A nonsynonymous polymorphism in IRS1 modifies risk of developing breast and ovarian cancers in BRCA1 and ovarian cancer in BRCA2 mutation carriers.

We previously reported significant associations between genetic variants in insulin receptor substrate 1 (IRS1) and breast cancer risk in women carrying BRCA1 mutations. The objectives of this study were to investigate whether the IRS1 variants modified ovarian cancer risk and were associated with breast cancer risk in a larger cohort of BRCA1 and BRCA2 mutation carriers. IRS1 rs1801123, rs1330645, and rs1801278 were genotyped in samples from 36 centers in the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Data were analyzed by a retrospective cohort approach modeling the associations with breast and ovarian cancer risks simultaneously. Analyses were stratified by BRCA1 and BRCA2 status and mutation class in BRCA1 carriers. Rs1801278 (Gly972Arg) was associated with ovarian cancer risk for both BRCA1 (HR, 1.43; 95% CI, 1.06-1.92; P = 0.019) and BRCA2 mutation carriers (HR, 2.21; 95% CI, 1.39-3.52, P = 0.0008). For BRCA1 mutation carriers, the breast cancer risk was higher in carriers with class II mutations than class I mutations (class II HR, 1.86; 95% CI, 1.28-2.70; class I HR, 0.86; 95% CI, 0.69-1.09; P(difference), 0.0006). Rs13306465 was associated with ovarian cancer risk in BRCA1 class II mutation carriers (HR, 2.42; P = 0.03). The IRS1 Gly972Arg single-nucleotide polymorphism, which affects insulin-like growth factor and insulin signaling, modifies ovarian cancer risk in BRCA1 and BRCA2 mutation carriers and breast cancer risk in BRCA1 class II mutation carriers. These findings may prove useful for risk prediction for breast and ovarian cancers in BRCA1 and BRCA2 mutation carriers.