e12548 Publication Only

Older-onset hereditary breast and ovarian cancer (HBOC) syndrome patients and clinical value of germline multigene testing.

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Background: Germline genetic testing referral of HBOC syndrome and relevant cancer patients is being undertaken using criteria that maximize the probability of finding a disease-causing variant and its actionability. In young onset breast cancer (BC, ≤50 y), invasive epithelial non-mucinous ovarian cancer, metastatic or node positive prostate cancer and exocrine pancreatic cancer, germline genetic testing is universally accepted. Genetic testing in older onset BC patients (>50 y) uses strict clinical criteria like triple negative phenotype or bilateral BC and the presence of family history (FH). This study investigated genetic differences between young- and older-onset HBOC patients to estimate whether the threshold of the likelihood of finding a disease-causing variant can be lowered. **Methods:** In this study we characterized the mutational landscape of a total of 7.694 suspected HBOC related syndrome individuals, that were referred- regardless of age and FH- for multigene genetic testing using NGS technology, during the period 2020-2024 in GENEKOR MEDICAL S.A. Among the examined individuals, 1,677 (21.8%) were carriers of a pathogenic/likely pathogenic variant and the reason of referral was breast cancer in 90.6%, ovarian cancer in 14.7%, pancreatic cancer in 3.50% and prostate cancer in 1.5% of the cases. **Results:** Among young BC patients the highest proportion of pathogenic variants were identified in *BRCA1* (21%), *CHEK2* (17.2%), *BRCA2* (14.5%), *ATM* (5.5%) and *PALB2* (3.8%), while FH does not change the landscape of genes mutated. In older BC patients the percentages were modified as following: *BRCA2* (14.6%), *CHEK2* (14.2%), *BRCA1*(13.4%), *PALB2* (3.8%) and *ATM* (5.6%). Even without FH, pathogenic variants, were still detected but in slightly lower percentages in the following genes *CHEK2* (7.7%), *BRCA1* (7.7%) and *PALB2* (7.7%) in this cohort. **Conclusions:** The results of this study provide some evidence that the mutational landscape among young-onset BC patients is not different from those of older-onset BC patients, even when taking FH into account. Following strictly the age limit cut-off combined with FH as proposed by international guidelines would result in overlooking 1% of gene-testing positive BC patients and defective management of their families. Research Sponsor: None.