Genetic Risk Stratification for Breast Cancer in Patients Considering or Undergoing Hormone Replacement Therapy

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Abstract

In a Brazilian oncogenetics service, 144 women who sought consultation regarding hormone replacement therapy (HRT) underwent comprehensive evaluation, including genetic counseling, germline testing, and CanRisk assessment.

Although HRT was the primary indication for referral, most patients (69.4%) met National Comprehensive Cancer Network (NCCN) criteria for genetic testing, and 135 proceeded with germline testing after appropriate counseling and assessment. The integration of these tools led to management changes in 21.5% (29/135) of tested women, involving both escalation and de-escalation of chemoprevention and MRI screening, as well as new indications for risk-reducing surgery.

Fourteen pathogenic variants (10.4%) were identified, primarily in *BRCA1/2*, *PALB2*, and *RAD51C/RAD51D*. These results demonstrate that HRT consultations represent a valuable opportunity to identify substantial unrecognized hereditary cancer risk, highlighting the utility of individualized risk assessment to optimize both HRT safety and clinical decision-making.

Introduction

Hormone replacement therapy (HRT) is a widely recommended strategy for relieving menopausal symptoms, particularly for healthy women under 60 years of age or within 10 years of menopause.

However, HRT has been excessively used in Brazil, including less studied compounds and delivery methods, such as subcutaneous implants of gestrinone.

Although HRT provides symptomatic benefits, the increased risk of breast cancer has already been confirmed with certain types of hormone therapy.

While numerous risk factors, such as age at menarche, menopause, parity, and obesity, are well established, 5–10% of breast cancer cases are linked to hereditary genetic predisposition. In this context, tools such as CanRisk, when integrated with genetic counseling (GC) and germline testing, enable personalized risk assessment and inform clinical decision-making.

Objective

To investigate how genetic counseling (GC) and CanRisk (v3.0.0) influence BC risk stratification and modify screening and prevention recommendations in women using or planning HRT

Methods

Hormone Replacement Therapy

Exploratory, quantitative, retrospective study
Sep/2022 - May/2025

Private oncogenetics clinic
Brazil

INCLUSION CRITERIA

≥ 18 Years old
no personal history of breast cancer
data recorded in medical record

1 **PRE-TESTING CONSULTATION**

Data Collected: Data Collected: personal history, family cancer history, sociodemographics, lifestyle, and gynecological history. We assessed whether samples met the NCCN criteria for genetic testing; genetic testing was requested accordingly, and **the initial CanRisk score was calculated**

2 **GENETIC TESTING**

Germline testing
Pathogenic variants
Risk genes analysis

Electronic medical records

3 **POST-TESTING CONSULTATION**

Updated CanRisk
Management changes
Chemoprevention
MRI surveillance
Risk-reducing surgery

Breast MRI for lifetime BC risk > 20%

Chemoprevention for 5-year BC risk > 1.7% 10-year 5%

Risk-reducing surgery for carriers of high-penetrance PVs

Descriptive Data Analysis

Results

144
Total Women
Mean age: **51 years**

→ **100**
69.4%
Met NCCN criteria

→ **135**
Total Women Tested

44 (30.6%)
Didn't meet criteria

21.5%
of patients were reclassified
29 out of 135 women had management changes

Chemoprevention
9.7%
Adjusted indication
↓9 lost | ↑4 gained

MRI Surveillance
9.6%
Modified indication
↓5 lost | ↑8 gained

Surgery
6.7%
new indications
9 women
with high-penetrance PVs

14 Pathogenic Variants

10.4% of tested women (n=14/135)

BRCA1	29%	4
ATM	21%	3
BRCA2	14%	2
PALB2, CHEK2, RAD51C, RAD51D, BARD1	36%	1/each

BRCA1 (4): Bilateral mastectomy + salpingo-oophorectomy

BRCA2 (2): Bilateral mastectomy (±salpingo-oophorectomy)

PALB2 (1): Bilateral mastectomy

RAD51C/D (2): Bilateral salpingo-oophorectomy

Clinical finding: 1 patient diagnosed with DCIS during prophylactic mastectomy

Discussion

The integration of genetic counseling, germline testing, and the CanRisk predictive model into hormone replacement therapy (HRT) consultations had an impact on cancer prevention strategies. This approach led to risk reclassification and management changes for 21.5% (29/135) of tested women, with significant adjustments to screening protocols, chemoprevention recommendations, and indications for risk-reducing surgery, encompassing both intensification and relaxation of interventions. Although HRT counseling was the main reason for referral, the majority of participants (69.4%, 100/144) met National Comprehensive Cancer Network (NCCN v.3.2025) criteria for genetic testing, highlighting that HRT consultations capture women with underlying hereditary cancer risk. Among those not meeting NCCN criteria (44 women), a high uptake of germline testing was observed (40/44, 90.9%), suggesting that the HRT decision-making process may enhance risk perception and support more informed shared choices. This study demonstrates that HRT evaluation provides a valuable opportunity to identify women eligible for genetic assessment, and that the integration of clinical, familial, and genetic factors via CanRisk modeling with germline testing results in alterations to clinical management in approximately one-fifth of tested patients. These findings support integrating comprehensive genetic risk assessment into routine HRT counseling workflows when patients present with clinical features or personal/family cancer history meeting established genetic testing criteria. Further research is warranted to assess long-term clinical outcomes and implementation feasibility across diverse healthcare settings.

Conclusions

The integration of genetic counseling, germline testing, and CanRisk modeling within hormone replacement therapy (HRT) evaluation led to management changes for 21.5% (29/135) of tested women.

Interventions included increase of screening protocols through the addition of breast MRI surveillance, adjustment of chemoprevention, and new recommendations for risk-reducing surgeries, including mastectomy and salpingo-oophorectomy. Risk reclassification was achieved through the identification of pathogenic variants and the incorporation of detailed family history into CanRisk modeling, which yielded updated lifetime risk estimates.

Notably, most women presenting for HRT consultation (100/144, 69.4%) already fulfilled established criteria for genetic evaluation, indicating that this clinical setting identifies a population with hereditary cancer risk that may not have been previously recognized or referred.

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