PS3-01-17: Brca1/2 mutation status and its prognostic implications in breast cancer: A 10-year survival analysis in Peru

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Background

Breast cancer is a heterogeneous disease with a multifactorial etiology involving genetic, environmental, and lifestyle factors. Among hereditary forms, mutations in the *BRCA1* and *BRCA2* genes are the most well-established genetic risk factors, accounting for approximately 20–25% of hereditary cases and 5–10% of all breast cancer diagnoses. These tumor suppressor genes play essential roles in maintaining genomic stability through homologous recombination DNA repair; when mutated, they increase susceptibility to early-onset breast cancer, bilateral tumors, and other associated malignancies, particularly ovarian cancer. The primary objective of this study was to characterize and compare the clinical, pathological, and survival profiles of Peruvian breast cancer patients according to *BRCA*1 and *BRCA*2 mutation status, and to evaluate the prognostic impact of these variants on overall survival within a national cohort.

Methods and Materials

This study includes individuals diagnosed with breast cancer who were referred for Medical Genetics evaluation at the Instituto Nacional de Enfermedades Neoplásicas (INEN) between August 2013 and March 2020. Patients who met the clinical criteria for inclusion in the inter-institutional protocol INEN13-48: "Study of Hereditary and Familial Cancer in the Peruvian Population," as part of the "Molecular Genetic Studies in Cancer Patients and Their Relatives" (IRB #96144, City of Hope [COH]), underwent genetic testing performed at COH. A total of 1,441 breast cancer patients were analyzed. Group comparisons according to BRCA status (*BRCA*1, *BRCA*2, and *BRCA*-negative) were performed using the Kruskal-Wallis test for age at diagnosis and Chi-squared or Fisher's exact tests for clinical stage, molecular subtype, Ki-67 index, and histological grade. Propensity score matching was applied in a 1:2 ratio, balancing age at diagnosis, clinical stage and first-degree family history, resulting in 426 matched patients. Ten-year overall survival was assessed using Cox proportional hazards regression models, incorporating left truncation at study entry to account for delayed inclusion.

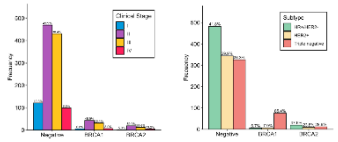
Results

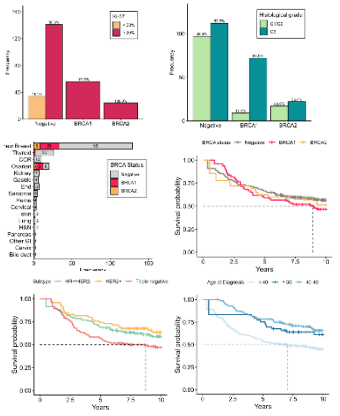
Only patients with breast cancer were included, and for those with multiple primary cancers, age, stage, subtype, Ki-67, and histological grade were selected specifically from the breast cancer diagnosis.

Table1. Female with CANCER_DIAGP = Breast or Breast/Ovarian (N = 1441)

Characteristic	Overall N = 1,441	Negative N = 1,269	BRCA1 N = 95	BRCA2 N = 47	p-value
Age at Diagnosis	41 (18-84)	41 (18-84)	39 (22-64)	42 (24-73)	0.042
Clinical Stage					
I	129 (10.3%)	121 (10.8%)	6 (6.8%)	2 (5.3%)	
II	532 (42.7%)	470 (41.9%)	43 (48.9%)	19 (50.0%)	
III	475 (38.1%)	431 (38.4%)	32 (36.4%)	12 (31.6%)	
IV	111 (8.9%)	99 (8.8%)	7 (8.0%)	5 (13.2%)	
Unknown	194	178	7	9	
Subtype					<0.001
HR+/HER2-	508 (39.6%)	482 (41.8%)	6 (6.7%)	20 (47.6%)	
HER2+	361 (28.1%)	344 (29.9%)	7 (7.9%)	10 (23.8%)	
Triple negative	414 (32.3%)	326 (28.3%)	76 (85.4%)	12 (28.6%)	
Unknown	158	147	6	5	
Ki-67					<0.001
≥ 20%	221 (86.7%)	141 (80.6%)	56 (100.0%)	24 (100.0%)	
< 20%	34 (13.3%)	34 (19.4%)	0 (0.0%)	0 (0.0%)	
Unknown	1,186	1,124	39	23	
Histological grade					<0.001
G3	206 (62.6%)	112 (53.6%)	72 (88.9%)	22 (56.4%)	
G1/G2	123 (37.4%)	97 (46.4%)	9 (11.1%)	17 (43.6%)	
Unknown	1,112	1,090	14	8	
Second Cancer					<0.001
No	1,213 (84.2%)	1,119 (86.1%)	59 (62.1%)	35 (74.5%)	
Yes	228 (15.8%)	180 (13.9%)	36 (37.9%)	12 (25.5%)	
Type of Second Cancer					
new Breast	129 (56.6%)	96 (53.3%)	25 (69.4%)	8 (66.7%)	
Thyroid	26 (11.4%)	24 (13.3%)	2 (5.6%)	0 (0.0%)	
Ovarian	20 (8.8%)	8 (4.4%)	9 (25.0%)	3 (25.0%)	
CCR	10 (4.4%)	10 (5.6%)	0 (0.0%)	0 (0.0%)	
End	7 (3.1%)	6 (3.3%)	0 (0.0%)	1 (8.3%)	
Kidney	7 (3.1%)	7 (3.9%)	0 (0.0%)	0 (0.0%)	
Gastric	6 (2.6%)	6 (3.3%)	0 (0.0%)	0 (0.0%)	
Sarcoma	5 (2.2%)	5 (2.8%)	0 (0.0%)	0 (0.0%)	
Cervical	4 (1.8%)	4 (2.2%)	0 (0.0%)	0 (0.0%)	
Heme	4 (1.8%)	4 (2.2%)	0 (0.0%)	0 (0.0%)	
H&N	2 (0.9%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	
Lung	2 (0.9%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	
skin	2 (0.9%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	
Bile duct	1 (0.4%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Cervix	1 (0.4%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Other GI	1 (0.4%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Pancreas	1 (0.4%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Bladder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown	1,213	1,119	59	35	

Kruskal-Wallis rank sum test; NA: Pearson's Chi-squared test; Fisher's exact test





Univariate and Multivariate Cox Proportional Hazards Regression Models for 10-Year Overall Survival from Diagnosis

Time-to-event was calculated from the date of cancer diagnosis to the date of death (uncensored), with follow-up for patients alive at 10 years. Some of the delayed entry patients were included in the risk set only from the time of study entry (left-truncation). Patients who were alive beyond 10 years were administratively censored at that time point.

Propensity Score Matching: It was performed in a ratio of 1:2 matching and balances covariates (Age at Diagnosis, Clinical Stage and First-Degree Family History (OCJD/PCJD)) between groups. Each BRCA1/2-positive case was matched to a BRCA1/2-negative control with a similar propensity score.

Table2. Female with CANCER_GROUP= Breast or Breast/Ovarian - unmatched cases after Propensity Score Matching (N = 426)

Characteristic	N	Univariate HR	Univariate 95% CI	Univariate p-value	N	Multivariate HR	Multivariate 95% CI	Multivariate p-value
Age at Diagnosis	371							
< 40		—	—					
≥ 50		0.57	0.31, 1.05	0.07				
40–49		0.65	0.43, 0.97	0.037				
BRCA status	371							
Negative		—	—					
BRCA1		1.58	1.05, 2.42	0.029				
BRCA2		1.02	0.55, 1.89	>0.9				
Clinical Stage	333				310			
I/II		—	—		—	—	—	
III/V		4.3	2.80, 6.62	<0.001	4.37	2.79, 6.85	<0.001	
Subtype	335							
HR+/HER2-		—	—					
HER2+		0.94	0.54, 1.61	0.8				
Triple negative		1.59	1.04, 2.44	0.033				
Ki-67	112							
< 20%		—	—					
≥ 20%		1.96	0.47, 8.11	0.4				
Histological grade	147							
G1/G2		—	—					
G3		1.37	0.72, 2.63	0.3				

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

Discussion

A total of 1,441 breast cancer patients were analyzed based on *BRCA* mutation status (*BRCA*-negative, *BRCA*1+, and *BRCA*2+). Significant clinicopathological differences were observed between the groups. The median age at diagnosis was 41 years (range: 18–84). *BRCA*1 carriers were diagnosed at a significantly younger age (median: 39 years) than *BRCA*-negative and *BRCA*2 patients (p = 0.042). Clinical stage II was the most frequent in all groups (~43%). Although no statistically significant differences were observed in stage distribution, stage IV was slightly more prevalent in *BRCA*2 (13.2%). Molecular subtypes differed significantly between groups (p < 0.001): *BRCA*1: Predominantly triple-negative tumors (85.4%) and *BRCA*2: Higher proportion of HR+/HER2– tumors (47.6%). Regarding tumor proliferation, a Ki-67 index ≥ 20% was observed in 100% of *BRCA*1 and *BRCA*2 patients, significantly higher than in *BRCA*-negative patients (80.6%, p < 0.001). The presence of a second cancer was more frequent in *BRCA*1+ (37.9%) and *BRCA*2+ (25.5%) patients compared to *BRCA*-negative individuals (13.9%, p < 0.001). The most common type was a second breast cancer (69.4% in *BRCA*1; 66.7% in *BRCA*2), and a notable proportion of ovarian cancer was found in *BRCA*1+ patients (25%). Survival analysis revealed that *BRCA*1+ patients had a significantly higher risk of death compared to *BRCA*-negative patients (HR = 1.59; 95% CI: 1.05–2.42; p = 0.029). Advanced clinical stage (III/IV vs. I/II) was associated with nearly a threefold increased risk of death (HR = 4.30; 95% CI: 2.80–6.62; p < 0.001), and the triple-negative subtype was associated with a significantly higher mortality risk (HR = 1.59; 95% CI: 1.04–2.44; p = 0.033).

Conclusions

*BRCA*1 mutation carriers were diagnosed at a younger age and exhibited a more aggressive clinical and pathological profile, characterized by a predominance of the triple-negative subtype, high Ki-67 index, and G3 histological grade. Additionally, they presented a higher frequency of second cancers (37.9%), particularly breast and ovarian cancer. These findings highlight the importance of considering BRCA status in prognosis assessment and treatment planning for breast cancer patients.

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