The prognosis of invasive early hormone receptor positive HER2 negative breast cancer in women harboring a pathogenic or likely pathogenic *TP53* germline variant.

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Introduction

Hormone receptor (HR) positive HER2 negative breast cancer (BC) is the most common cancer affecting women in general as well as women with a pathogenic/likely pathogenic (P/LP) germline variant in *TP53* (*TP53*-associated BC). However, while most HR+/HER2- BC in the general population has a good prognosis, early HR+/HER2- invasive BC in *TP53* carriers seems to have a worse prognosis in comparison to other BC subtypes.[1] To investigate the prognostic value of HR expression in *TP53*-associated BC, we analyzed real-world data from a large international cohort of *TP53* germline P/LP women with BC and comprehensive treatment data and follow-up.

1.Sandoval RL, et al. J Natl Cancer Inst. 2024 Aug 1;116(8):1246-1254.

Materials and Methods

Women (age ≥18 years) with a first invasive nonmetastatic *TP53*-associated BC, diagnosed between 2000 and 2020, were identified from an international multicenter database created in 2022. This ongoing international collaboration involves 10 institutions from USA, Brazil, France, and Italy.

Total cohort (data pull May 2025)	**N= 463**
Exclusions	
First BC diagnosis <2000 or >2020	105 (22.7%)
TP53 variant downgrade	1 (0.2%)
P/LP germline variant in other BC genes	11 (2.4%)
Clonal hematopoiesis of indeterminate potential	6 (1.3%)
DCIS or stage IV de novo	83 (17.9%)
HR status missing	7 (1.5%)
Final cohort for this analysis	**n= 250 (54.0%)**

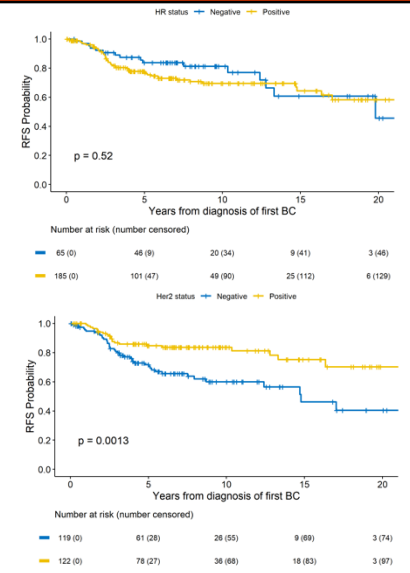
Restrospective and prospective data are collected. Tumor size, nodal involvement and tumor features were based on pathological staging and final surgical specimens. For patients who received neoadjuvant therapy, we used clinical staging and pathology reports from the initial biopsy. Recurrence free survival in 5 years was estimated by Kaplan-Meier method according to HR status and BC subtype. Log-rank test was reported. RFS was defined as time from primary diagnosis of the first BC to first recurrence (local, regional, distant) or death. Patients without events were censored at last follow-up date. Univariate analyses included age, year of diagnosis, tumor size, grade, nodal involvement, HER2 status, type of breast surgery, radiation therapy and neo/adjuvant chemotherapy. Chi-square test was used for comparison of type of recurrence events by HR status and BC subtype.

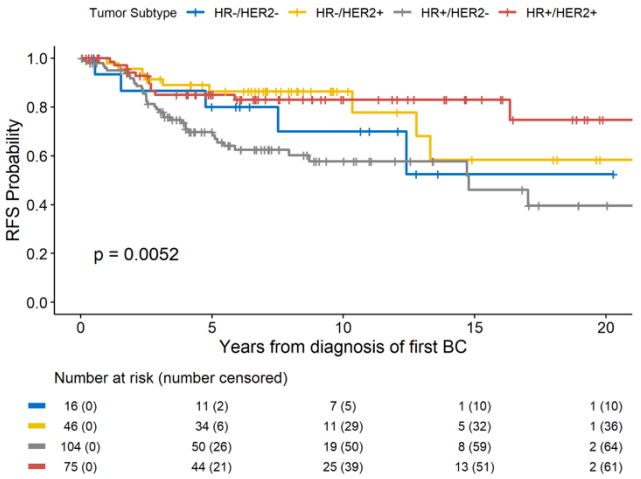
Results

	Overall (N=250)
Age at first BC diagnosis	
Age< =45	196 (78.4%)
Age >45	54 (21.6%)
Year of diagnosis	
2000-2010	70 (28.0%)
2011-2020	180 (72.0%)
Tumor size	
Occult carcinoma	1 (0.4%)
T1,T2	212 (84.8%)
T3,T4	20 (8.0%)
Unknown	17 (6.8%)
Stage	
I-II	182 (72.8%)
III	51 (20.4%)
Unknown	17 (6.8%)
Nodal involvement	
N0	109 (43.6%)
N1	81 (32.4%)
N2	28 (11.2%)
N3	12 (4.8%)
Nx	20 (8.0%)
Tumor grade	
Grade 1	5 (2.0%)
Grade 2/3	214 (85.6%)
Unknown	31 (12.4%)

	Overall (N=250)
Hormone receptor	
Negative	65 (26.0%)
Positive	185 (74.0%)
HER2 status	
Negative	119 (47.6%)
Positive	122 (48.8%)
Unknown	9 (3.6%)
Tumor subtype	
HR+/HER2+	75 (30.0%)
HR+/HER2-	104 (41.6%)
HR-/HER2+	46 (18.4%)
HR-/HER2-	16 (6.4%)
HR+/HER2 unknown	6 (2.4%)
HR-/HER2 unknown	3 (1.2%)
Surgery type	
Breast-conserving surgery	55 (22.0%)
Mastectomy	186 (74.4%)
Unknown	9 (3.6%)
Adjuvant radiation therapy	
Yes	93 (37.2%)
No	142 (56.8%)
Unknown	15 (6.0%)
Chemotherapy (any)	
Yes	203 (81.2%)
No	45 (18.0%)
Unknown	2 (0.8%)
Endocrine therapy	
Yes	166 (66.4%)
No	72 (28.8%)
Unknown	12 (4.8%)

The median age of first BC diagnosis was 34.5 years (range 19.0-81.0), 74.0% were HR+. Most tumors were HR+/HER2- (41.6%). With a median follow-up of 7.2 years (IQR 4.7-13.4), the 5-year RFS for the overall cohort was 79% (95%CI: 74%-85%). In total 55 patients had recurrences, 25 loco-regional only, and 30 distant relapses.





RFS was not statistically different between HR+ vs HR- tumors. HER2- tumors were associated with a worse outcome in comparison to HER2+ tumors (5y-RFS rate 72% vs 85%, p<.01).

By BC subtype, HR+HER2- tumors also had a worse outcome in comparison to other subtypes (5y-RFS rate 70% vs 86%, p<.001), and relapsed more frequently as distant metastasis (66.7% vs 36.4%, p=0.027).

Recurrence events	HR+/HER2- n=33	Others n=22	p value
Recurrence type			0.027
Loco-regional	11 (33.3%)	14 (63.6%)	
Distant	22 (66.7%)	8 (36.4%)	

In the univariate analysis, age, year of diagnosis, tumor size, grade, nodal involvement, surgery type, chemotherapy and radiation therapy were not associated with RFS in this cohort.

Conclusions

In this large cohort of *TP53*-associated BC, we confirmed a worse outcome for HR+/HER2- tumors, with higher rates of distant relapse, as is seen in other young women with this subtype. Further work will focus on possible mechanisms and therapeutic implications.

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