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Title: Breast Cancer Risk Estimation Using the OncoVue® Model Compared to Combined GWAS Single Nucleotide Polymorphisms.

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Background: We have developed a new breast cancer risk assessment model (OncoVue) that integrates information from 22 single nucleotide polymorphisms (SNPs) and 5 personal risk factors. It has been shown to effectively stratify risk in three independent validation populations. Genome wide association studies (GWAS) have identified seven candidate SNPs independently associated with breast cancer risk. Using estimates of relative risks and allele frequencies derived from these studies, a theoretical examination of these SNPs has concluded that they have the potential to modestly improve clinical risk estimation. We have examined both the OncoVue model and these GWAS SNPs in the same case-control population to determine their utility in risk estimation.

Materials and Methods: A randomly selected subset of participants (376 cases and 982 controls) that had enrolled in a larger case-control study conducted in six distinct geographic regions of the United States were examined. DNAs were genotyped for the 22 SNP variants in OncoVue and combined with personal factors to calculate the risk scores for the individual participants. DNAs were also genotyped for the following GWAS SNPs: rs2981582 (FGFR2), rs3817198 (LSP1), rs889312 (MAP3K), rs4415084 (MRPS30), rs13281615 (POU5F1P1), rs13387042 (TNP1), and rs3803662 (TOX3, formerly TNRCR9). Association of individual GWAS SNP genotypes with breast cancer risk was evaluated by calculating odds ratios (ORs). Assuming independent contribution of each SNP to risk, a combined GWAS risk score was calculated using a multiplicative model. Positive likelihood ratios (PLRs) were calculated using a risk threshold of 1.5-fold the control population mean risk to evaluate the proportion of individuals placed at elevated risk by OncoVue compared to the combined GWAS risk scores.

Results: OncoVue exhibited significant ability to stratify risk at the 1.5-fold mean with a PLR of 2.2 and at a risk level of 2.5-fold mean the PLR increased to 5.0. In analyses of individual GWAS SNPs, statistically significant associations with breast cancer were identified for homozygous carriers of the rare allele for the FGFR2, MAP3K and TOX3 genes. However, the PLR for the combined GWAS risk scores at 1.5-fold mean was 1.0 indicating no ability to discriminate risk in this study population.

Conclusions: In this case-control population OncoVue effectively stratified risk by accurately assigning elevated risk to breast cancer cases. In the same population, a combined risk score produced from seven GWAS SNPs did not effectively stratify risk. These results indicate that the OncoVue model has clinical utility for identifying elevated risk women who might benefit from additional screening and prevention.