Analysis of large mutations in *BARD1* in patients with breast and/or ovarian cancer.

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Objectives:
Aside from *BRCA1/2* genes and several genetic factors associated with hereditary syndromes increasing risk of breast and/or ovarian cancer, a considerable fraction of breast and/or ovarian predisposing factors (>50%) is still unknown. Initial reports indicate that the *BARD1* gene, encoding a protein indispensable for *BRCA1*-mediated tumor suppression function, can be affected by several single-nucleotide mutations predisposing to breast and/or ovarian cancer. Although it was suggested that large mutations (multi-exon deletions or duplications) may contribute substantially to the deleterious variation of *BARD1*, no systematic study of large mutations in *BARD1* was performed so far.

Methods:
To elucidate further the role of large mutations in *BARD1*, we designed and generated a multiplex ligation-dependent probe amplification (MLPA) assay covering all exons and flanking sequences of *BARD1*. The assay was designed according to a previously developed strategy using exclusively short, chemically synthesized probes. The MLPA test was used for the analysis of 504 DNA specimens from patients with familial breast and/or ovarian cancer and 313 DNA samples from women with unselected ovarian cancer.

Results:
Conducted investigation did not reveal any large mutations in the *BARD1* gene. As a side effect of the analysis, confirming the precision of our test, we detected seven samples with an affected signal of a single MLPA probe that was specific for either exon 8 or 10. Sequencing analysis led to the identification of three different sequence variants, located within the target sequences of the respective MLPA probes. All of the sequence variants were reported earlier, either as definitively deleterious [nonsense c.1690C>T (pGln564*); splicing c.1977A>G (p.Cys53_Trp635delinsfs*12)] or potentially deleterious [missense c.1972C>T (p.Arg658Cys)] mutations.

Conclusions:
Concluding, although we cannot exclude the presence of large mutations in *BARD1*, our study indicates that such mutations do not contribute substantially to the risk of breast and/or ovarian cancer.

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