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Associations between hereditary cancer panel predisposition genes and breast cancer histological subtypes

Section: Epidemiology—Genetic & Molecular

Background: Clinical panel testing has become routine practice for patients that are diagnosed with breast cancer at a young age and/or have a personal or family history of cancer. Associations with known breast cancer genes and breast cancer subtypes have been previously identified, such as *BRCA1* associations with estrogen receptor negative (ER-) and triple negative (ER-/PR-/HER2-) breast cancers. However, the cancer predisposition genes associated with each of the four clinical subtypes of breast cancer have not been fully defined. We evaluated 24,901 Caucasian female breast cancer cases receiving clinical panel testing for 23 cancer predisposition genes and assessed associations between mutations in each gene and breast cancer subtypes.

Methods: Germline hereditary cancer multigene panel testing results for cancer predisposition genes were obtained for 24,901 Caucasian female breast cancer cases evaluated by a clinical testing laboratory. Information on tumor histology, personal and family history of cancer, age at diagnosis, and previous genetic testing was provided by clinical care providers of patients receiving clinical cancer genetic testing. Breast cancer cases were classified into clinical breast cancer subtypes based on estrogen/progesterone hormone receptor status (HR) and HER2 status: Luminal A (HR+/HER2-), Luminal B (HR+/HER2-), HER2 subtype (HR-/HER2+), and Triple Negative (HR-/HER2-). The frequency of pathogenic or likely pathogenic mutations observed in each subtype was compared against the Exome Aggregation Consortium (ExAC) non-TCGA non-Finnish European population to estimate risks.

Results: *ATM* was associated with moderate risks (odds ratio (OR)>2.0) of Luminal A, Luminal B, and HER2 subtypes of breast cancer, but was not associated with the Triple Negative subtype. *PALB2* was associated with moderate risk for Luminal B subtype, but high risk (OR>5.0) for Luminal A, HER2, and triple negative subtypes. *TP53* was associated with high risks for Luminal B and HER2 tumors. *NBN, MRE11A*, and *RAD50* were not associated with any subtype of breast cancer.

Conclusions: Identifying associations between inherited mutations (odds ratio (OR)>2.0) and breast cancer subtypes can inform clinical risk management, treatment options, and therapeutic development efforts.