Constitutional methylation of BRCA1 gene as breast cancer risk factor.

Anna Jakubowska Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

It has been proposed that methylation signatures in blood-derived DNA may correlate with cancer risk. In this study, we evaluated whether methylation of the promoter region of the BRCA1 gene detectable in DNA from peripheral blood cells is a risk factor for breast cancer, in particular for tumors with pathologic features characteristic for cancers with BRCA1 gene mutations. We conducted a case-control study of 66 breast cancer cases and 36 unaffected controls. Cases were triple-negative or of medullary histology, or both; 30 carried a constitutional BRCA1 mutation and 36 did not carry a mutation. Blood for DNA methylation analysis was taken within three months of diagnosis. Methylation of the promoter of the BRCA1 gene was measured in cases and controls using methylation-sensitive high-resolution melting (MS-HRM). A sample with any detectable level of methylation was considered to be positive. Methylation of the BRCA1 promoter was detected in 15 of 66 cases and in 2 of 36 controls (OR 5.0, $p = 0.03$). Methylation was present in 15 of 36 women with breast cancer and without germline BRCA1 mutation, but in none of 30 women with breast cancer and a germline mutation ($p < 0.01$). The association between methylation and breast cancer was restricted to women with no constitutional BRCA1 mutation (OR 12.1, $p = 0.0006$). Methylation of the promoter of the BRCA1 gene detectable in peripheral blood DNA may be a marker of increased susceptibility to triple-negative or medullary breast cancer.