

The risk of ovarian cancer in sisters of ovarian cancer patients with a *BRCA1* germline mutation

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Background: In the process of cancerogenesis of ovarian carcinoma among *BRCA1* pathogenic variant carriers, there are two major features: *BRCA1* germline mutation, giving the risk of ovarian cancer at the level of around 40% and modifiers, contributing around 60% of features leading to cancer. Modifiers are shared between the sisters at different levels, which explains the different risks of ovarian cancer. The level of risk of cancers in sisters of ovarian cancer patients with a *BRCA1* pathogenic variant has not been studied in Poland. This paper aims to study the cancer risk in both groups - sisters with and without the *BRCA1* mutation.

Methods: We developed a register of **1018** unselected cases of women carrying a *BRCA1* mutation and suffering from ovarian cancer from hospitals throughout Poland. Based on pedigree data, we were able to identify **147** sisters, who had a confirmed result of genetic testing for the *BRCA1* mutation. It allowed us to calculate the estimated risk of developing breast and ovarian cancer for sisters of women suffering from this disease, both when the sibling inherits the mutation and when only modifiers seem to play a causative role.

Results: Out of 147 sisters - 66 were carriers of a pathogenic variant of the *BRCA1* gene and in case of 81 others - no abnormality was detected. Mean age was 66 years. Among both groups - a total of 20 ovarian cancers were detected, 16 in the *BRCA1*(+) and 4 in the *BRCA1*(-) subgroup. Between the *BRCA1* pathogenic variant carriers 34 adnexectomy procedures were performed, while among non-carriers just 11. Taking into account all of our subdivision criteria, we managed to calculate the risk for post-adnexectomy patients and those with preserved ovaries and fallopian tubes both with the inheritance of pathogenic variant of *BRCA1* and without it. Post-adnexectomy risk of developing ovarian malignancy was absolutely reduced both in the *BRCA1*(+) (0/34), as well as *BRCA1*(-) (0/11). Patients with preserved ovaries and fallopian tubes were much more likely to develop ovarian cancer (*BRCA1*(+) (n=16/32); *BRCA1*(-) (4/70)). Depending on whether the pathogenic variant was inherited or not, OR was estimated at 16,6.

Conclusions: The risk of developing ovarian cancer in sisters of *BRCA1*- dependent ovarian cancer patients is increased among both carriers as well as non-carriers. Adnexectomy is a very effective risk-reducing measure and should be performed, if the pathogenic variant is detected and may be considered, if the pathogenic variant is not detected, but further research on greater numbers should verify these speculations.