DNA glycosylases involved in base excision repair may be associated with cancer risk in BRCA1 and BRCA2 mutation carriers.

Single Nucleotide Polymorphisms (SNPs) in genes involved in the DNA Base Excision Repair (BER) pathway could be associated with cancer risk in carriers of mutations in the high-penetration susceptibility genes BRCA1 and BRCA2, given the relation of synthetic lethality that exists between one of the components of the BER pathway, PARP1 (poly ADP ribose polymerase), and both BRCA1 and BRCA2. In the present study, we have performed a comprehensive analysis of 18 genes involved in BER using a tagging SNP approach in a large series of BRCA1 and BRCA2 mutation carriers. 144 SNPs were analyzed in a two stage study involving 23,463 carriers from the CIMBA consortium (the Consortium of Investigators of Modifiers of BRCA1 and BRCA2). Eleven SNPs showed evidence of association with breast and/or ovarian cancer at p<0.05 in the combined analysis. Four of the five genes for which strongest evidence of association was observed were DNA glycosylases. The strongest evidence was for rs1466785 in the NEIL2 (endonuclease VIII-like 2) gene (HR: 1.09, 95% CI (1.03-1.16), p = 2.7 × 10(-3)) for association with breast cancer risk in BRCA2 mutation carriers, and rs2304277 in the OGG1 (8-guanine DNA glycosylase) gene, with ovarian cancer risk in BRCA1 mutation carriers (HR: 1.12 95%CI: 1.03-1.21, p = 4.8 × 10(-3)). DNA glycosylases involved in the first steps of the BER pathway may be associated with cancer risk in BRCA1/2 mutation carriers and should be more comprehensively studied.
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