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Titel des Beitrags: Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia.

Abstract: The distribution of histopathological features of invasive breast tumors in BRCA1 or BRCA2 germline mutation carriers differs from that of individuals with no known mutation. Histopathological features thus have utility for mutation prediction, including statistical modeling to assess pathogenicity of BRCA1 or BRCA2 variants of uncertain clinical significance. We analyzed large pathology datasets accrued by the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) and the Breast Cancer Association Consortium (BCAC) to reassess histopathological predictors of BRCA1 and BRCA2 mutation status, and provide robust likelihood ratio (LR) estimates for statistical modeling. Selection criteria for study/center inclusion were estrogen receptor (ER) status or grade data available for invasive breast cancer diagnosed younger than 70 years. The dataset included 4,477 BRCA1 mutation carriers, 2,565 BRCA2 mutation carriers, and 47,565 BCAC breast cancer cases. Country-stratified estimates of the likelihood of mutation status by histopathological markers were derived using a Mantel-Haenszel approach. ER-positive phenotype negatively predicted BRCA1 mutation status, irrespective of grade (LRs from 0.08 to 0.90). ER-negative grade 3 histopathology was more predictive of positive BRCA1 mutation status in women 50 years or older (LR = 4.13 (3.70 to 4.62)) versus younger than 50 years (LR = 3.16 (2.96 to 3.37)). For BRCA2, ER-positive grade 3 phenotype modestly predicted positive mutation status irrespective of age (LR = 1.7-fold), whereas ER-negative grade 3 features modestly predicted positive mutation status at 50 years or older (LR = 1.54 (1.27 to 1.88)). Triple-negative tumor status was highly predictive of BRCA1 mutation status for women younger than 50 years (LR = 3.73 (3.43 to 4.05)) and 50 years or older (LR = 4.41 (3.86 to 5.04)), and modestly predictive of positive BRCA2 mutation status in women 50 years or older (LR = 1.79 (1.42 to 2.24)). These results refine likelihood-ratio estimates for predicting BRCA1 and BRCA2 mutation status by using commonly measured histopathological features. Age at diagnosis is an important variable for most analyses, and grade is more informative than ER status for BRCA2 mutation carrier prediction. The estimates will improve BRCA1 and BRCA2 variant classification and inform patient mutation testing and clinical management.

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