AHOT | Acta Haematologica Oncologica Turcica

Acta Haematol Oncol Turc 2025;58(3):226-231

Original Article

DOI: 10.4274/ahot.galenos.2025.2025-10-4

Clinical and Pathological Characteristics of Breast Cancer Cases with Germline Alterations in Homologous Recombination Defect-associated Genes

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ABSTRACT

Aim: Approximately 5-10% of breast cancer (BC) cases are hereditary, most frequently associated with germline variants in homologous recombination repair (*HRR*) genes such as *BRCA1/2*. However, non-*BRCA HRR* gene alterations, including *ATM* gene and *CHEK2*, may also influence tumor biology and clinical outcomes. This study aimed to evaluate the clinical relevance of germline homologous recombination deficiency (HRD)-related variants in BC and to compare the clinicopathological features and survival outcomes between *BRCA* and non-*BRCA* carriers.

Methods: A retrospective cohort of 148 BC patients with germline HRD-related variants identified by next-generation sequencing between 2018 and 2022 was analyzed. Variants were classified according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology 2015 criteria. Clinical, pathological, and survival data were assessed using descriptive statistics and Kaplan-Meier survival analysis with the Log-Rank test.

Results: Of 148 patients (mean age 45.2±10.1 years), 80 (54%) carried *BRCA* variants and 68 (46%) non-*BRCA* variants, most frequently *ATM* and *CHEK2*. Pathogenic or likely pathogenic variants were more frequent in *BRCA* carriers (77.5% vs. 58.8%, p=0.014). Disease-free survival (DFS) did not differ significantly between *BRCA* and non-*BRCA* groups (p=0.42). Prophylactic mastectomy and oophorectomy were performed significantly more often in *BRCA* carriers (p<0.05).

Conclusions: Although DFS was comparable between *BRCA* and non-*BRCA* carriers, relapse was more frequent in *BRCA1* and pathogenic variant carriers. These results emphasize the clinical importance of integrating germline *HRR* gene analysis into personalized surveillance and management strategies in BC.

Keywords: *BRCA*, breast cancer, disease free survival, germline mutations

Introduction

Breast cancer (BC) is the most frequent type of cancer among women, and approximately 5-10% of BC cases are attributable to hereditary factors. *BRCA1/2* are tumor suppressor genes that belong to the homologous recombination repair (HRR) family, which plays a crucial role in repairing deoxyribonucleic acid (DNA) double-strand breaks, which are harmful to cells. In addition to *BRCA1* and *BRCA2*, the HRR gene group includes genes such as *ATM*, *CHEK2*, *PALB2* (partner and localizer of *BRCA2*), and RAD51 (RAD51 recombinase). If a pathogenic variant is found in any of the HRR genes, the proteins encoded by these genes cannot perform their normal functions, resulting in homologous recombination deficiency (HRD) [1].

Women carrying pathogenic variants in *BRCA1* have a lifetime risk of BC of 50-80% and of ovarian cancer of 20-50%. For the *BRCA2* gene, the lifetime risks are 50% for BC and 20%

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Received: 25.11.2025 **Accepted:** 14.10.2025 **Publication Date:** 12.12.2025

Cite this article as: Keser M, Özer Kaya Ö, Özdemir TR, Pala EE, Ünal OÜ, Kubat G. Clinical and pathological characteristics of breast cancer cases with germline alterations in homologous recombination defect-associated genes. Acta Haematol Oncol Turc. 2025;58(3):226-231

for ovarian cancer [2]. In addition to *BRCA* germline variants, alterations can be detected in other genes associated with HRD, including those with high penetrance (*CDH1*, *TP53*, *PTEN*) and those with moderate penetrance (*PALB2*, *ATM*, *CHEK2*, *BRCA1*, *BRIP1*) [3,4]. These variants have been reported to increase BC risk by up to fourfold compared with the general population [5]. *ATM* and *CHEK2* variants, which, along with the PALB2 variant, play a role in DNA repair, are important in the context of hereditary BC [6,7]. In addition to known pathogenic variants, variants of uncertain clinical significance (VUS) may be detected [8]. Individuals with these variants may develop other malignancies alongside BC, presenting with substantially different pathological and clinical profiles [9]. Current guidelines emphasize that recommendations for treatment or preventive surgery based on these types of variants should not be made [10]. However, evaluating germline HRD-related genes is crucial for improving clinical outcomes through personalized therapies, such as targeted poly (ADP-ribose) polymerase (PARP) inhibitors for various cancers, particularly breast and ovarian cancers [11,12].

Although several studies have collected data on various malignancies associated with *BRCA* variants in our country [11,12], no study has clinically and pathologically evaluated *BRCA* and non-*BRCA* variants together, particularly among BC patients. This study aims to evaluate the clinical utility of germline variant analysis in BC for diagnosis and follow-up, and to determine its contribution to understanding the clinical significance of non-*BRCA* variants.

Methods

Study Design

This study had a retrospective design. All procedures and measurements in this study were performed according to the 1964 Helsinki Declaration or comparable ethical standards. Ethical board approval was granted by the Ethical Board for Clinical Studies at University of Health Sciences Türkiye, Tepecik Education and Research Hospital, with the following protocol number: approval number: 2021/05-37, date: 17.05.2021.

Patients

Data from patients diagnosed with BC, found to have germline HRD gene variants, and referred to the medical oncology clinic at University of Health Sciences, İzmir Tepecik Training and Research Faculty of Medicine Hospital were screened retrospectively between 2018 and 2022. The inclusion criteria were: (1) a confirmed diagnosis of BC, (2) age over 18 years, and (3) the presence of pathogenic germline variants. Patients whose clinical data were unavailable or whose germline variant analysis results were incomplete were excluded from the study. A total of 148 patients met the eligibility criteria and were included in the final analysis.

Genetic Testing

Peripheral blood samples were collected from patients for germline DNA extraction. DNA isolation was performed using standard commercial kits, following the manufacturer's instructions. The extracted DNA was analyzed with next-generation sequencing to identify germline variants in genes related to HRR and hereditary cancer predisposition. Only variants in HRR-associated genes were considered for analysis. Targeted sequencing included *BRCA1, BRCA2, APC, ATM, BARD1, BLM, BMPR1A, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PRSS1, PTEN, RAD50, RAD51C, RAD51D, SLX4, SMAD4, STK11, TP53,* and *VHL*. Sequence data were processed through a web-based bioinformatics pipeline (Genomize Seq Analysis v16.7.2) using the GRCh37 (hg19) human reference genome. All coding regions and exon-intron boundaries (±20 bp) were analyzed, ensuring at least 20× coverage depth across 100% of targeted areas. Detected variants were filtered based on a minor allele frequency<5% in population databases such as gnomAD, 1000 Genomes, ESP6500, and ExAC. Variant classification followed the ACMG/AMP 2015 guidelines [13]. Pathogenic and likely pathogenic variants were confirmed by Sanger sequencing before reporting. VUS were noted but not considered actionable for clinical decisions in accordance with current recommendations. The analysis excluded 3' and 5' untranslated regions, pseudogenes, and other homologous regions where accurate alignment was not feasible. Copy number variations, large deletions or duplications, repeat expansions, and mosaic variants were beyond the detection limits of this method.

Statistical Analysis

The data were expressed as mean and standard deviation for metric variables and as counts and percentages for nominal variables. Normality was assessed using Kolmogorov-Smirnov test and by examining Skewness and Kurtosis values. Univariate survival analysis was performed using the Kaplan-Meier method and the Log-Rank test for dichotomous data. Survival outcome was based on "death" for overall survival (OS) or "relapse" for disease-free survival (DFS) during the follow-up period, respectively. Data were analyzed at the 95% confidence level, and a p-value of 0.05 was considered significant. IBM Statistical Package for the Social Sciences version 27 (Chicago, IL, USA) was used for the analysis.

Results

This study included 148 patients with BC. Only one patient was male. The mean age of the patients was 45.18±10.11 years. The great majority of patients (n=104, 70.3%) were under the age of 40 at the time of diagnosis. 107 of 147 patients were premenopausal. The vast majority of patients (87.1%) had invasive ductal carcinoma. Nearly all patients had histological grades IIIII (97%). Thirteen of 148 patients had malignancies other than BC. By molecular subtype, 35 of 148 patients had triple-negative BC. Over half of the patients reported no HRD-related cancer (n=83, 56.5%). 23.4% and 19.7% of patients underwent prophylactic mastectomy and oophorectomy, respectively. The clinical and demographic characteristics of patients are shown in Table 1.

Table 1. Clinical and demographic characteristics of patients

	n	%
Sex		
Female	147	99.3
Male	1	0.7
Age groups		
>40	44	29.7
<40	104	70.3
Menapause		
Premenapause	108	73.0
Postmenapause	40	27.0
Histopathological Type		
Invasive ductal	130	87.8
Invasive lobular	10	6.7
Medullary	2	1.3
Solid papillary	1	0.67
Other	5	3.54
Grade		
I	4	2.7
II	76	51.3
III	68	46
Other malignities		
Yes	10	6.75
No	138	93.25
Molecular subtypes		
HR: +, Her2: -	79	53.3
HR: +, Her2: +	22	14.8
HR: -, Her2: +	12	8.1
TN	35	23.8
HRD related cancer		
Yes	64	43.3
No	84	56.7
RRM		
Yes	34	23.0
No	114	77.0
RRSO		
Yes	29	19.6
No	119	80.4
Pathogenity		
LP/P	9	6.1
P	93	62.8
VUS	46	31.1
Gene mutations		
BRCA	80	54.1
Non-*BRCA*	68	45.9

TN: Triple-negative, HR: Hormone receptor, Her2: Human epidermal growth factor receptor 2, RRM: Risk-reducing mastectomy, RRSO: Risk-reducing salpingo-oophorectomy, HRD: Homologous recombinant defect, LP/P: Likely pathogenic/pathogenic, VUS: Variants of uncertain clinical significance

The median follow-up time of patients was 50.46 months (interquartile range, 25-75: 33.80-81.10). During the follow-up period, 8 of 148 patients (5.4%) died of BC, while 26 (17.6%) experienced a relapse. 80 out of 148 patients had *BRCA*-related variants. The percentage distribution of *BRCA1* and *BRCA2* variants within the *BRCA*-related group was 46.8% and 53.2%, respectively. In the non-*BRCA* group, the most frequent types of variants were *ATM* (n=25, 38.5%) and *CHEK2* (n=24, 36.9%). Among variants from 148 patients, 102 (68.9%) were classified as likely pathogenic or pathogenic (LP/P), while the remainder were classified as VUS. Comparison of the distribution of variant pathogenicity between *BRCA* and non-*BRCA* groups revealed a significant difference (χ^2=5.985, p=0.014): 77.5% vs 58.8% LP/P in *BRCA* and non-*BRCA* groups, respectively. The frameshift variant was most frequent in the *BRCA* group (n=25, 31.6%), whereas the missense variant was most frequent in the non-*BRCA* group (n=40, 58.8%). 80.8% of patients who relapsed had an LP/P variant; however, there was no significant association between relapse and pathogenicity (χ^2=2.068, p=0.150), with relapse proportions of 80.8% versus 19.2% in the LP/P and VUS groups, respectively. There were also significant differences between *BRCA* and non-*BRCA* groups with respect to prophylactic mastectomy (χ^2=7.201, p=0.027; 30.8% vs 14.9% in the *BRCA* and non-*BRCA* groups, respectively) and prophylactic oophorectomy [χ^2(2)=9.904, p=0.007; 27.5% vs 10.4% in the *BRCA* and non-*BRCA* groups, respectively]. Among patients who relapsed, 54.2% had a *BRCA1* variant; nearly 70% of those patients had missense or frameshift variants. The Comparison of the clinical characteristics of patients with and without *BRCA* mutations is shown in Table 2.

[χ^2(1)=0.633, p=0.426], prophylactic mastectomy [χ^2(1)=1.678, p=0.190], prophylactic oophorectomy [χ^2(1)=1.506, p=0.223], histological grade [χ^2(2)=0.931, p=0.621], having HRD related cancer [χ^2(1)=0.103, p=0.747], menopausal state [χ^2(1)=0.048, p=0.822], age groups (<40<) [χ^2(1)=0.038, p=0.843] except for variant pathogenity [LP/P vs VUS, χ^2(1) =3.907, p=0.048]. Though the non-BRCA group showed higher median DFS time than the BRCA group (47.83 vs 37.13 months), the Log-Rank test was not significant [χ^2(1)=0.915, p=0.333]. The DFS also did not differ significantly between pathogenicity groups (LP/P vs P) [χ^2(1)=1.402, p=0.235]. Menopausal status, age groups, HRD-related cancer history, prophylactic mastectomy, and oophorectomy were also not significantly associated with DFS (p>0.050).

Discussion

In this retrospective cohort of 148 BC patients, with a median follow-up of more than four years, we observed no significant difference in DFS between *BRCA* carriers and non-*BRCA* carriers. Although the non-*BRCA* group showed a longer median DFS than the *BRCA* group, this difference did not reach statistical significance. Similarly, relapse was more frequently associated with *BRCA1* LP/P variants, but this association was not statistically significant. Prophylactic mastectomy and oophorectomy were significantly more common among *BRCA*

Table 2. Comparison of the clinical characteristics of patients with and without *BRCA* mutation

		BRCA		Non-*BRCA*		p
		n	%	n	%	
IHK_FISH	HR: +, Her2: -	35	44.3	44	55.7	0.001*
	HR: +, Her2: +	9	40.9	13	59.1	
	HR: -, Her2: +	3	50.0	3	50.0	
	TN	29	82.9	6	17.1	
Histological grade	I	1	25.0	3	75.0	0.286
	II	31	47.0	35	53.0	
	III	35	57.4	26	42.6	
Stage at the diagnosis	I	23	46.9	26	53.1	0.405
	II	20	57.1	15	42.9	
	III	30	58.8	21	41.2	
	IV	4	80.0	1	20.0	
Gene	*BRCA1*	37	97.4	1	2.6	0.000*
	BRCA2	42	100.0	0	0.0	
	ATM	0	0.0	25	100.0	
	BARD1	0	0.0	3	100.0	
	BRIP1	0	0.0	6	100.0	
	CHEK2	0	0.0	24	100.0	
	NBN	0	0.0	3	100.0	
	PALB2	0	0.0	3	100.0	
Pathogenity	LP/P	62	60.8	40	39.2	0.014*
	VUS	18	39.1	28	60.9	
Event	Censored	74	52.9	66	47.1	0.222
	Exitus	6	75.0	2	25.0	
Menopause	Menopause	21	52.5	19	47.5	0.775
	Premonapause	59	55.1	48	44.9	
Age	<40	30	68.2	14	31.8	0.025*
	>40	50	48.1	54	51.9	
Ki-67	<14	21	55.3	17	44.7	0.862
	>14	59	53.6	51	46.4	
Relapse	No	62	50.8	60	49.2	0.087
	Yes	18	69.2	8	30.8	
HRD associated cancer	No	42	50.6	41	49.4	0.402
	Yes	38	59.4	26	40.6	

*: Statistically significant at the level of p<0.05.
IHK_FISH: Immunohistochemistry+fluorescence *in situ* hybridization, VUS: Variants of uncertain clinical significance, HR: Hormone receptor, Her2: Human epidermal growth factor receptor 2

carriers, reflecting current clinical practice guidelines [14,15]. The distribution of variants in our cohort was consistent with previous studies, showing a higher proportion of *BRCA*-related variants and a predominance of invasive ductal carcinoma and luminal molecular subtypes [16]. In addition, the most frequently observed variants in the non-*BRCA* group were *ATM* and *CHEK2* [2,7]. Age, menopausal status, and histological grade were not significantly associated with DFS in our cohort, a finding that may be explained by the predominance of advanced-stage disease and the relatively small sample size.

Our findings are consistent with several prior studies reporting comparable survival outcomes between *BRCA* and non-*BRCA* carriers [17]. Liu et al. [18] reported that patients with *BRCA* variants have lower OS rates based on analysis of data from nearly 36,000 patients. While some reports suggest that *BRCA1* variants may be linked to a worse prognosis due to their association with aggressive tumor biology [17,19], others have found no significant differences in long-term survival [20,21]. Nevertheless, it should be noted that *BRCA* variant carriers have a lifetime risk of BC exceeding 50% [22]. The lack of statistical significance in our study might

have originated from limited sample size, heterogeneity in treatment modalities, or the impact of novel therapeutic approaches, including the increasing use of PARP inhibitors and platinum-based chemotherapy, which may mitigate the adverse prognostic impact of *BRCA* variants. Moreover, data from the literature [23] suggest that many confounding factors beyond *BRCA* status may influence OS. In our study, nearly half of the patients who experienced relapse were *BRCA1* carriers, a finding consistent with previous reports [17,19].

The distribution of variant pathogenicity in our cohort is also noteworthy. A higher proportion of LP/P variants was detected in *BRCA* carriers than in non-*BRCA* patients, suggesting potential clinical implications for genetic counseling and risk-adapted management [14,15]. On the other hand, the most common variant types differed between groups: frameshift variants predominated in *BRCA* carriers, whereas missense variants predominated in non-*BRCA* carriers. Similarly, Yazıcı et al. [24] reported that frameshift variants were the most frequent type, accounting for 63.5% of *BRCA1/2* carriers in their study. From a clinical perspective, our results support the notion that genetic testing should not only focus on *BRCA* variants but also encompass non-*BRCA* variants such as *ATM* and *CHEK2*, which were frequent in our cohort. Toss et al. [25] also reported that these two variants are associated with a higher risk of developing BC. In our study, nearly 40% of patients within groups with *ATM* and *CHEK2* variants had positive family history, which is comparable yet lower than the rates of over 60% reported by Toss et al. [25]. Given the increased risk of BC in *ATM* and *CHEK2* variant carriers, the National Comprehensive Cancer Network recommends annual mammography beginning at age 40 [10]. Moreover, since those variants are also reported to be associated with other malignancies, such as ovarian, colorectal, and kidney cancers, individuals with a positive family history should be thoroughly investigated [26]. Consistent with this observation, six of our patients with other malignancies—most commonly ovarian cancer—carried *BRCA* variants, while four carried *CHEK2* variants. Although the prognostic implications of these variants remain uncertain, their detection has potential value for individualized surveillance strategies and familial risk assessment [25]. Metcalfe et al. [15] reported that nearly 50% of *BRCA* carriers in their study underwent risk-reducing mastectomy (RRM), and that the risk of death from BC was approximately 1% within 15 years following RRM. The higher rate of prophylactic surgery among *BRCA* carriers in our study underscores adherence to guideline-based preventive strategies, which may contribute to long-term outcomes regardless of differences in DFS.

In conclusion, our study demonstrated no significant DFS differences between *BRCA* carriers and non-*BRCA* carriers in BC, though relapse events were more frequent among carriers of *BRCA1* and LP/P variants. These findings highlight the complexity of interpreting genetic variants in BC and the importance of integrating molecular, clinical, and therapeutic factors into prognostic assessment. Larger, multicenter studies with longer follow-up are warranted to validate these observations and to clarify the prognostic impact of *BRCA* and non-*BRCA* variants. These findings emphasize the need for broader genetic testing panels in routine clinical practice, particularly in young BC patients without *BRCA1/2* variants. Future studies integrating germline and somatic HRD profiles with treatment outcomes could help define molecular prognostic models for BC.

Study Limitations

The strengths of this study include a relatively long follow-up period and a detailed molecular characterization of variants. Several limitations should be acknowledged in this study. The single-center design, relatively small sample size, and inclusion of only one male patient limit the generalizability of our results. Moreover, subgroup analyses (e.g., *BRCA1* vs *BRCA2*, LP/P vs VUS) may have been underpowered to detect small but clinically relevant differences. In addition, since nearly all patients in our study were white women, the generalizability of our results to other ethnic groups may be limited.

Conclusion

Our findings suggest that while DFS did not significantly differ between *BRCA* and non-*BRCA* carriers, relapse was more common among *BRCA1* pathogenic variant carriers. This highlights the biological and clinical heterogeneity within HRR gene alterations. Incorporating germline HRR gene testing into the diagnostic and follow-up process can support more individualized risk assessment, surveillance, and preventive strategies for BC patients.

Ethics

Ethics Committee Approval: Ethical board approval was granted by the Ethical Board for Clinical Studies at University of Health Sciences Türkiye, Tepecik Education and Research Hospital, with the following protocol number: approval number: 2021/05-37, date: 17.05.2021.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., Concept: M.K., Ö.Ö.K., E.E.P., O.Ü.Ü., Design: M.K., T.R.Ö., Data Collection or Processing: M.K., Ö.Ö.K., T.R.Ö., Analysis or Interpretation: M.K., T.R.Ö., E.E.K., O.Ü.Ü., G.K., Literature Search: M.K., Ö.Ö.K, E.E.P., Writing: M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Balmaña J, Díez O, Castiglione M; ESMO Guidelines Working Group. BRCA in breast cancer: ESMO clinical recommendations. Ann Oncol. 2009;20:19-20.

2. Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol. 2016;34:1460-1468.
3. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006;24:5091-5097.
4. Han MR, Zheng W, Cai Q, et al. Evaluating genetic variants associated with breast cancer risk in high and moderate-penetrance genes in Asians. Carcinogenesis. 2017;38:511-518.
5. Hollestelle A, Wasielewski M, Martens JW, Schutte M. Discovering moderate-risk breast cancer susceptibility genes. Curr Opin Genet Dev. 2010;20:268-276.
6. Reiner AS, Sisti J, John EM, et al. Breast cancer family history and contralateral breast cancer risk in young women: an update from the women's environmental cancer and radiation epidemiology study. J Clin Oncol. 2018;36:1513-1520.
7. Fan Z, Ouyang T, Li J, et al Identification and analysis of CHEK2 germline mutations in Chinese BRCA1/2-negative breast cancer patients. Breast Cancer Res Treat. 2018;169:59-67.
8. Taylor A, Brady AF, Frayling IM, et al. Consensus for genes to be included on cancer panel tests offered by UK genetics services: guidelines of the UK Cancer Genetics Group. J Med Genet. 2018;55:372-377.
9. Kwong A, Ho CYS, Shin VY, Au CH, Chan TL, Ma ESK. How does re-classification of variants of unknown significance (VUS) impact the management of patients at risk for hereditary breast cancer? BMC Med Genomics. 2022;15:122.
10. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19:77-102.
11. Demir S, Tozkir H, Gurkan H, et al. Genetic screening results of individuals with high risk BRCA-related breast/ovarian cancer in Trakya region of Turkey. J BUON. 2020;25:1337-1347.
12. Manguoğlu E, Güran S, Yamaç D, et al. Germline mutations of BRCA1 and BRCA2 genes in Turkish breast, ovarian, and prostate cancer patients. Cancer Genet Cytogenet. 2010;203:230-237.
13. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424.
14. Jacobson M, Coakley N, Bernardini M, et al. Risk reduction strategies for BRCA1/2 hereditary ovarian cancer syndromes: a clinical practice guideline. Hered Cancer Clin Pract. 2021;19:39.
15. Metcalfe K, Huzarski T, Gronwald J, et al. Risk-reducing mastectomy and breast cancer mortality in women with a BRCA1 or BRCA2 pathogenic variant: an international analysis. Br J Cancer. 2024;130:269-274.
16. Celik Demirbas B, Kilic Erciyas S, Sukruoglu Erdogan O, et al. Genetic insights into BRCA1/2 associated breast cancer in Türkiye: focus on early-onset and aggressive subtypes. Discov Oncol. 2025;16:746.
17. Zhu Y, Wu J, Zhang C, et al. BRCA mutations and survival in breast cancer: an updated systematic review and meta-analysis. Oncotarget. 2016;7:70113-70127.
18. Liu M, Xie F, Liu M, Zhang Y, Wang S. Association between BRCA mutational status and survival in patients with breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2021;186:591-605.
19. Lee EH, Park SK, Park B, et al. Effect of BRCA1/2 mutation on short-term and long-term breast cancer survival: a systematic review and meta-analysis. Breast Cancer Res Treat. 2010;122:11-25.
20. Sambiasi D, Lambo R, Pilato B, et al. BRCA1/2 and clinical outcome in a monoinstitutional cohort of women with hereditary breast cancer. Oncol Rep. 2014;31:365-369.
21. Huzarski T, Byrski T, Gronwald J, et al. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. J Clin Oncol. 2013;31:3191-196.
22. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25:1329-1333.
23. Dwornik R, Białkowska K. Insights into genetic modifiers of breast cancer risk in carriers of BRCA1 and BRCA2 pathogenic variants. Hered Cancer Clin Pract. 2025;23:15.
24. Yazıcı H, Kılıç S, Akdeniz D, et al. Frequency of rearrangements versus small indels mutations in *BRCA1* and *BRCA2* genes in Turkish patients with high risk breast and ovarian cancer. Eur J Breast Health. 2018;14:93-99.
25. Toss A, Tenedini E, Piombino C, et al. Clinicopathologic profile of breast cancer in germline ATM and CHEK2 mutation carriers. Genes (Basel). 2021;12:616.
26. Cybulski C, Górski B, Huzarski T, et al. CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet. 2004;75:1131-1135.