Racial and ethnic differences in hereditary cancer multi-gene panel testing results among breast cancer patients

Hermela Shimelis, Eric C. Polley, Jenna Lilyquist, Jie Na, Chunling Hu, Kun Y. Lee, Steven Hart, Raymond Moore, David E. Goldgar, Amal Yussuf, Brigette Tippin-Davis, Tina Pesaran, Jill S. Dolinsky, Fergus J. Couch, Holly LaDuca

Recently, the use of next-generation sequencing panels to aid in the diagnosis of hereditary cancer predisposition has increased. The discovery of pathogenic variants (PVs) in known susceptibility genes leads to focused screening and prevention strategies of individuals at increased risk of cancer. However, studies supporting the utility of multi-gene panel testing have focused on Caucasian individuals. In order to understand the influence of results from panel testing on breast cancer (BC) risk in non-Caucasian individuals, we studied BC cases who underwent hereditary cancer panel testing at Ambry Genetics between 2012 and 2016. The frequency of PVs and variants of unknown significance (VUS) in African American, Asian, Caucasian and Hispanic populations was assessed, and gene-specific BC risk associations were estimated for each population by comparing PV frequencies between BC cases and gnomAD African/African American, East Asian, non-Finnish European and Latino reference controls, respectively. African American, Hispanic and Asian (non-white) BC cases had significantly younger ages at testing relative to Caucasians ($p<0.05$), suggesting population-specific differences in panel testing referral. Across 21 known and candidate BC predisposition genes, similar overall frequencies of PVs were identified in African American, Hispanic, and Caucasian BC cases (~11%) whereas the PV frequency was relatively lower in Asian cases (~8%). VUS frequency was significantly higher in non-Caucasian BC cases, with the VUS frequency highest among Asian cases. In an exploratory analysis of population-specific BC risk associations, PVs in *BRCA1*, *BRCA2*, and *PALB2* were associated with high risk of BC across all ethnic groups. However, PVs in the *ATM*, *CHEK2*, *MSH6*, *BARD1* and *RAD51D* moderate risk genes showed population-specific associations with BC. These studies provide important insights into the risks of BC associated with predisposition gene mutations in non-Caucasian populations and demonstrate the need for continued investigation of population-specific factors contributing to inherited BC risk.