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1143 – Genetic and model-based risk stratification reshapes clinical management in women considering hormone replacement therapy

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Introduction: Hormone replacement therapy (HRT) effectively relieves menopausal symptoms, yet its association with breast cancer (BC) risk varies substantially by regimen and individual genetic susceptibility. In Brazil, HRT has also been utilized in less studied formulations, such as subcutaneous gestrinone implants. To our knowledge, no previous study has systematically examined the impact of integrating genetic counseling (GC) and genomic risk modeling specifically within the HRT decision-making context.

Methods: A retrospective cohort study of 144 women referred to a Brazilian private oncogenetics service between September 2022 and May 2025 for BC risk assessment related to HRT initiation or continuation. Genetic testing followed 2025 NCCN criteria; however women that did not meet the formal criteria could still undergo testing after shared decision-making. Clinical recommendations were based on CanRisk v3.0.0 thresholds for MRI surveillance, chemoprevention, and risk-reducing surgery.

Results: Among 144 women (mean age: 51 years), 135 underwent genetic testing. Fourteen (10.4%) carried pathogenic variants in BC susceptibility genes, including BRCA1/2, PALB2, ATM, CHEK2, RAD51C/D, and BARD1. The integration of GC and CanRisk changed clinical management in 29 patients (21.5%). Chemoprevention recommendations were modified in 13 women (9.7%), and MRI surveillance recommendations changed in 13 (9.6%). In addition, 9 women (6.7%) received new recommendations for risk-reducing surgery due to high-penetrance variants. Notably, one prophylactic mastectomy revealed early-stage ductal carcinoma in situ.

Conclusion: The HRT consultation may represent a valuable opportunity to identify women with unrecognized hereditary BC risk and refine prevention strategies. To our knowledge, this is the first Brazilian study to integrate personal and family history, germline testing, and CanRisk modeling within the HRT decision-making context. These findings propose a structured, risk-stratified pathway for managing this population, a novel paradigm to be further validated in larger, multicenter cohorts.

Ethics: CAEE 88951825.5.0000.5249.

Keywords: hormone replacement therapy; genetic risk score; breast neoplasms; hereditary breast and ovarian cancer syndrome; precision medicine.