Association of death receptor 4 variant (683A>C) with ovarian cancer risk in BRCA1 mutation carriers.

Dysregulation of apoptosis plays an important role in carcinogenesis. Therefore, apoptosis-associated genes like the death receptor 4 (DR4, TRAIL-R1) are interesting candidates for modifying the penetrance of breast and ovarian cancer in carriers of BRCA1 and BRCA2 mutations. The DR-4 haplotype 626C-683C [626C>G, Thr209Arg (rs4871857) and 683A>C, Glu228Ala (rs17088993)] has recently been linked to an increased risk of breast cancer. To evaluate whether DR4 626C>G or DR4 683A>C modifies the risk of breast or ovarian cancer in carriers of BRCA1 and BRCA2 mutations, we undertook a national multicenter study including data of 840 carriers of breast cancer gene (BRCA) mutations. DNA samples were collected from 12 German research centers between 1996 and 2005 and were genotyped by the Taqman allelic discrimination assay. The association between genotypes and incidence of breast or ovarian cancer data was evaluated using a Cox proportional hazards regression model. We found evidence for a significant association of DR4 683A>C with a higher risk for ovarian cancer in carriers of BRCA1 mutations \([n = 557, \text{hazard ratio } 1.78 \ (1.24-2.55), \ p = 0.009]\). Our results thus indicate that the DR4 683A>C variant modifies the risk of ovarian cancer in carriers of BRCA1 mutations.