

Associations between breast cancer subtypes and mutations in cancer predisposition genes identified by clinical genetic testing of breast cancer patients

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Clinical genetic testing of individuals with a personal or family history of breast and ovarian cancer using panels for *BRCA1/2* and other candidate cancer predisposition genes has become routine clinical practice. Several of the genes on hereditary cancer testing panels have been strongly associated with specific subtypes of breast cancer. In particular, individuals with germline mutations in *BRCA1* predominantly develop estrogen receptor (ER)-negative and triple negative (TN) (estrogen receptor negative, progesterone receptor negative, HER2 negative) breast tumors. In contrast, *CHEK2* and *ATM* mutations have been associated with ER-positive breast cancer. In this study, associations between mutations in panel genes and breast cancer subtypes were evaluated. A cohort of 50,000 breast cancer patients tested for germline cancer predisposing mutations using hereditary cancer gene panels was utilized. Information on personal and family cancer history, age of diagnosis, tumor pathology, and ethnicity of patients was obtained from test requisition forms or by follow up with ordering health care providers. Mutations in each gene were combined into four histological subtypes (triple negative; HER2 positive; ER-positive,HER2-positive; and ER-positive,HER2 negative). Associations for each subtype were estimated by case-control analyses comparing the frequencies of pathogenic mutations in each subtype with frequencies from non-TCGA controls from the Exome Aggregation Consortium (ExAC) database. In addition, case-case analyses were conducted to assess enrichment of gene mutations in specific breast cancer subtypes. This large study of panel tested breast cancer patients provides important information on pathological correlates that may prove important for clinical risk management of patients with inherited mutations.