestry may yield new variants that are informative for this population and will improve the predictive power of PRS in Latin American populations. This potential was demonstrated in the first Latina GWAS, published in 2014 (3). That study, which included only about one-tenth the sample size of the largest European-ancestry-based GWAS, identified a novel variant in the estrogen receptor gene associated with a decreased risk of developing breast cancer. Additional GWASs in Latin American women are clearly needed.

Finally, although the paper by Shieh et al. is notable in demonstrating for the first time that a PRS based on genetic information from largely European-ancestry populations is equally useful for women whose ancestry is primarily a mix of Indigenous American and European ancestry, we can and should go beyond genetic risk scores for improving risk stratification for breast cancer. Population-specific risk-prediction models based on nongenetic risk factors must be developed and tested. Identification of the most informative set of nongenetic risk factors for incorporation into a risk-prediction model along with the PRS will undoubtedly improve prediction and facilitate screening recommendations that are more personalized.

Notes

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