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Co-occurrence of germline pathogenic variants in breast cancer predisposition genes: a study in Northeast Brazil

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Introduction: Breast cancer is the most common and deadliest cancer diagnosed in women worldwide. Approximately 5–10% of cases are attributed to germline pathogenic (P) or likely pathogenic (LP) variants in cancer predisposition genes. Increased use of next-generation sequencing to detect these mutations, driven by their predictive and prognostic value for patients and families, has led to greater identification of individuals with multiple (P/LP) variants. However, the co-occurrence of multiple germline pathogenic variants in breast cancer genes is rare, and their impact on carrier cancer risk remains unclear. **Objective:** To comprehensively define the pattern and frequency of co-occurring pathogenic/likely pathogenic mutations within a breast cancer patient cohort from Ceará. **Methods:** This cross-sectional study examined patients from a private oncology clinic in Ceará, Brazil, who met the clinical criteria for Hereditary Breast and Ovarian Cancer predisposition (HBOC). Molecular analyses were conducted using commercial multi-gene cancer panels from accredited laboratories between 2018 and 2023. Sequencing was performed using next-generation sequencing capture panels that included 27 to 84 genes depending on clinical suspicion. **Results:** Among 1,055 patients, 141 (13.4%) carried a germline P/LP variant in HBOC genes. Of those, 135 (95.4%) had one (P/LP) variant, while 6 (4.6%) had two (P/LP) variants. In the entire cohort, the most frequently mutated gene was BRCA1 (34.8%), followed by BRCA2 (15.2%), CHEK2 (14.1%), PALB2, ATM, MUTYH, RAD51, TP53, and NF1. Among patients with co-occurring mutations, a common pattern involved variants in BRCA1 and MUTYH, observed in five patients. One patient presented with a triple co-occurrence of BRCA1, MUTYH, and BARD. The remaining co-occurrence case involved ATM and BRCA2. **Conclusion:** This study uncovers co-occurring germline variants in breast cancer predisposition genes in Northeast Brazil, highlighting potential regional genetic specificities. The clinical implications of these co-occurrences remain uncertain, emphasizing the necessity for prospective cohorts to ascertain whether current risk assessments need adaptation for this population and to guide personalized management.

Keywords: breast neoplasms; risk management; mutation.