# Hereditary Breast Cancer in the Moderate-Risk Spectrum: Surgical Practices and Risk of Second Primary Tumors

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## Introduction

Hereditary breast cancer represents 5–10% of all cases. While *BRCA1/2* mutations are well-established, moderate-penetrance genes also contribute to risk, though their clinical implications remain underexplored. Optimal surgical strategies and surveillance, particularly regarding second primary tumors (SPTs), lack consensus.

## Methods and Materials

A retrospective study was conducted at A.C. Camargo Cancer Center, São Paulo, Brazil, including women diagnosed with breast câncer (BC) and pathogenic variants (PVs) in moderate-penetrance genes (*PALB2, CHEK2, ATM, RAD family, BRIP, BARD, FANC*) between 2016–2025.

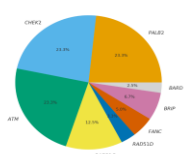
## Results

Among the 1,429 patients who underwent genetic testing, 120 showed mutations in genes with moderate penetrance. Table 1 contains the clinical and histopathological characteristics of the patients. The type of surgery performed, prevalence of SPTs, as well as rate of distant recurrence are represented in the graphs on the side

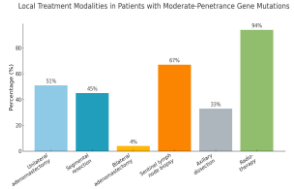
Table 1. Clinical and Histopathological Characteristics of Patients With Moderate-Penetrance Gene Mutations

| Characteristic | n= 120 |
|---|---|
| **Sex** | 100% Female |
| **Median Age** | 42 (±9,27) |
| **Ethnicity** | White 70%; Mixed-race 12%; Black 4%; Asian 1%; Undeclared 13% |
| **Family history of cancer** | 73% |
| **Stage at breast cancer diagnosis** | I: 54%<br>II: 27%<br>III: 19% |
| **Histology** | Invasive ductal carcinoma: 79%<br>Invasive lobular carcinoma: 11%<br>Others: 10% |
| **SBR Grade** | 3: 63%<br>2: 30%<br>1: 7% |
| **Nuclear Grade** | 2: 57%<br>3: 40%<br>1: 3% |
| **Molecular subtypes** | Luminal B: 24%;<br>Luminal HER2-low: 23%;<br>HER2-overexpressing Luminal B: 19%;<br>Triple-negative (TNBC): 18%;<br>Luminal A: 10% |
| **Contralateral synchronous breast cancer** | 2% (3 patients) |

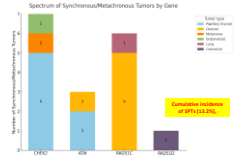
Relative Frequency of Moderate-Penetrance Gene Mutations




Local Treatment Modalities in Patients with Moderate-Penetrance Gene Mutations




Spectrum of Synchronous/Metachronous Tumors by Gene




Local vs Distant Recurrence by Gene




## Conclusions

The most frequent surgery was unilateral mastectomy. Carriers of PVs in moderate-penetrance genes had a low BC recurrence rate (6.6%) but a high cumulative incidence of second primary tumors (**13.2%**), primarily thyroid and ovarian cancers. This highlights the critical need for extended, organ-specific surveillance strategies

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