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Performance of a polygenic risk score combined with clinical assessment for breast cancer risk

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Abstract:
Background: Polygenic risk scores (PRS) based on a large number of SNPs associated with breast cancer have recently been made available in combination with multigene panel testing for clinical management of breast cancer risk. Breast cancer risk assessment has historically been performed using various non-genetic risk models, which predict lifetime risk of breast cancer in unaffected women based on personal and family history information. While clinical use of PRS in combination with these models continues to increase, the predictive performance of a PRS combined with clinical information in real-world patient populations has not been thoroughly investigated. **Methods:** We assessed a 100-SNP breast cancer PRS in combination with the Tyrer-Cuzick model-estimated lifetime breast cancer risk in 5,374 Caucasian women from the case-control Mayo Clinic Breast Cancer Study (MCBCS), comprised of 3,373 breast cancer cases and 2,001 unaffected controls seen at Mayo Clinic from 2004 to 2016. Clinical, family history, and demographic information was collected on all MCBCS participants via questionnaires and medical record review. SNPs were selected for the PRS if they exceeded genome-wide significance in ≥2 large-scale breast cancer genome wide association studies (GWAS) in women of European descent. Selected SNPs were then used to construct a population standardized PRS, accounting for per-allele odds ratios reported in the largest GWAS to date and population-specific allele frequencies. PRS and Tyrer-Cuzick model associations with breast cancer and related clinical features were tested using multivariate logistic regression. **Results:** Among cases and controls, mean±SD age at diagnosis and study enrollment was 56.4±12.4 and 56.2±14.1, respectively. Approximately 36.9% of cases and 16.9% of controls had ≥1 first- or second-degree relative with breast or ovarian cancer, respectively. Among unaffected women, the median (IQR) estimated lifetime risk of breast cancer to age 85 based on Tyrer-Cuzick alone was 8.3% (6.9%), and 2.6% had a clinically actionable lifetime risk of ≥20%. The mean±SD sum of the risk alleles across 100 SNPs was significantly higher for cases vs. controls (94.8±6.3 vs. 92.7±6.2, $p<0.001$). Compared to women in the lowest quartile of PRS, those in the 2nd, 3rd and 4th quartiles were 1.47 (95% CI: 1.26-1.72), 1.87 (95% CI: 1.60-2.19), and 2.22 (95% CI: 1.89-2.61) times more likely to have breast cancer after adjustment for age and family history. The AUC was 0.59 (95% CI: 0.58-0.61) for PRS and 0.60 (95% CI: 0.58-0.61) for Tyrer-Cuzick model estimated risk alone; but when combined, the model achieved an AUC of 0.63 (95% CI: 0.62-0.65). Among unaffected women, 6.7% had ≥20% lifetime risk of breast cancer based on the combined PRS-clinical model. **Conclusions:** These findings suggest that the 100-SNP PRS significantly improves estimation of breast cancer risk based on non-genetic models, and can be used to further identify women at

increased lifetime risk who would otherwise not be identified by clinical assessment alone.
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Author Disclosure Information:

M. Black: S; A; Ambry Genetics. **S. Li:** S; A; Ambry Genetics. **H. LaDuca:** S; A; Ambry Genetics. **S. Armasu:** None. **E.C. Polley:** None. **P. Fitz-Gibbon:** None. **C.G. Scott:** None. **S.J. Winham:** None. **J.E. Olson:** None. **K.J. Ruddy:** None. **C.M. Vachon:** None. **F.J. Couch:** None.

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