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Titel des Beitrags: Common variants at 12p11, 12q24, 9p21, 9q31.2 and in ZNF365 are associated with breast cancer risk for BRCA1 and/or BRCA2 mutation carriers.

Abstract: Several common alleles have been shown to be associated with breast and/or ovarian cancer risk for BRCA1 and BRCA2 mutation carriers. Recent genome-wide association studies of breast cancer have identified eight additional breast cancer susceptibility loci: rs1011970 (9p21, CDKN2A/B), rs10995190 (ZNF365), rs704010 (ZMIZ1), rs2380205 (10p15), rs614367 (11q13), rs1292011 (12q24), rs10771399 (12p11 near PTHLH) and rs865686 (9q31.2). To evaluate whether these single nucleotide polymorphisms (SNPs) are associated with breast cancer risk for BRCA1 and BRCA2 carriers, we genotyped these SNPs in 12,599 BRCA1 and 7,132 BRCA2 mutation carriers and analysed the associations with breast cancer risk within a retrospective likelihood framework. Only SNP rs10771399 near PTHLH was associated with breast cancer risk for BRCA1 mutation carriers (per-allele hazard ratio (HR) = 0.87, 95% CI: 0.81 to 0.94, P-trend = 3 x 10^{-4}). The association was restricted to mutations proven or predicted to lead to absence of protein expression (HR = 0.82, 95% CI: 0.74 to 0.90, P-trend = 3.1 x 10^{-5}, P-difference = 0.03). Four SNPs were associated with the risk of breast cancer for BRCA2 mutation carriers: rs10995190, P-trend = 0.015; rs1011970, P-trend = 0.048; rs865686, 2df-P = 0.007; rs1292011 2df-P = 0.03. rs10771399 (PTHLH) was predominantly associated with estrogen receptor (ER)-negative breast cancer for BRCA1 mutation carriers (HR = 0.81, 95% CI: 0.74 to 0.90, P-trend = 4 x 10^{-5}) and there was marginal evidence of association with ER-negative breast cancer for BRCA2 mutation carriers (HR = 0.78, 95% CI: 0.62 to 1.00, P-trend = 0.049). The present findings, in combination with previously identified modifiers of risk, will ultimately lead to more accurate risk prediction and an improved understanding of the disease etiology in BRCA1 and BRCA2 mutation carriers.

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