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BRCA1 mutation in breast cancer patients: Analysis of prognostic factors and survival

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Abstract. The presence of BRCA1 mutations is associated with an increased risk of breast and ovarian cancer. The present study compared clinicopathological characteristics and overall survival (OS) of hereditary and sporadic breast cancer. Using data collected from a previous study conducted between 2007-2016 at the Maria Skłodowska Curie Cancer Center and Institute of Oncology (Gliwice, Poland), the prognostic factors and survival in 60 breast cancer mutation carriers were analyzed. A control group was selected from the breast cancer patients without BRCA mutations (n=386). BRCA mutation carriers had significantly worse survival when compared with non-carriers (P=0.017). The 10-year OS rate was 78.0% for all analyzed groups: 65.9% for BRCA mutation carriers and 81.1% for non-carriers. In the univariate analyses, BRCA mutation carriers had a significantly higher risk of mortality in comparison to non-carriers [hazard ratio (HR)=1.87; 95% confidence interval (CI) 1.08-3.25]. Increased tumor size (HR=3.64), lymph node metastases (HR=2.45) and higher histological grade (HR=2.84) were significant factors for worse OS. Positive estrogen receptor status was associated with a better OS (HR=0.49, P=0.022). Age ≤40 years (HR=0.48, P=0.081) was an insignificantly favorable factor. The 10-year survival rate was significantly decreased in patients with BRCA1 mutation. Therefore, negative factors for OS in mutation carriers included lymph nodes metastases, negative steroid receptor status and increased tumor size.

Introduction

The presence of *BRCA* mutations increases the risk of breast (~80%) and ovarian cancer (~40%). The incidence of *BRCA* mutations in breast and ovarian cancer are <1-7% for *BRCA1* and 1-3% for *BRCA2* independently from family history or age at diagnosis. In literature, a family history of breast or ovarian cancer, young age at diagnosis, male breast cancer or multiple tumors (bilateral breast cancer or breast and ovarian cancer in the same patient) occur more often in *BRCA* mutation carriers. The median time of diagnosis of breast cancer in patients with germline *BRCA* mutation is lower (in age under 50 years) than for patients with sporadic cancer (1). External factors which can modify *BRCA* associated breast cancer risk are hormonal and reproductive factors such as pregnancy, history of breast feeding and oral contraceptives (2,3).

It has previously been demonstrated that tumors in patients with *BRCA1* mutation frequently exhibit negative steroid receptor status, with expression of p53 protein. Mutations in *TP53* gene also seem to be increased in tumors with *BRCA1* mutation. A previous study indicated that familial breast cancers with *BRCA1* mutation are different from *BRCA2* tumors and sporadic cancers (4).

The triple negative breast cancer (TNBC) phenotype is the most commonly observed molecular subtype in patients with *BRCA1* mutation. The presence of triple negative diseases in *BRCA1* mutation carriers is higher than in sporadic breast cancer patients and is 11-20% (5). Recent data show that survival rate of *BRCA* carriers who were administrated systemic treatment (chemotherapy) was similar to non-carriers (6,7). Various studies both clinical and preclinical, showed that *BRCA* is an important factor affecting chemotherapy response and treatment toxicity in breast cancer patients (8). In Poland, three founder mutations in *BRCA1* (i.e., 5382insC, C61G, 4153delA) are under investigation (9).

In the present study, we compare hereditary and sporadic breast cancer according to clinicopathological factors and overall survival (OS) time.

Materials and methods

In a study conducted in the years 2007-2016 in the Maria Skłodowska Curie Memorial Cancer Center and Institute of Oncology (COI; Gliwice, Poland), we analyzed prognostic factors and survival in 60 patients with breast cancer with confirmed *BRCA1* mutations. A control group was selected from breast cancer patients without the *BRCA* mutation (n=386). The patients in both groups were treated according to

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the same protocol. All patients had signed a written informed consent allowing their biological material to be used in clinical research.

All patients were females diagnosed, treated and followed up at the COI in Gliwice. Patients underwent clinical follow-up examinations every three months in the first two years, every six months afterwards until the fifth year after diagnosis and every year subsequently. Inclusion criteria were: Breast cancer confirmed by microscopic examination, performance status ZUBROD 0-1, age above 18, the correct value of renal and liver function and normal values of bone marrow. The data of age at onset, menopausal status, surgical procedure, disease stage according to TNM classification, histology, estrogen and progesterone receptor (PR) status, HER2 status and contralateral breast cancer were gathered from hospital records and pathology reports. The analysis of patient medical records was performed according to national law regulation.

All patients had genetic tests and consultation in Genetic Outpatient Clinic. Mutation profile was assessed by RFLP-PCR technique. We evaluated the three most common mutations in the Polish population, including 5382insC, C61G and 4153delA. All patients were tested for the presence of *BRCA1* and *BRCA2* mutations. Mutation analysis was conducted by a multiplex allele-specific polymerase chain reaction assay.

Statistical analysis was carried out using STATISTICA 7 software (StatSoft, Inc., Tulsa, OK, USA). The frequency of side effects was monitored. The qualitative features were presented as the percentage of their occurrence and evaluated with Fisher's test and χ^2 test with Yates correction. $P<0.05$ was considered to indicate a statistically significant difference. Prognostic factors of OS were estimated by Cox proportional hazards model. The probability of survival was estimated using the Kaplan-Meier method.

Results

Patient characteristics. For the total group of 446 cases, the median age at diagnosis was 51.8 years (range, 23.7-78.3 years). In *BRCA* mutation carriers (n=60) and non-carriers (n=386) the median age was 43.5 years (range, 23.7-74.4 years) and 53.1 years (range, 25.6-78.3 years), respectively. *BRCA* carriers were significantly younger (P<0.0001) than non-carriers. A total of 263 women (59.0%) were in premenopausal period (80% carriers and 56% non-carriers) (P=0.0004). The majority of patients had early stage breast cancer. Distant metastases were observed only in 7 (1.6%) of women (1 case in *BRCA* mutation carriers and 6 in non-carriers). Lymph node metastases (N+) was detected more frequently in non-carriers (45.9%; vs. 18.3%, P=0.0001). Conversely, locally advanced breast cancer (T3-T4) was reported frequently in *BRCA* mutation carriers (38.3% vs. 19.4%, P=0.002). Lobular invasive carcinoma was reported more often in patients without *BRCA* mutation than in *BRCA* carriers (12.2% vs. 5%). As expected, patients with *BRCA* mutation had more frequent estrogen receptor (ER; 66.7% vs. 35.5%, P=0.0001) and PR (71.7% vs. 41.7%, P=0.0002) negative receptor status, higher histological grade (G3; 50% vs. 29.5%, P=0.002), negative HER2 receptor status (98.3% vs. 56.2%, P=0.0001) and TNBC (61.7% vs. 15.0%, P=0.0001). There was also an observed predisposition to the development of secondary cancers in mutation carriers (35% vs. 9.6%, P=0.0001). Clinicopathological patient characteristics are presented in Table I.

In the subgroup analysis, there were no significant differences between younger (≤40 years) and older (> 40 years) *BRCA* mutation carriers according to clinicopathological factors. Among younger patients (≤40 years) there was an observed increased occurrence of TNBC (68% vs. 58%; P=0.583), tumors with negative ER status (ER-) (77% vs. 60%; P=0.258) and with negative PR status (PR-) (77% vs. 68%; P=0.560) and without HER2 overexpression (100% vs. 97.4%, P=1.00) (Table II). In *BRCA* non-carriers, younger patients (≤40 years) in comparison to older exhibited an increased rate of diagnosis of TNBC (20.0% vs. 14.4%, P=0.373), tumors with ER- status (42.2% vs. 34.6%, P=0.324) and HER2 overexpression (48.9% vs. 43.1%, P=0.524). There were no differences observed in negative PR status (PR-) (42.2% vs. 41.6%).

Treatment strategies. Treatment strategies are presented in Table III. The surgical treatment was performed in 402 (90.1%) patients, including mastectomy for 292 (65.5%) and breast conserving treatment (BCT) for 110 (24.7%). BCT was conducted more often in non-carriers in comparison to carriers (28.2% vs. 21.6%, P=0.401). Radiotherapy was administered to 66.7% of mutation carriers and 67.1% non-carriers (P=1.00). The total radiotherapy dose administered was 50 Gy in 25 fractions. If indicated, a boost was delivered. All patients underwent chemotherapy. A total of 97.3% (434) patients received anthracycline based chemotherapy (AC, FAC) at The Clinical and Experimental Oncology Department. Chemotherapy regiments with taxanes (paclitaxel) were used in 13% of patients. Patients with steroid positive receptor breast cancer were treated with anti-estrogen therapy: 61.1% of non-carriers and 30.0% of *BRCA* mutation carriers (P<0.0001). The lower frequency of HT in carriers was due to the high frequency of ER (-) in that group. Trastuzumab was used in women with HER2 positive breast cancer confirmed by immunohistochemistry examination or by the FISH method (gene amplification) (1.7% *BRCA* carriers and 41.2% non-carriers, P<0.0001).

Survival analysis in BRCA (-) negative patients. Patients with positive nodes (N +) exhibited a significantly worse OS than those without node involvement (5-year survival rate 82% vs. 93%, P=0.0008) (Fig. 1). Risk of mortality was 2.7 fold higher for patients with lymph node metastases. The 5 year OS rate depending on the depth (T) was 97% for T1, 88% for T2 and 74% for the T3-T4 (Fig. 2). The risk of mortality depended on the stage of the disease and was higher at the advanced T3-T4 stages, HR=4.7; (P=0.0006). Patients with positive ER status (ER+) had a longer OS rate (5-year OS 91% vs. 82%, P=0.054) however this was not significant (Fig. 3). Patients with tumor HER2 overexpression had a lower OS rate (5-year OS 86% vs. 89%, P=0.273) (Fig. 4), which was also not significant. Younger patients (≤40 years) had an increased OS rate (5-year OS 93% vs. 87%; P=0.167) (Fig. 5) however this was again not significant. They also had a lower risk of mortality (HR=0.36; P=0.167) compared with

Table I. Clinicopathological patient's characteristics according to *BRCA1* mutation carriers.

Factors	n	Percentage of total n (%)	*BRCA1* carriers		*BRCA1* non carriers		P-value
			n	% of n	n	% of n	
Total cases	446	100	60	100	386	100	-
Age (range, 24-78 years; median 52 years)							
≤65	386	86.5	55	91.7	331	85.8	0.308
>65	60	13.5	5	8.3	55	14.2	
Age (years)							
≤40	67	15.0	22	36.7	45	11.7	0.0001
>40	379	85.0	38	63.3	341	88.3	
Menopausal status							
Postmenopausal	183	41.0	12	20.0	171	44.3	0.0004
Premenopausal	263	59.0	48	80.0	215	55.7	
Clinical staging							
I	90	20.2	8	13.3	82	21.2	0.030
IIA	136	30.5	23	38.3	113	29.3	
IIB	128	28.7	23	38.3	105	27.2	
IIIA	69	15.5	2	3.3	67	17.4	
IIIB	11	2.5	3	5.0	8	2.1	
IIIC	5	1.1	0	0.0	5	1.3	
IV	7	1.6	1	1.7	6	1.6	
T							
T1	131	29.4	10	16.7	121	31.3	0.0001
T2	217	48.7	27	45.0	190	49.2	
T3	77	17.3	14	23.3	63	16.3	
T4	21	4.7	9	15.0	12	3.1	
Clinical staging nodes							
N0	258	57.8	49	81.7	209	54.1	0.001
N1	133	29.8	8	13.3	125	32.4	
N2	47	10.5	3	5.0	44	11.4	
N3	8	1.8	0	0.0	8	2.1	
G							
G1	27	6.1	1	1.7	26	6.7	0.002
G2	111	24.9	6	10.0	105	27.2	
G3	144	32.3	30	50.0	114	29.5	
Missing	164	36.8	23	38.3	141	36.5	
Tumor type							
Ductal invasive	363	81.4	56	93.3	307	79.5	0.035
Lobular invasive	50	11.2	3	5.0	47	12.2	
Other	33	7.4	1	1.7	32	8.3	
ER							
Negative	177	39.7	40	66.7	137	35.5	0.0001
Positive	269	60.3	20	33.3	249	64.5	
PR							
Negative	204	45.7	43	71.7	161	41.7	0.0002
Positive	242	54.3	17	28.3	225	58.3	
Steroid receptor							
Negative	161	36.1	37	61.7	124	32.1	0.0002
Positive	285	63.9	23	38.3	262	67.9	

Table I. Continued.

Factors	n	Percentage of total n (%)	*BRCA1* carriers		*BRCA1* non carriers		P-value
			n	% of n	n	% of n	
HER2 overexpression							
Negative	276	61.9	59	98.3	217	56.2	0.0001
Positive	170	38.1	1	1.7	169	43.8	
Triple negative							
No	351	78.7	23	38.3	328	85.0	0.0001
Yes	95	21.3	37	61.7	58	15.0	

T, tumor size; N, node; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; G, grade.

Table II. Patient's characteristics according to age.

Factors	Total n	Percentage of total n (%)	Age ≤40 years		Age >40 years		P-value
			n	% of n	n	% of n	
BRCA1 carriers	60	100	22	100	38	100	-
T							
T1	10	16.7	4	18.2	6	15.8	0.635
T2	27	45.0	8	36.4	19	50.0	
T3-T4	23	38.3	10	45.5	13	34.2	
Clinical staging nodes							
N0	49	81.7	20	90.9	29	76.3	0.0001
N+	11	18.3	2	9.1	9	23.7	
G							
G1-G2	7	11.7	1	4.5	6	15.8	0.261
G3	30	50.0	10	45.5	20	52.6	
Missing	23	38.3	11	50.0	12	31.6	
ER							
Negative	40	66.7	17	77.3	23	60.5	0.258
Positive	20	33.3	5	22.7	15	39.5	
PR							
Negative	43	71.7	17	77.3	26	68.4	0.560
Positive	17	28.3	5	22.7	12	31.6	
HER2 overexpression							
Negative	59	98.3	22	100.0	37	97.4	1.00
Positive	1	1.7	0	0.0	1	2.6	
Triple negative							
No	23	38.3	7	31.8	16	42.1	0.583
Yes	37	61.7	15	68.2	22	57.9	

T, tumor size; N, node; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; G, grade.

older patients. In uni- and multivariate analyses, increased tumor size, lymph node metastasis and higher tumor grade were all associated with increased risk of mortality (Table IV). Similarly, steroid receptor status (ER negative) insignificantly increased risk of mortality.

Survival analysis in BRCA (+) mutation carriers. The 5-year OS rate was 77.3% [95% confidence interval (CI), 66.4-88.2%]. Patients with lymph node metastases (N +) had a significantly lower 5-year OS compared with patients without lymph node involvement (52% vs. 83%, P=0.03) and 3.0 fold higher risk of

Table III. Treatment strategy according to *BRCA1* mutation.

			BRCA1 carriers		*BRCA1* non carriers		
Treatment	Total n	Percentage of total n (%)	n	% of n	n	% of n	P-value
Total cases	446	100	60	100	386	100	-
Chemotherapy regimen							
AC FAC	376	84.3	44	73.3	332	86.0	0.005
AC + taxanes	58	13.0	11	18.3	47	12.2	
CMF	12	2.7	5	8.3	7	1.8	
Trastuzumab therapy							
Yes	160	35.9	1	1.7	159	41.2	0.0001
No	286	64.1	59	98.3	227	58.8	
Hormonotherapy							
Yes	254	57.0	18	30.0	236	61.1	0.0001
No	192	43.0	42	70.0	150	38.9	
Local treatment							
Mastectomy	292	65.5	40	66.7	252	65.3	0.224
Breast conservation surgery	110	24.7	11	18.3	99	25.6	
Without surgery	44	9.9	9	15.0	35	9.1	
Radiotherapy							
Yes	299	67.0	40	66.7	259	67.1	1.00
No	147	33.0	20	33.3	127	32.9	

AC, Adriamycin (or doxorubicin; 60 mg/m^2) and Cyclophosphamide (600 mg/m^2) treatment; FAC, Fluorouracil (500 mg/m^2), Adriamycin (or doxorubicin; 50 mg/m^2) and Cyclophosphamide (500 mg/m^2) treatment; CMF, Cyclophosphamide (100 mg/m^2), Methotrexate (40 mg/m^2) and Fluorouracil (600 mg/m^2) treatment.

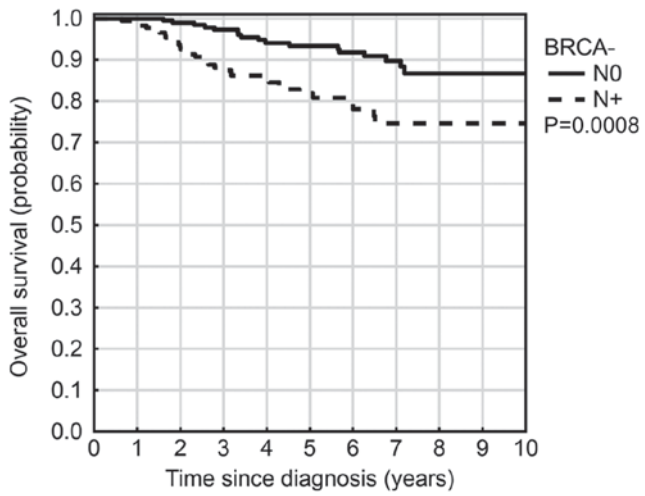

Figure 1. Overall survival analysis in BRCA(-) negative patients according to lymph node involvement. P=0.0008. N, node.

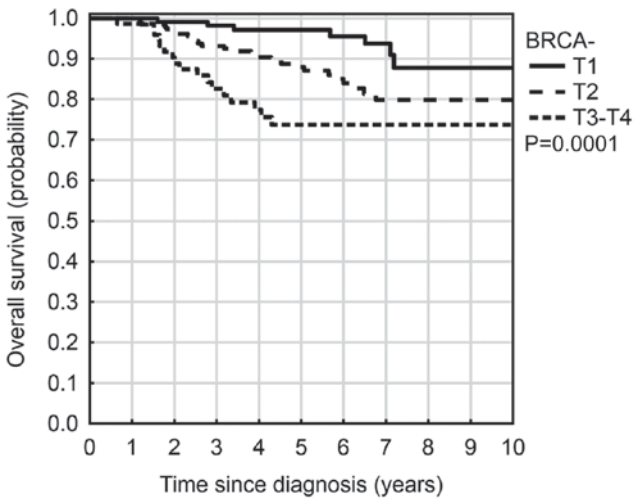

Figure 2. Overall survival analysis in BRCA(-) negative patients according to tumor size. P=0.0001. T, tumor size.

death (Fig. 6). 5-year OS was associated with tumor size (T) and was 90% for T1, 84% for T2 and 63% for T3-T4. The risk of mortality depended on stage of disease and was the greatest at the advanced T3-T4 stages, HR=5.07; (95% CI, 0.64-40.33 P=0.125) (Fig. 7). Patients who had tumors with ER+ status had an insignificantly higher 5-year OS (83% vs. 74%, P=0.417) (Fig. 8). Younger patients (≤40 years) exhibited an insignificantly higher OS (82% vs. 75%; P=0.310) (Table IV). In univariate analysis, lymph node metastasis was a significant prognostic factor. In multivariate analysis, lymph node metastases (HR=3.29, P=0.036) and ER- status (HR=7.14, P=0.049) were identified as negative prognostic factors in *BRCA* mutation carriers. Conversely, TNBC was a favorable prognostic factor in this group (HR=0.20, P=0.073) (Table IV).

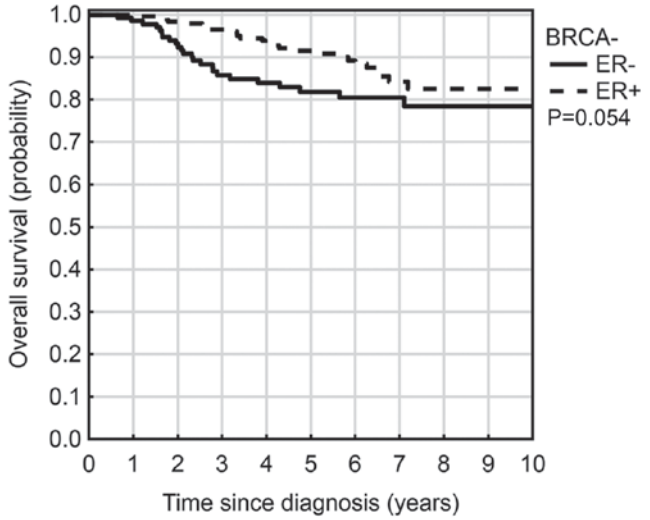

Figure 3. Overall survival analysis in BRCA(-) negative patients according to steroid receptor status. P=0.054. ER, estrogen receptor.

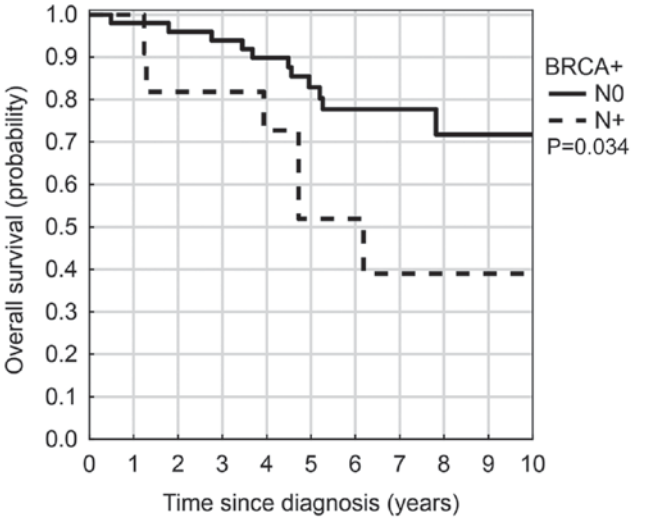

Figure 6. Overall survival analysis in BRCA(+) positive patients according to lymph node involvement. P=0.034. N, node.

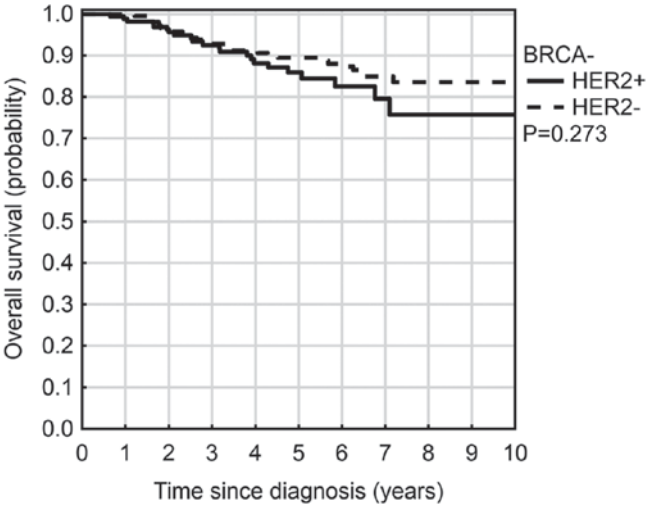

Figure 4. Overall survival analysis in BRCA(-) negative patients according to HER2 overexpression. P=0.273. HER2, human epidermal growth factor receptor 2.

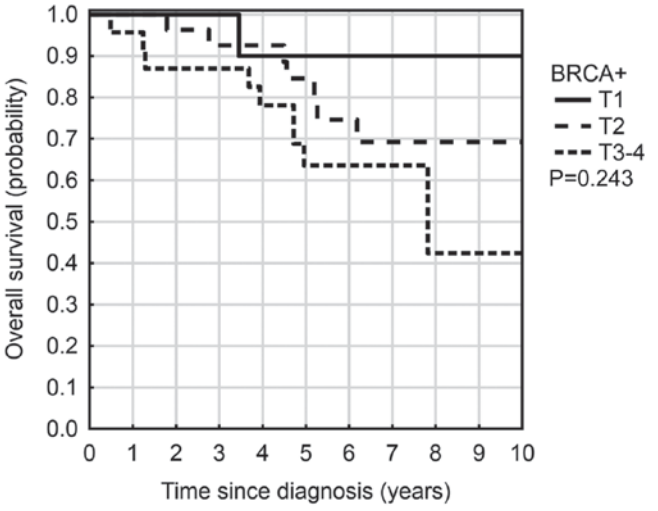

Figure 7. Overall survival analysis in BRCA(+) positive patients according to tumor. P=0.243. T, tumor size.

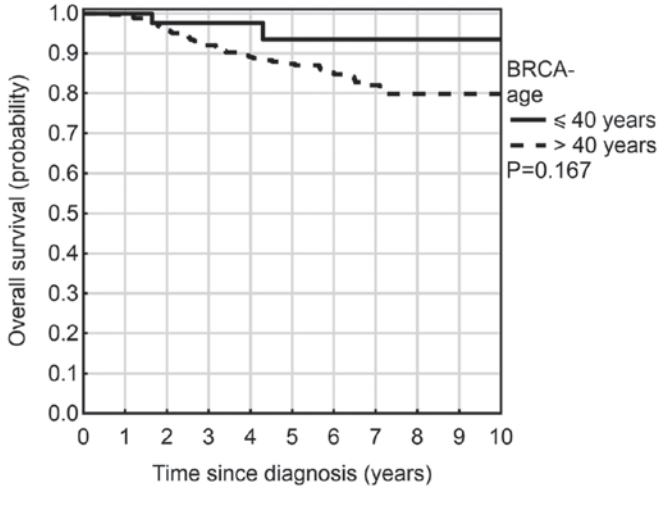

Figure 5. Overall survival analysis in BRCA(-) negative patients according to patients age. P=0.273.

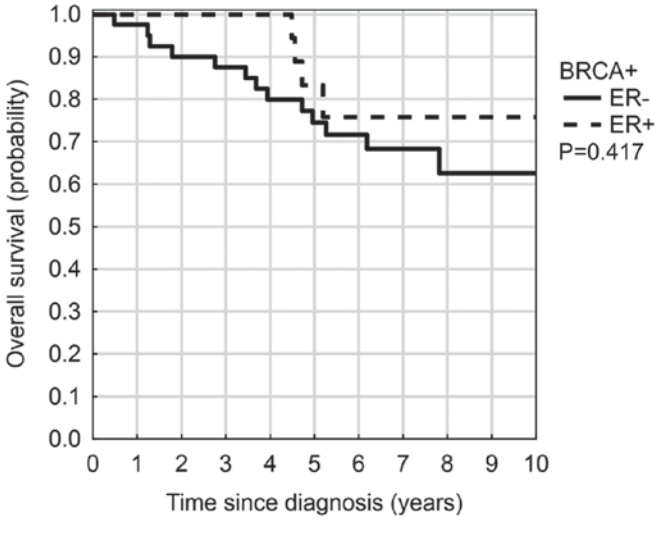

Figure 8. Overall survival analysis in BRCA(+) positive patients according to steroid receptor status. P=0.417. ER, estrogen receptor.

Table IV. 5-year survival rates, and uni- and multivariate hazard ratios for mortalities in *BRCA1* non-carriers and carriers.

A, *BRCA1* non-carriers

Factor	Total n	5-year survival rate (%)	Test log rank P-value	Univariate		Multivariate		
				HR	P-value	HR	95% CI	P-value
Total cases	386	88.1	-	-	-	-	-	-
Age (years)								
≤40	45	93.5		0.36	0.161	0.37	0.09-1.53	0.169
>40	341	87.4	0.167	1.0		1.0		
T Stage								
T1	121	97.1		1.0		1.0		
T2	190	87.9	0.0001	2.59	0.026	2.26	0.98-5.22	0.057
T3-T4	75	73.7		4.71	0.0006	3.32	1.34-8.20	0.009
Clinical staging nodes								
N0	209	93.4		1.0		1.0		
N+	177	81.9	0.0008	2.67	0.001	2.40	1.30-4.42	0.005
G								
G1-G2	131	94.8		1.0		1.0		
G3	114	84.0	0.0039	3.71	0.004	2.93	1.19-7.19	0.019
Missing	141	85.3		3.04	0.009	2.95	1.27-6.86	0.012
ER status								
Negative	137	81.8		1.0		1.0		
Positive	249	91.5	0.054	0.58	0.057	0.54	0.28-1.04	0.064
Triple negative								
No	328	88.5		1.0		1.0		
Yes	58	85.2	0.745	1.12	0.754	0.69	0.30-1.59	0.382

B, *BRCA1* carriers

Factor	N	5-year survival rate	Test log rank P-value	Univariate		Multivariate		
				HR	P-value	HR	95% CI	P-value
Total cases	60	77.3	-	-	-	-	-	-
Age (years)								
≤40	22	81.8	0.310	0.59	0.326	0.44	0.12-1.60	0.213
>40	38	75.0		1.0		1.0		
T Stage								
T1	10	90.0		1.0		1.0		
T2	27	84.5	0.243	2.91	0.318	2.71	0.31-23.4	0.365
T3-T4	23	63.5		5.07	0.125	5.39	0.64-45.1	0.120
Clinical staging nodes								
N0	49	82.9	0.034	1.0		1.0		
N+	11	51.9		3.00	0.031	3.29	1.08-9.99	0.036
G								
G1-G2	7	83.3		1.0		1.0		
G3	30	75.3	0.798	1.98	0.516	1.61	0.19-13.72	0.663
Missing	23	77.8		1.77	0.596	1.37	0.15-12.14	0.779
ER status								
Negative	40	74.4	0.417	1.0		1.0		
Positive	20	83.3		0.63	0.419	0.14	0.02-0.99	0.049

Table IV. Continued.

B, *BRCA1* carriers

Factor	N	5-year survival rate	Test log rank P-value	Univariate		Multivariate		
				HR	P-value	HR	95% CI	P-value
Triple negative								
No	23	81.3		1.0		1.0		
Yes	37	75.1	0.884	1.08	0.883	0.20	0.03-1.17	0.073

HR, hazard ratio; CI, confidence interval; T, tumor size; N, node; G, grade; ER, estrogen receptor.

BRCA mutation carriers had a significantly worse survival rate compared with non-carriers (P=0.017) (Fig. 9). The ten-year OS rate was 78.0% for all analyzed groups: 65.9% for *BRCA* mutation carriers and 81.1% for non-carriers. The 5-year (OS) rate was 86.2% for all analyzed groups: 77.3% for *BRCA* mutation carriers and 88.1% for non-carriers. In univariate analyses, *BRCA* mutation carriers had a significantly higher risk of mortality in comparison to non-carriers (HR=1.87, 95% CI, 1.08-3.25) (Table V). After adjusting for other prognostic factors, there was a significant difference in survival between carriers and non-carriers (HR=2.28, P=0.019). Higher tumor grade (T3-4) (HR=3.64), lymph node metastases (N+) (HR=2.45) and G3 (HR=2.84) were significant factors for a worse OS. ER+ status was associated with a better OS (HR=0.49, P=0.022). Younger age (≤40 years) (HR=0.48, P=0.081) was a favorable factor, but was not significant. Detailed results for multivariate analysis are shown in Table V.

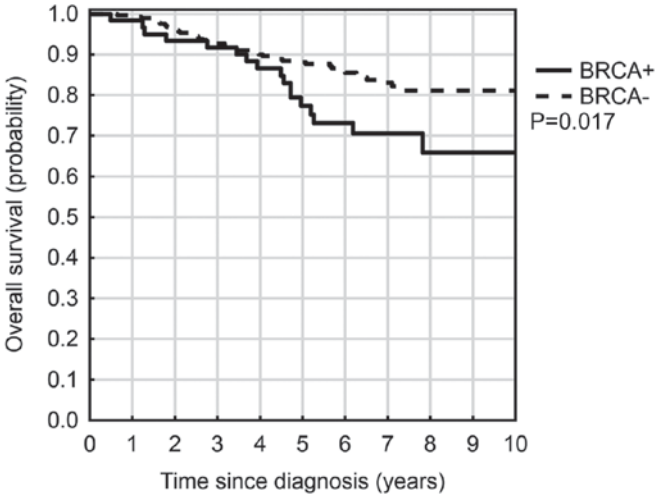

Figure 9. Overall survival analysis according to the presence of BRCA mutation. P=0.017.

Discussion

In this retrospective study, we reported the negative factors for OS in breast cancer patients with *BRCA* mutation which were: Infiltration of armpit lymph nodes (P=0.034), increased size of primary tumor (T3-T4, P=0.243), age >40 years (P=0.310) and negative steroid receptor status (P=0.417). In case of non-carriers, negative factors for OS were also: Lymph node metastasis (N+) (P=0.0008), increased tumor size (T3-T4) (P=0.0001), negative steroid receptor status (P=0.054) and HER2 overexpression, however this was not significant (P=0.273).

In a previous study involving a group of patients with stage I breast cancer, *BRCA* mutation carriers, the ten-year survival rate was 89.9%. Huzarski *et al* (9) reported that the ten-year OS among breast cancer patients with *BRCA1* mutation is similar to OS in women without a *BRCA1* mutation. Similarly, survival outcomes of *BRCA1* mutation carriers were similar to those of sporadic breast cancer patients in a study conducted by Goodwin *et al* (10). Worse survival outcomes in *BRCA2* mutation carriers were observed in univariable analysis (more adverse tumor characteristics). However, similar outcomes of *BRCA2* mutation carriers and sporadic disease were identified in multivariable analyses (10). In previous reports, breast cancer *BRCA* mutation carriers exhibited a worse prognosis compared with breast cancer patients of the same age that did not have the *BRCA* mutation (11,12). In our study, the ten-year OS rate was 65.9% for BRCA mutation carriers and 81.1% for non-carriers, irrespective of disease stage. Lee *et al* (4) showed that the presence of *BRCA1* mutation decreases short-term and long-term OS rate, and short-term progression-free survival rate (PFSR). Conversely, there was no reported association between *BRCA2* mutation and short-term or long-term survival rate. This suggests that carcinogenic pathways for *BRCA1* and *BRCA2* are different (13). Baretta *et al* (14) revealed that patients with *BRCA1* mutation have worse OS in comparison to *BRCA*-sporadic patients (HR 1.30; 95% CI, 1.11-1.52). Similarly, worse breast cancer-specific survival was reported in *BRCA1* mutation carriers among patients with stage I-III breast cancer (HR, 1.45; 95% CI, 1.01-2.07) (14). The meta-analyses conducted by Van der Broek *et al* (15) did not support worse survival in breast cancer for patients with *BRCA1/2* mutation in the adjuvant treatment. They only improved a 10% worse unadjusted recurrence-free survival for *BRCA1* mutation carriers (15). In the present study, *BRCA* mutation carriers had a significantly worse survival rate compared with non-carriers (P=0.017). However, patients with the *BRCA* mutation had an increased rate of TNBC diagnosis in comparison to those with sporadic breast cancer (61.7% vs. 15.0%, P=0.0001).

Clinicopathological factors affecting OS were also analyzed in various studies. The survival rate for *BRCA*

Table V. Multivariate analysis for overall survival.

Factor	Hazard ratio	95% CI	P-value
BRCA mutation carriers vs. non carriers (univariable)	1.87	1.08-3.25	0.026
BRCA mutation carriers vs. non carriers (adjusted)	2.28	1.15-4.55	0.019
Adjusted for:			
Age (years)	0.48	0.21-1.10	0.081
T2 vs. T1	2.33	1.07-5.08	0.033
T3-4 vs. T1	3.64	1.61-8.20	0.002
N+ vs. N0	2.45	1.45-4.14	0.001
G3 vs. G1-2	2.84	1.26-6.42	0.012
G missing vs. G1-2	2.82	1.29-6.16	0.009
ER positive vs. ER negative	0.49	0.27-0.90	0.022
TNBC vs. others	0.61	0.29-1.28	0.192

T, tumor size; N, node; G, histological grade; ER, estrogen receptor; TNBC, triple negative breast cancer; CI, confidence interval.

positive women without lymph node infiltration and tumor size <1 cm was not increased, compared with patients with tumor size between 1 and 2 cm (10). In the present study, the risk of mortality depended on the stage of the disease and was higher at the advanced T3-T4 stages in *BRCA* mutation non-carriers and in patients with the *BRCA* mutation. Huzarski *et al* (9) reported that oophorectomy significantly improved survival among women with a *BRCA1* mutation. *BRCA1* mutation carriers who received chemotherapy had better survival in comparison to women treated without chemotherapy (9). In the Goodwin *et al* (10) study, the survival of *BRCA1* mutation carriers treated with chemotherapy was similar to that of *BRCA 1* non-carriers. However, in case of treatment without chemotherapy, the survival of *BRCA1* mutation carriers was worse (HR=1.97; 95% CI, 0.65-5.94) (10). In our study, all patients received chemotherapy; 97.3% of patients received chemotherapy regimens with anthracycline.

Foulkes *et al* (11) confirmed that *BRCA1* mutation carrier status was associated with clinicopathological factors of breast cancer associated with worse prognosis, including young age at diagnosis, high nuclear grade, negative steroid receptor status (ER-), and the presence of somatic *TP53* mutations. In the group of patients with negative steroid receptor status (ER-) tumors, higher nuclear grade 3 and tumor size <20 mm the *BRCA1* positive status was associated with a significantly worse prognosis (11). Previous studies have confirmed these results (7,16,17). Osin and Lakhani reported that *BRCA1*-associated tumors are more likely to be steroid receptor negative, and more frequently express p53 protein. Mutations in the *TP53* gene also appear to be increased in tumors with *BRCA1* mutation (18). The presence of steroid receptor status (ER) in tumors with *BRCA1* mutation was significantly lower (8 vs. 26%) in comparison with a grade-matched control group. In contrast, the presence of ER in tumors with *BRCA2* mutation appears to be similar to that in sporadic breast cancers (13,19). In some studies, there was no difference between mutation carriers and non-carriers according to HER2/neu overexpression or amplification (17,20). Crook *et al* (20) showed that tumors with *BRCA* mutation were more often p53 positive in comparison to sporadic breast cancers (77% *BRCA1*, 45% *BRCA2*, 35% sporadic). The presence of mutations in the *TP53* gene have also been reported to be increased in *BRCA1* tumors (18). In our analysis, negative prognostic factors for both groups (*BRCA* mutation carriers and non-carriers) were lymph node metastases, negative steroid receptor status and larger tumor size.

BRCA mutation carriers were characterized by younger age, negative steroid receptor status, tumors without HER2 overexpression and larger tumor size (T3-T4). The ten-year survival rate among breast cancer patients with the *BRCA1* mutation was significantly worse than in patients without a *BRCA1* mutation. Negative factors for OS in breast cancer patients who were carriers of *BRCA* mutations included infiltration of armpit lymph nodes, negative steroid receptor status and increased size of the primary tumor.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JH analyzed and interpreted the patient data and was a major contributor in writing the manuscript. ZK performed statistical analysis, and analyzed and interpreted the patient data.

EG made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All patients provided written informed consent allowing for their biological material to be used in clinical research.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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