RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies.
RAD51 is an important component of double-stranded DNA-repair mechanisms that interacts with both BRCA1 and BRCA2. A single-nucleotide polymorphism (SNP) in the 5’ untranslated region (UTR) of RAD51, 135G-->C, has been suggested as a possible modifier of breast cancer risk in BRCA1 and BRCA2 mutation carriers. We pooled genotype data for 8,512 female mutation carriers from 19 studies for the RAD51 135G-->C SNP. We found evidence of an increased breast cancer risk in CC homozygotes (hazard ratio [HR] 1.92 [95% confidence interval [CI] 1.25-2.94) but not in heterozygotes (HR 0.95 [95% CI 0.83-1.07]; P=.002, by heterogeneity test with 2 degrees of freedom [df]). When BRCA1 and BRCA2 mutation carriers were analyzed separately, the increased risk was statistically significant only among BRCA2 mutation carriers, in whom we observed HRs of 1.17 (95% CI 0.91-1.51) among heterozygotes and 3.18 (95% CI 1.39-7.27) among rare homozygotes (P=.0007, by heterogeneity test with 2 df). In addition, we determined that the 135G-->C variant affects RAD51 splicing within the 5’ UTR. Thus, 135G-->C may modify the risk of breast cancer in BRCA2 mutation carriers by altering the expression of RAD51. RAD51 is the first gene to be reliably identified as a modifier of risk among BRCA1/2 mutation carriers.