Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction.

The known breast cancer susceptibility polymorphisms in FGFR2, TNRC9/TOX3, MAP3K1, LSP1, and 2q35 confer increased risks of breast cancer for BRCA1 or BRCA2 mutation carriers. We evaluated the associations of 3 additional single nucleotide polymorphisms (SNPs), rs4973768 in SLC4A7/NEK10, rs6504950 in STXBP4/COX11, and rs10941679 at 5p12, and reanalyzed the previous associations using additional carriers in a sample of 12,525 BRCA1 and 7,409 BRCA2 carriers. Additionally, we investigated potential interactions between SNPs and assessed the implications for risk prediction. The minor alleles of rs4973768 and rs10941679 were associated with increased breast cancer risk for BRCA2 carriers (per-allele HR = 1.10, 95% CI: 1.03-1.18, P = 0.006 and HR = 1.09, 95% CI: 1.01-1.19, P = 0.03, respectively). Neither SNP was associated with breast cancer risk for BRCA1 carriers, and rs6504950 was not associated with breast cancer for either BRCA1 or BRCA2 carriers. Of the 9 polymorphisms investigated, 7 were associated with breast cancer for BRCA2 carriers (FGFR2, TOX3, MAP3K1, LSP1, 2q35, SLC4A7, 5p12, P = 7 × 10^{-11} - 0.03), but only TOX3 and 2q35 were associated with the risk for BRCA1 carriers (P = 0.0049, 0.03, respectively). All risk-associated polymorphisms appear to interact multiplicatively on breast cancer risk for mutation carriers. Based on the joint genotype distribution of the 7 risk-associated SNPs in BRCA2 mutation carriers, the 5% of BRCA2 carriers at highest risk (i.e., between 95th and 100th percentiles) were predicted to have a probability between 80% and 96% of developing breast cancer by age 80, compared with 42% to 50% for the 5% of carriers at lowest risk. Our findings indicated that these risk differences might be sufficient to influence the clinical management of mutation carriers.
Occurences:

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