Polygenic Risk Score for Breast Cancer in High-Risk Women

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Background: While assessment of genetic contribution to breast cancer (BC) risk was once limited to high-penetrance genes such as *BRCA1*/*2*, additional genes conferring two- to five-fold increased risks of BC, as well common SNPs with relative risks ranging 1.03-1.57, have recently been identified. Although several reports suggest that a score based on combined genotypes across a large number of SNPs may have substantial predictive value for risk stratification in the general population, few studies have examined the performance of such a score in high-risk women.

Methods: We genotyped 102 BC-associated SNPs using next-generation sequencing in order to examine whether a risk score based on these SNPs was predictive of BC in 2,910 women (1,758 cases with no other cancer primaries and 1,152 controls unaffected with any cancer) referred for genetic testing at a single diagnostic laboratory. All women were self-reported Caucasian, 18-85 years of age and provided family history information at the time of testing, and tested negative for pathogenic variants in BC-related genes (mean±SD age at testing 52±13 years). We constructed a polygenic risk score (PRS), with each SNP weighted by per-allele relative risks in Caucasians from large genome-wide association studies and population-specific allele frequencies, and tested PRS association with BC using logistic regression.

Results: The PRS was significantly higher in cases than controls (mean±SD 1.41±0.86 vs. 1.06±0.66, $p<0.0001$). Compared to women in the 1st quartile of PRS, those in the 2nd, 3rd and 4th quartile were 1.65 (95% CI: 1.34-2.05), 2.12 (95% CI: 1.71-2.64) and 2.75 (95% CI: 2.20-3.44) times as likely to have BC (all $p<0.0001$). PRS predictive performance was consistent with prior literature (AUROC=0.61).

Conclusions: These data suggest that a 102-SNP PRS assessed in high-risk patients performs similarly to risk scores reported in the broader population, and has direct implications for their clinical management. Our ongoing analysis of the ability of the PRS to discriminate among specific pathologic subtypes, as well as validity and utility of a PRS combined with clinical models to estimate residual lifetime risk, has the potential to further inform screening guidelines and improve patient care.

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Suggested category: Cancer Prevention, Hereditary Genetics, and Epidemiology