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Original Article

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Clinicopathological Features and Oncological Outcomes of Germline Partner and Localizer of Breast Cancer 2-Mutated Breast Cancer in Korea

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ABSTRACT

Purpose: The partner and localizer of breast cancer 2 (PALB2) mutation is a predisposition to breast cancer development. However, limited clinical data are available for the Korean population. Therefore, this study aimed to compare the characteristics and oncological outcomes of patients with PALB2-mutated and non-mutated PALB2 in Korea.
Methods: A total of 1,463 breast cancer (BRCA) 1/2 mutation-negative breast cancer underwent comprehensive multigene sequencing between 2016 and 2019 at Severance Hospital, Seoul, Korea. Clinicopathological data and oncological results of PALB2 mutated patients were prospectively collected and compared with those of the non-mutated group.
Results: PALB2 mutations were identified in 1.2% (17/1,463) of the patients. The median age at diagnosis was 46 (30–73) years, and the median tumor size was 1.8 (0.05–3.5) cm. All patients with PALB2 mutations had histologic grades II–III, and a triple-negative subtype was found in 23.5% (4/17); however, there were no significant differences in clinicopathological data between the groups. During the median follow-up time of 38.5 months, locoregional recurrence occurred in 4.2% (44/1,043), distant recurrence was reported in 3.0% (31/1,043), and contralateral breast cancer was diagnosed in 0.8% (9/1,043) of patients, with no significant difference observed between the groups. All-cause mortality was observed in 1.8% (19/1,028) of the non-mutated group and none in the PALB2 mutation group. However, survival analyses demonstrated no significant differences in all-cause mortality ($p = 0.524$)

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Conflict of Interest

Hyung Seok Park received honoraria from Medtronic and Intuitive Surgical; however, it had no relationship with this study. The other authors report no proprietary or commercial interests in any product mentioned or concept discussed in this article.

Data Availability

The data used in the current study were provided by request to the principal investigator, Hyung Seok Park, after the acceptance of the manuscript.

Author Contributions

Conceptualization: Park JS, Park HS; Data curation: Sae-lim C, Jo S, Park S, Kweon T, Lee J, Lee Y, Lee SH, Won D, Han JW, Kim TI, Park JS; Formal analysis: Sae-lim C, Jo S, Nam EJ; Investigation: Sae-lim C, Jo S; Methodology: Sae-lim C, Jo S, Park HS; Project administration: Park JS, Park HS; Resources: Lee J, Lee Y, Lee SH, Won D, Nam EJ, Han JW, Kim TI, Park JS, Park HS; Software: Park HS; Supervision: Park HS; Validation: Sae-lim C, Jo S; Visualization: Sae-lim C; Writing - original draft: Sae-lim C, Jo S; Writing - review & editing: Sae-lim C, Park HS.

and recurrence-free survival (p = 0.319).

Conclusion: Clinicopathological features and oncological outcomes of PALB2 mutated breast cancer were not significantly different from those of non-mutated breast cancer in the Korean population.

Keywords: Breast Neoplasms; Germ-Line Mutation; PALB2 Protein, Human; Survival Analysis

INTRODUCTION

Partner and localizer of breast cancer 2 (PALB2) is a critical binding partner for breast cancer (BRCA) 2 and plays a pivotal role in homologous recombination, an essential process in DNA double-strand break repair [1]. Pathogenic variants of PALB2 can precipitate increased genomic instability, thereby predisposing individuals to breast [2-4], pancreatic [5], and ovarian cancers [6]. Studies have indicated that PALB2 mutations are associated with a significantly higher relative risk of developing breast cancer, ranging from 2 to 10 times higher [7-10]. However, the prevalence and clinical outcomes of PALB2-mutated breast cancers vary significantly, making it essential to understand the specific impact of these mutations on patients with breast cancer.

PALB2 mutations account for approximately 0.5%–1% of all breast cancer cases in certain populations, such as Chinese [9,11,12], Malaysian [13], Saudi [14], Polish [8], and Canadian cohorts [15]. In contrast, higher prevalence rates, ranging from 2%–2.8%, have been observed in the Jamaican [16], Argentinian [17], African American [18,19], and Finnish populations [20].

Distinct clinical characteristics of patients with breast cancer carrying PALB2 mutations are typically present compared to patients with non-mutated PALB2. Patients with PALB2 mutations are more likely to be diagnosed at a younger age [9,11,12,14] and present with larger and higher-grade tumors [9,12,14,19,20]. Regarding tumor subtypes, some studies reported that the majority of PALB2-related breast cancers are hormone receptor-positive human epidermal growth factor receptor 2 (HER2) negative (HER2−) [8,10,12,14,16,17,19,20]. Meanwhile, other studies reported a high prevalence of triple-negative breast cancer (TNBC) among PALB2-mutated patients, ranging from 24%–54.5%, compared to 9%–13% in those without mutations [8-10,12,13,20]. However, the prognostic impact of PALB2 mutations remains uncertain, as studies have reported conflicting survival outcomes, with some indicating a worse prognosis [8,20] while others showed no significant difference in survival [12]. These disparities highlight the importance of studying PALB2 mutations across diverse populations to fully characterize their clinical implications in breast cancer.

Recent advances in targeted therapies have demonstrated the promising efficacy of poly (ADP-ribose) polymerase inhibitor (PARPi) in patients with PALB2 mutations. Phase-II Olaparib Expanded (TBCRC 048) [21] and Talazoparib Beyond BRCA [22] demonstrated significant responses to PARPi in patients with gPALB2-mutated breast cancer. These results support the potential benefit of PARPi in improving the outcomes of patients with gPALB2-mutated breast cancer.

However, data regarding the clinical outcomes of PARPi treatment in Korean patients with PALB2 mutations are limited. To address this knowledge gap, we conducted a prospective

cohort study comparing the patient characteristics and oncological outcomes between non-BRCA1/2 PALB2-mutated breast cancer patients and non-mutated PALB2 patients with high hereditary risk. These results provide valuable insights into the implications of PALB2 mutations and support future research on the efficacy of PARPi in the Korean population.

METHODS

Study population

This current research was a prospective study that demonstrated the clinicopathological characteristics, spectrum of PALB2 mutations, and oncological outcomes of high-risk breast cancer patients with pathological/likely pathological (PV/LPV) PALB2 mutations in the Korean population. Patients with BRCA1/2 mutation-negative breast cancer with at least one high-risk factor for hereditary breast cancer syndrome were enrolled between March 2016 and December 2019 at Severance Hospital, Seoul, Republic of Korea. Risk factors for hereditary breast cancer were defined as follows: 1) the presence of breast or ovarian cancer in at least one of the first- or second-degree relatives; 2) a first diagnosis of breast cancer before the age of 40 years; 3) bilateral breast cancer; 4) male breast cancer; and 5) concurrent diagnoses of breast cancer and other cancers in the same patient. Clinicopathological characteristics were obtained from the database of the PLEASANT study [23] with participant permission, including age at first breast cancer diagnosis, tumor size, staging, histological grade, and molecular subtypes. Although the PLEASANT study was prospectively designed to assess the clinical implications of multigene panel testing beyond BRCA genes in Korean patients, additional clinical information such as clinical N staging, types of breast and axillary surgeries, neoadjuvant and adjuvant treatments, and oncological outcomes, including locoregional and distant recurrence and all-cause mortality, were retrospectively collected. All the participants provided written informed consent. Ethical approval was obtained from the PLEASANT study (Institutional Review Board at Severance Hospital, approval numbers: 4-2015-0819 and 4-2018-0259) [23]. This study was approved by the Institutional Review Board at Severance Hospital, Seoul, Korea (IRB approval number: 4-2023-1682).

Comprehensive multigene panel-based variant analysis

Peripheral blood samples were obtained from all participants for DNA extraction and genotyping, which was conducted using a NextSeq 550Dx instrument (Illumina, San Diego, USA). The multigene sequencing process is described in detail in our previous study [23]. Genetic variants were classified using a five-tier system according to the guidelines of the American College of Medical Genetics and Genomics [24], with PV/LPV considered as mutations in this study [25]. The prevalence and spectrum of germline PALB2 mutations were collected and reported.

Outcome measures and statistical analyses

The main outcomes in our study included differences in clinicopathological characteristics and oncological outcomes between PALB2 mutated carriers and patients without mutation. Oncologic safety was evaluated based on the incidence of locoregional and distant recurrences and all-cause mortality. Locoregional recurrence was defined as cancer reappearance at the ipsilateral breast tumor recurrence or chest wall or nodal recurrence in the ipsilateral axilla, supraclavicular, or internal mammary regions [26]. Distant recurrence was defined as any recurrence in distant organs [26]. The term contralateral invasive breast cancer is preferred over second primary breast cancer on the opposite side of the initial

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breast cancer [26]. Continuous data with non-normal distributions are shown as median and interquartile range and were analyzed using the Mann-Whitney *U* test. The χ^2 test or Fisher's exact test was used for categorical variables when appropriate. All tests were two-sided, and the *p*-value demonstrated the difference between the PALB2 mutated and the non-mutated groups, which was considered statistically significant when the *p*-value was lower than 0.05.

Kaplan-Meier curves were generated to estimate actuarial survival in patients, and the log-rank test was used to compare groups. The incidences of recurrence and mortality were ascertained at the most recent follow-up, which ended on April 15, 2024. All statistical analyses were performed using the statistical packages SPSS for Windows (version 22.0; IBM Corp., Armonk, USA) and R (version 4.3.1; Posit, Boston, USA).

As previously mentioned, some data were missing in this study because certain clinical information was retrospectively collected. To ensure accuracy, patients with missing data were excluded from the relevant statistical analyses, and patients lacking oncological outcome information were excluded from the survival analysis.

RESULTS

Patient characteristics and PALB2 mutated variants

A total of 1,463 patients with breast cancer underwent comprehensive multigene sequencing at Severance Hospital, Republic of Korea, between March 2016 and December 2019. Among them, germline PALB2 mutations were identified in 1.2% (17/1,463) of the patients, while the remaining 98.8% (1,446/1,463) had non-mutated PALB2. There were no differences in median age (46 years for PALB2 mutation vs. 47 years for non-mutation, $p = 0.320$) or median tumor size (1.8 cm for PALB2 mutation vs 1.5 cm for non-mutation, $p = 0.947$) between the groups. However, patients with PALB2 mutations had a significantly higher incidence of clinically positive axillary lymph nodes than the non-mutated group (26.7% vs. 10.3%, $p = 0.041$; data not shown). All patients with PALB2 mutations (17/17) had histologic grades II–III and HER2− tumors, 76.5% (13/17) had estrogen receptor (ER)-positive (ER+) tumors, and 23.5% (4/17) had TNBC subtypes, showing no significant differences compared to the non-mutated group. None of the participants with PALB2 mutation reported coexisting cancer at other sites, whereas it was diagnosed in 16 patients in the non-mutated group (1.6%, 16/1,446), with no significant difference observed ($p = 1.000$). Systemic therapy and radiation treatment did not differ significantly between the groups. Patient characteristics are summarized in **Table 1**.

In this cohort, 17 patients carried 15 types of pathogenic mutations, including five nonsense mutations and four cases each of frameshift mutations, exon deletions, and splicing mutations. The most frequent mutations were exon 11 deletions (2/17; 11.8%) and c.3350+5G>A (2/17; 11.8%). Of these, three (17.7%) were novel mutations that have not been previously reported, including c.235dup, c.3302_3306delinsAATT, and c.3317_3324delinsG. A summary of the pathogenic PALB2 variants is presented in **Table 2** [23,27-33].

Oncological safety

At the cutoff date for the survival analysis (April 15, 2024), the median follow-up time was 38.5 months [IQR = 16.5,51.7], with a total of 1,043 patients completing all treatments and remaining under follow-up at our institute, which included 15 patients in the PALB2 mutation group and

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Table 1. Patient characteristics of breast cancer patients with germline partner and localizer of breast cancer 2 mutation and non-mutated partner and localizer of breast cancer 2

Characteristics	All (n = 1,463)	Germline PALB2 mutation (n = 17)	Non-mutated PALB2 (n = 1,446)	*p*-value*
Age (yr)				
Median [IQR]	47 [39–55]	46 [36.5–49.5]	47 [39–56]	0.320
Mean ± SD	(47.8 ± 11.4)	(45.2 ± 10.6)	(47.9 ± 11.4)	
Age ≤ 50	921 (63.0)	14 (82.3)	907 (62.7)	0.129
Age > 50	542 (37.0)	3 (17.7)	539 (37.3)	
Tumor size (cm) (NA = 7)				
Median [IQR]	1.5 [0.8–2.3]	1.8 [0.7–2.2]	1.5 [0.8–2.3]	0.947
Mean ± SD	(1.8 ± 1.4)	(1.6 ± 1.1)	(1.8 ± 1.4)	
Tumor ≤ 2 cm	970 (66.6)	10 (62.5)	960 (84.2)	0.791
Tumor > 2 cm	486 (33.4)	6 (37.5)	480 (15.8)	
Clinical T staging (NA = 7)†				0.563
I	1,008 (69.3)	10 (62.5)	998 (69.3)	
II	404 (27.7)	6 (37.5)	398 (27.6)	
III	44 (3.0)	0 (0.0)	44 (3.1)	
Clinical N staging (NA = 420)†				0.049*
0	933 (89.5)	11 (73.3)	922 (89.7)	
I	81 (7.8)	4 (26.7)	77 (7.5)	
II	12 (1.2)	0 (0.0)	13 (1.3)	
III	16 (1.5)	0 (0.0)	16 (1.5)	
Distant metastasis	31 (2.1)	0 (0.0)	31 (2.1)	1.000
Neoadjuvant treatment				0.589
Yes	416 (28.4)	6 (35.3)	410 (28.6)	
No	1,047 (71.6)	11 (64.7)	1,036 (71.4)	
Breast operation (NA = 736)†				0.348
Breast conservation	386 (53.1)	4 (33.3)	382 (53.4)	
Total mastectomy	150 (20.6)	3 (25.0)	147 (20.6)	
Nipple/Skin sparing mastectomy	191 (26.3)	5 (41.7)	186 (26)	
Axillary operation (NA = 809)†				0.663
SLNB	544 (83.2)	7 (77.8)	537 (83.3)	
ALND	110 (16.8)	2 (22.2)	108 (16.7)	
Histologic grade (NA = 13)†				0.053
I	197 (13.6)	0 (0.0)	197 (13.7)	
II	771 (53.2)	11 (68.8)	760 (53)	
III	482 (33.2)	5 (31.2)	477 (33.3)	
Subtype				0.444
Luminal A	616 (42.1)	6 (35.3)	610 (42.2)	
Luminal B	420 (28.7)	7 (41.2)	413 (28.6)	
HER2	126 (8.6)	0 (0.0)	126 (8.7)	
TNBC	301 (20.6)	4 (23.5)	297 (20.5)	
ER				0.790
Positive	1,035 (70.7)	13 (76.5)	1,022 (70.7)	
Negative	428 (29.3)	4 (23.5)	424 (29.3)	
PR				0.806
Positive	845 (57.8)	9 (52.9)	836 (57.8)	
Negative	618 (42.2)	8 (47.1)	610 (42.2)	
HER2 (NA = 15)†				0.091
Positive	251 (17.3)	0 (0.0)	251 (17.5)	
Negative	1,197 (82.7)	16 (100.0)	1,181 (82.5)	
Ki-67 (NA =11)†				0.222
≤ 14	758 (55.2)	6 (35.3)	752 (52.4)	
> 14	694 (44.8)	11 (64.7)	683 (47.6)	
Coexisting other primary cancer‡	16 (1.5)	0 (0.0)	16 (1.6)	1.000
Adjuvant treatments				
Adjuvant chemotherapy (NA = 418)†	229 (21.9)	5 (33.3)	224 (21.7)	0.149
Adjuvant radiation therapy (NA = 417)†	528 (50.5)	8 (53.3)	520 (50.4)	0.297
Adjuvant hormonal therapy (NA = 417)†	506 (48.4)	7 (46.7)	499 (48.4)	0.303

Data shown are number (%) not otherwise specified.
PALB2 = partner and localizer of breast cancer 2; IQR = interquartile range; SD = standard deviation; NA = not available; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; ER = estrogen receptor; PR = progesterone receptor.
*p-value ≤ 0.05, which was calculated by Mann-Whitney U test for continuous variables and χ^2 test for categorical variables.
†Some data was missing because it was not included in the PLEASANT study database and therefore had to be collected retrospectively.
‡Other primary cancer includes 7 thyroid cancers, 2 colorectal cancers, 1 lung cancer, and 6 other cancers.

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Table 2. Pathogenic partner and localizer of breast cancer 2 variants identified in this study

Location	Nucleotide	Protein	Molecular consequence	Genotype	No. (%)	Reference
Intron 2	c.109-2A>G	NA	Splicing	Hetero	1 (5.9)	[27]
Exon 4	c.235dup	p.Tyr79LeufsTer2	Frameshift	Hetero	1 (5.9)	Novel
Exon 4	c.355C>T	p.Gln119Ter	Nonsense mutation	Hetero	1 (5.9)	[23]
Exon 4	c.1048C>T	p.Gln350Ter	Nonsense mutation	Hetero	1 (5.9)	[28]
Exon 4	c.1056_1057del	p.Lys353IlefsTer7	Frameshift	Hetero	1 (5.9)	[29]
Exon 4	c.1426del	p.Arg476GlufsTer9	Frameshift	Hetero	1 (5.9)	[23]
Exon 5	c.2485C>T	p.Gln829Ter	Nonsense mutation	Hetero	1 (5.9)	[23]
Intron 7	c.2748+2T>G	NA	Splicing	Hetero	1 (5.9)	[30]
Exon 7	Exon 7 deletion	NA	Exon deletion	Hetero	1 (5.9)	[31]
Exon 8	Exon 8 deletion	NA	Exon deletion	Hetero	1 (5.9)	[23]
Exon 11	Exon 11 deletion	NA	Exon deletion	Hetero	2 (11.8)	[23]
Exon 12	c.3256C>T	p.Arg1086Ter	Nonsense mutation	Hetero	1 (5.9)	[32]
Exon 12	c.3302_3306delinsTTAA	p.Thr1099IlefsTer7	Frameshift	Hetero	1 (5.9)	Novel
Exon 12	c.3317_3324delinsG	p.Met1106SerfsTer16	Frameshift	Hetero	1 (5.9)	Novel
Intron 12	c.3350+5G>A	NA	Splicing	Hetero	2 (11.8)	[30,33]

NA = not applicable.

Table 3. Oncological outcomes of breast cancer patients with germline partner and localizer of breast cancer 2 mutation and non-mutated partner and localizer of breast cancer 2

Outcomes	All (n = 1,043)	Germline PALB2 mutation (n = 15)	Non-mutated PALB2 (n = 1,028)	*p*-value*
Locoregional recurrence	44 (4.2)	1 (6.7)	43 (4.2)	0.478
IBTR	33 (3.2)	0	33 (3.2)	1.000
IBTR and regional	2 (0.2)	0	2 (0.2)	1.000
Regional only	9 (0.9)	1 (6.7)	8 (0.8)	0.123
Distance recurrence	31 (3)	0	29 (2.8)	1.000
Visceral only	15 (1.4)	0	15 (1.5)	1.000
Visceral and bone	14 (1.3)	0	14 (1.4)	1.000
Contralateral breast cancer	9 (0.8)	1 (6.7)	8 (0.8)	0.123
All-cause mortality	19 (1.8)	0	19 (1.8)	1.000
Follow-up duration (mon)				0.156
Median [IQR]	38.5 [16.5–51.7]	45.7 [25–56.5]	36.7 [16.3–51.7]	
Mean ± SD	37.9 ± 29.1	54.5 ± 49.7	37.6 ± 28.6	

Data shown are number (%) not otherwise specified.
PALB2 = partner and localizer of breast cancer 2; IBTR = ipsilateral breast tumor recurrence; IQR = interquartile range; SD = standard deviation.
*p-value was calculated by Mann-Whitney U test for continuous variables and χ^2 test for categorical variables.

1,028 patients in the non-mutated PALB2 group. Locoregional recurrence occurred in 4.2% (44/1,043) of the participants, distant recurrence in 3% (31/1,043), and contralateral breast cancer in 0.8% (9/1,043). No significant differences were found between the PALB2 mutation and non-mutated groups in terms of locoregional recurrence (p = 0.478), distant recurrence (p = 1.000), and contralateral breast cancer (p = 0.123). Detailed comparisons of the oncological outcomes between the PALB2 mutated and non-mutated groups are shown in **Table 3**.

All-cause mortality was observed in 1.8% (19/1,028) of the non-mutated group and none in the PALB2 mutation group; however, the Kaplan-Meier curves demonstrated no significant difference of overall survival between the two groups (log-rank p = 0.524, **Figure 1A**). Additionally, significance between the groups for recurrence-free survival was not reached (log-rank p = 0.319, **Figure 1B**), with events occurring in 7.1% (73/1,028) of the non-mutated group and 6.7% (1/15) of the PALB2 mutation group. The Kaplan-Meier curves for survival analysis are shown in **Figure 1**.

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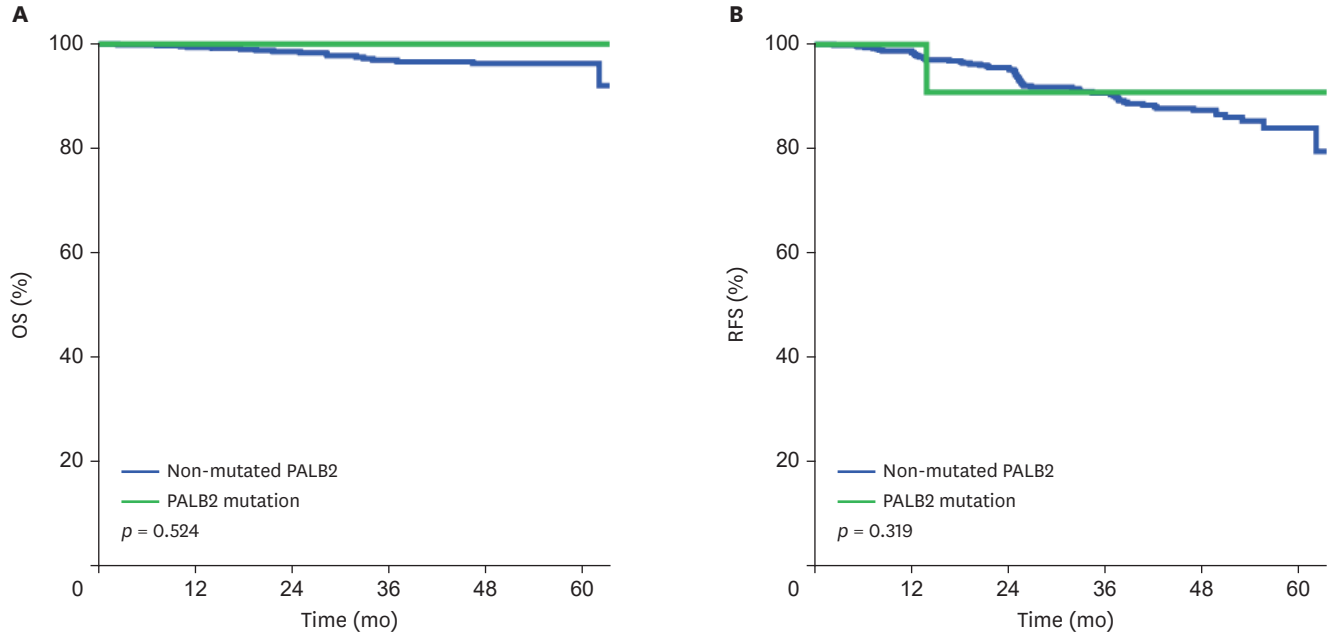

Figure 1. The Kaplan-Meier curves of partner and localizer of breast cancer 2 mutated and non-mutated breast cancer patients.
(A) OS and (B) RFS.
OS = overall survival; RFS = recurrence-free survival; PALB2 = partner and localizer of breast cancer 2.

DISCUSSION

In this prospective study, we compared the clinicopathological characteristics and oncological outcomes of high-hereditary-risk breast cancer patients with PALB2 mutations and those with non-mutated PALB2 in the Korean population. A total of 1,463 patients receiving comprehensive multigene sequencing at Severance Hospital, Republic of Korea, between March 2016 and December 2019 were included. The results indicated no significant differences between the groups in terms of age at diagnosis, tumor size, histologic grade, or tumor subtype. Furthermore, no significant differences were observed in the incidence of coexisting cancers in the same patient, recurrence rate, or survival outcomes.

PALB2 mutations are associated with a significantly elevated risk of breast cancer development [7-10]. However, the prevalence of PALB2 mutations [8,9,11-14,16-20], characteristics and outcomes associated with these PALB2-mutated breast cancers have been reported to vary across different countries worldwide [8-12,14,16,17,19,20]. Despite this, limited data are available for Korean cohorts. Therefore, we conducted this study to assess the patient characteristics and oncological outcomes of PALB2-mutated patients and compare them to those of non-mutated PALB2 patients in this population, which has rarely been reported.

The prevalence of PALB2 mutations in this cohort was 1.2% (17/1,463; **Table 1**), which is comparable to studies in Chinese, Polish, Saudi, Malaysian, and African-American populations. However, this frequency is lower than that in Jamaica and Argentina (**Table 4**) [8,9,11-14,16,17,19,20]. This may be attributed to the diversity in inclusion criteria, definitions of family history, methods of mutation detection, and mutation spectra [20]. In this study, the most prevalent hotspot region was exon 4, similar to a previous study conducted in China [9].

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Table 4. Published literature reporting clinicopathological characteristics and outcomes of partner and localizer of breast cancer 2 mutation carriers

Study	Nationality of participants	Prevalence and the number	Age at diagnosis, year	Tumor size	Histologic grade	Positive ALN	Distant metastasis	Tumor subtype	Contralateral breast cancer	Survival
Comparison studies with non-mutated PALB2										
Zhou et al., 2020 [9]	Chinese	160 (1%)	[Younger] ≤ 30 years (6.88%)	[Larger] ≥ 2 cm (55.93%)	-	[More often] 49.6%	-	More TNBC 22.83%	[More often] 6.29%	-
Cybulski et al., 2015 [8]	Polish	116 (0.93%)	[NS] 53.3	[NS] ≥ 2 cm (58%)	[NS] Grade 3 (25%)	[NS] 46%	-	More TNBC 24%, Fewer ER+ 60%	[More often] 10%	Worse, especially in tumor ≥ 2 cm and TNBC
Wu et al., 2020 [12]	Chinese	54 (0.71%)	[Younger] 47.52	[Larger] > 2 cm (72.2%)	[NS] Grade 2,3 (93.7%)	[NS] 38.5%	-	More TNBC 24.1%	[NS] 1.9%	NS
Deng et al., 2019 [11]	Chinese	24 (0.9%)	[Younger] 45.1	[NS] > 2 cm (52.2%)	[NS] Grade 2,3 (94.2%)	[NS] 50%	[NS] 16.7%	[NS] TNBC 20.8%, ER+ 60.9%	[More often] 12.5%	-
Heikkinen et al., 2009 [20]	Finnish	19 (2%) in familial, 8 (0.6%) in sporadic	[NS] 53.1	[NS] > 2 cm (39.4%)	[Higher] Grade 2,3 (90.6%)	[NS] 54.5%	[NS] 3%	More TNBC 54.5%, Fewer ER+ 53.5%	[NS] 10.7%	Worse, especially in HER2– and/or familial breast cancer
Recent study	Korean	17 (1.2%)	[NS] 46	[NS] > 2 cm (37.5%)	[NS] Grade 2,3 (100%)	[NS] 29.4%	[NS] 0%	[NS] TNBC 23.5%, ER+ 76.5%	[NS] 6.7%	NS
Descriptive studies										
Gonzalez et al., 2022 [17]	Argentinian	53 (2.78%)	42.2	-	-	-	-	TNBC 22%, ER+ 62%	-	-
Siraj et al., 2023 [14]	Saudis	6 (0.76%)	34–49	> 2 cm (83.3%)	Grade 2,3 (100%)	50%	-	TNBC 16.7%, ER+ 66.7%	-	-
Lerner-Ellis et al., 2017 [16]	Jamaican	5 (2.8%)	41, 50, 52, 52, 60	-	-	-	-	ER+, HER2– 100%	-	-
Yang et al., 2017 [13]	Malaysian	4 (0.86%)	24, 38, 49, 64	-	-	-	-	TNBC 50%, ER+ 25%	-	-
Zheng et al., 2012 [19]	African-American	3 (1.08%)	36, 45, 60	-	Grade 2,3 (100%)	-	-	TNBC 0%, ER+ 66.7%	-	-

ALN = axillary lymph node; PALB2 = partner and localizer of breast cancer 2; TNBC = triple negative breast cancer; NS = not significantly different; ER+ = estrogen receptor-positive; HER2– = human epidermal growth factor receptor 2-negative.

In previous studies, tumors in PALB2 carriers often displayed higher risk characteristics, such as earlier onset [9,11,12], larger size [9,12], higher grade [20], and a higher prevalence of TNBC, accounting for over 20% of cases [8,9,11-13,17,20], compared with approximately 9%–13% in non-mutated tumors [8,9,20]. In the present study, clinically positive axillary lymph nodes were significantly more prevalent in the PALB2 mutation group. However, other high-risk features were observed at similar frequencies in the PALB2-mutated and non-mutated groups. This discrepancy may stem from differences in the inclusion criteria, as our study focused on high-risk patients, whereas previous studies often included unselected breast cancer populations.

Neoadjuvant systemic therapy was administered to six patients in the PALB2-mutated group (35.3%), showing no significant difference from the non-mutated group (**Table 1**). The indication for this approach was a locally advanced disease with nodal metastases. Among these six patients, four (66.7%) had the luminal subtype, achieving partial clinical and pathological responses. The remaining two patients, one HER2-positive and one TNBC subtype achieved complete pathological response in the final pathology.

Despite limited oncological data in PALB2-mutated breast cancer patients, worse survival has been demonstrated in larger cohorts from Polish [8] and Finnish populations [20], particularly among higher-risk patients with tumor size ≥ 2 cm, TNBC subtype, and

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hereditary breast cancer (**Table 4**) [8,9,11-14,16,17,19,20]. However, our study found no significant differences in survival outcomes (**Table 3**). This may be due to the small sample size, which limited the detailed stratification and analysis of survival under specific conditions. Nevertheless, our study provided additional data on locoregional and distant recurrence and showed no significant differences between the groups (**Table 3**).

Targeted therapies, particularly PARPi, have shown promising efficacy in patients with PALB2 mutations. In the phase-II Olaparib Expanded (TBCRC 048) trial [21], metastatic breast cancer patients with PALB2 mutations achieved an objective response rate (ORR) of 82% and a median progression-free survival (PFS) of 13.3 months with Olaparib treatment. Additionally, 71% of those who responded had ER+, HER2− breast cancer, emphasizing the importance of targeting patients with homologous recombination deficiency in this subtype. Similarly, the Talazoparib Beyond BRCA study [22] demonstrated an ORR of 50% and a median PFS of 6.9 months with talazoparib in ER+, HER2− breast cancer patients. In our study, 76.5% of breast cancer patients with PALB2 mutations also had the ER+, HER2− subtype, mirroring the populations in these trials. This alignment supports further investigations into the potential clinical benefits of PARPi in Korean patients with PALB2 mutations.

Although this study provides valuable insights, it has certain limitations. This study had a small sample size due to the generally low prevalence of PALB2 mutations and a relatively short follow-up period to determine long-term oncological outcomes. However, monitoring for a more comprehensive understanding of long-term oncological outcomes has continued at our institute. Despite these limitations, our study contributes to the understanding of patient characteristics and oncological outcomes of PALB2 mutated patients compared to non-mutated patients in the Korean population, which has rarely been explored.

In conclusion, germline PALB2 mutations have been identified in 1.2% of breast cancer patients with high hereditary risk in the Republic of Korea. Furthermore, our study found no significant differences in the clinicopathological features or oncological outcomes compared to the non-mutated group in this population.

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