Association Between Loss-of-Function Mutations Within the FANCM Gene and Early-Onset Familial Breast Cancer.

Germline mutations in established moderately or highly penetrant risk genes for breast cancer (BC) and/or ovarian cancer (OC), including BRCA1 and BRCA2, explain fewer than half of all familial BC and/or OC cases. Based on the genotyping of 2 loss-of-function (LoF) variants c.5101C>T (p.Gln1701Ter [rs147021911]) and c.5791C>T (p.Arg1931Ter [rs144567652]), the FANCM gene has been suggested as a novel BC predisposition gene, while the analysis of the entire coding region of the FANCM gene in familial index cases and geographically matched controls is pending. To assess the mutational spectrum within the FANCM gene, and to determine a potential association of LoF germline mutations within the FANCM gene with BC and/or OC risk. For the purpose of identification and characterization of novel BC and/or OC predisposition genes, a total of 2047 well-characterized familial BC index cases, 628 OC cases, and 2187 geographically matched controls were...
screened for LoF mutations within the FANCM gene by next-generation sequencing. All patients previously tested negative for pathogenic BRCA1 and BRCA2 mutations. All data collection occurred between June 1, 2013, and April 30, 2016. Data analysis was performed from May 1, 2016, to July 1, 2016. FANCM LoF mutation frequencies in patients with BC and/or OC were compared with the FANCM LoF mutation frequencies in geographically matched controls by univariate logistic regression. Positive associations were stratified by age at onset and cancer family history. In this case-control study, 2047 well-characterized familial female BC index cases, 628 OC cases, and 2187 geographically matched controls were screened for truncating FANCM alterations. Heterozygous LoF mutations within the FANCM gene were significantly associated with familial BC risk, with an overall odds ratio (OR) of 2.05 (95% CI, 0.94-4.54; P = .049) and a mutation frequency of 1.03% in index cases. In familial patients whose BC onset was before age 51 years, an elevated OR of 2.44 (95% CI, 1.08-5.59; P = .02) was observed. A more pronounced association was identified for patients with a triple-negative BC tumor phenotype (OR, 3.75; 95% CI, 1.00-12.85; P = .02). No significant association was detected for unselected OC cases (OR, 1.74; 95% CI, 0.57-5.08; P = .27). Based on the significant associations of heterozygous LoF mutations with early-onset or triple-negative BC, FANCM should be included in diagnostic gene panel testing for individual risk assessment. Larger studies are required to determine age-dependent disease risks for BC and to assess a potential role of FANCM mutations in OC pathogenesis.