

## Association analysis of recurrent mutations in *BRCA1*, *BRCA2* and *CHEK2* genes with a predisposition to ductal carcinoma in situ in the Polish population

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Ductal carcinoma in situ (DCIS) is the most common form of noninvasive breast cancer. A few studies have suggested a genetic link in some cases of DCIS. The aim of this study was to investigate the role of pathogenic variants of the *BRCA1*, *BRCA2* and *CHEK2* genes in the etiology of DCIS and their impact on the survival of patients with DCIS. 564 Polish women diagnosed with DCIS were screened for 14 Polish founder mutations, including six in the *BRCA1* gene (c.181T>G, c.4035delA, c.5266dupC, c.3700\_3704del, c.68\_69delAG, and c.5251C>T), four in *BRCA2* (c.658\_659delGT, c.3847\_3848delGT, c.5946delT, and c.7913\_7917del), and four in *CHEK2* (c.1100delC, c.444+1G>A, del5395, and c.470T>C).

A total of 69 mutations were identified in the study group- seven mutations in the *BRCA1* gene, eight in *BRCA2*, and 54 in *CHEK2* (of which the missense variant in 40 cases). During an average follow-up of 11.5 years, no deaths were recorded among mutation carriers, while 18 women died in the group of noncarriers.

The study showed an association of both *BRCA2* (OR = 11.3;  $p < 0.0001$ ) and *BRCA1* (OR = 3.27;  $p = 0.01$ ) mutations with DCIS. Three of 15 cases with *BRCA1/2* mutations developed ipsilateral or contralateral invasive breast cancer, a median of 6 years after DCIS diagnosis. *CHEK2* mutation (all variants combined) was also associated with an increased risk of DCIS (OR = 1.7;  $p = 0.003$ ). The risk was higher for *CHEK2* truncating mutations (OR = 3.0;  $p = 0.001$ ) than for the c.470T>C missense variant (OR = 1.5;  $p = 0.04$ ), and the highest risk was observed in *CHEK2* truncating mutation carriers with a positive family history of breast cancer (OR = 4.2;  $p = 0.01$ ).

Based on this study, DCIS should be considered part of the hereditary breast/ovarian cancer syndrome and women with mutations in the *BRCA1/2* and *CHEK2* genes are at clinically significant risk for DCIS. Therefore, patients diagnosed with DCIS should receive genetic counseling and be tested for *BRCA1/2* and *CHEK2* mutations. It cannot be ruled out that mutations in the *BRCA1/2* and *CHEK2* genes predispose to a good prognosis for DCIS, but further studies are needed.