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HEREDITARY BREAST AND OVARIAN CANCER – UNIVERSITY HOSPITAL OF SPLIT EXPERIENCES

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Summary

Aim: To investigate the clinical and pathohistological tumor characteristics, treatment, and treatment outcomes in patients with hereditary breast and ovarian cancer who were diagnosed, treated, and monitored at the University Hospital of Split from October 1999 to April 2021.

Methods: The data were collected retrospectively from the medical history of 15 patients. They included the patient's age at diagnosis, family history of malignancies, histological subtype, grade, breast cancer immunophenotype, stage of disease, status and types of BRCA mutations, type of surgical and oncological treatment, the specifics of metachronous bilateral breast cancers, the specifics of synchronous breast and ovarian cancers, and the outcome of treatment through overall survival (OS).

Results: The median age of patients at the time of diagnosis of breast cancer was 53 years, and for ovarian cancer it was 56 years. A positive family history was confirmed in 13 patients (87%). All ovarian cancer patients had a high-grade serous histologic type, most often diagnosed in FIGO stages III and IV. Breast cancers were most commonly diagnosed in stages IA and IIA, with equally represented triple-negative and luminal immunophenotypes. The most common mutation was *BRCA1* c.5266dup. The median OS of our patients was not reached.

Conclusion: The clinical features of patients, pathohistological characteristics of tumors, and treatment outcomes in our study population are comparable with reports in the literature, respecting the specifics of different nations and races.

KEYWORDS: *breast and ovarian cancer; BRCA mutations; outcomes*

INTRODUCTION

Breast cancer is the most common cancer among females worldwide, with an estimated 2.26 million new cases, representing 11.7% of all cancer cases, and 684 996 deaths in 2020. Ovarian cancer is the most lethal gynecological malignancy worldwide. According to global estimates, 313 959 new cases were detected in 2020, and 207 252 women died from the disease(1). In Croatia, breast cancer is the leading cancer in women, with 2,869 new cases and 722 deaths in 2020. Ovarian cancer is the eighth most common cancer in women, with 368 new cases, and the leading cause of death from gynecological cancer, with 316 deaths in 2020(2).

According to the American National Cancer Institute, hereditary breast and ovarian cancer (HBOC) is defined as *an inherited disorder in which*

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the risk of breast cancer (especially before the age of 50 years) and ovarian cancer is higher than normal(3). Familial breast cancer involves families with a history of multiple breast or ovarian cancers, accounting for about 15% of all breast cancer patients. Women with such families are genetically predisposed to cancer (HBOC), mostly due to pathogenic mutations in the *BRCA1* and *BRCA2* genes(4). Besides *BRCA1* and *BRCA2* mutations, alterations in a number of other homologous recombination genes with moderate penetrance, including *PALB2, RAD51C, RAD51D, BRIP1*, and others, have also been described in HBOC patients(5,6). People with HBOC syndrome may also have an increased risk of developing other types of cancer, including melanoma, pancreatic, and prostate cancer(3,5).

The results from 24 studies showed that the risk of developing breast cancer by the age of 70 for women who carry a germline mutation in the *BRCA1* gene is 46-87%, and for *BRCA2* mutation carriers, the risk is 38-84% higher than in the general population. The risk of developing ovarian cancer for women with *BRCA1* mutations is higher by 39-63% and for *BRCA2* mutations by 16.5-27%. Carriers of *BRCA1* and *BRCA2* mutations (BRCA1m and BRCA2m) also have a higher risk of developing pancreatic cancer (1-3% for BRCA1m; 2-7% for BRCA2m) and prostate cancer in men up to 65 years of age (8.6%; 15%)(7). BRCA1/2 mutation carriers also have a significantly increased risk of developing contralateral breast cancer. The 5-, 10-, and 15-year cumulative contralateral breast cancer risk of female breast cancer patients with BRCA1/2 mutations is 13.7%, 23.8%, and 36.1% for BRCA1, and 12%, 18.7%, and 28.5% for BRCA2, respectively(8). A prospective cohort study with more than 2,000 BRCAm breast cancer patients found that the risk of contralateral breast cancer 20 years after initial breast cancer diagnosis was 40% for BRCA1 and 26% for BRCA2(9).

Breast cancer diagnosed in *BRCA1* mutation carriers is frequently high-grade, with lymphocyte-rich (medullary) morphology, a triple-negative immunophenotype and/or a basal-like molecular profile(5). In contrast, breast cancer in *BRCA2* mutation carriers is similar to sporadic HER2-negative luminal-type breast cancers. Cancers arising in the fallopian tube and ovary are almost exclusively of high-grade serous histological type, with pronounced nuclear atypia and a high mitotic index(5). Both BRCA1/2- related breast and ovarian cancers are typically highly aggressive(3,5). An abnormality in the BRCA gene impairs the DNA repair pathway, resulting in the accumulation of mutations in a large number of cancer-related genes. Patients with BRCA mutations are highly sensitive to drugs that cause DNA damage, such as platinum doublets and poly (ADP-ribose) polymerase (PARP) inhibitors(3,10). Two phase III studies tested PARP inhibitors (olaparib, talazoparib) for metastatic recurrent HER2-negative, germline BRCA-mutated (gBRCAm) breast cancer, and both of them showed significantly prolonged progression-free survival (PFS) in comparison with monochemotherapy(11,12). In the OlimpiA study, adjuvant olaparib showed benefit in patients with gBRCAm with high-risk recurrence(13). PARP inhibitors (olaparib, niraparib) are effective targeted therapies in BRCAm ovarian cancer in first-line treatment as well as in maintenance therapy after platinum-based chemotherapy for ovarian cancer recurrence(14-17). Regardless of the line of treatment, PARP inhibitors statistically significantly prolong PFS, and in first-line treatment, alone or with bevacizumab, they significantly prolong overall survival (OS)(14,18).

The primary purpose of this retrospective study was to analyze the clinical and pathohistological characteristics, including status and type of BRCA mutations, treatments, and clinical outcome, of 15 patients with hereditary breast and ovarian cancer who were diagnosed, treated, and monitored at the University Hospital of Split.

PATIENTS AND METHODS

This retrospective study included 15 patients with hereditary breast and ovarian cancer who were diagnosed, treated, and monitored in the Department of Oncology and Radiotherapy of the University Hospital of Split in the period from October 1999 to April 2021. In the period from June 2016 to April 2021, an analysis of pathogenic variants of the BRCA1/2 genes from the blood of patients was carried out at the Department of Pathology, Forensic Medicine, and Cytology of the University Hospital of Split. Only patients with a confirmed pathogenic germline variant of the *BRCA1* and/or *BRCA2* genes who were diagnosed

with both breast and ovarian cancer were included in the study. The study was conducted following the ethical guidelines of the Declaration of Helsinki. We collected data on the demographic and clinical characteristics of these patients as well as the pathological and molecular features of their tumors. This includes the age of onset of breast and ovarian cancer diagnosis, personal and family history related to malignant diseases, tumor site and clinical stage of the disease, histological type, grade, and immunophenotype of the breast cancer, as well as BRCA mutational status and type of BRCA mutation.

The stage of breast cancer is determined according to the TNM, that is, the AJCC classification (American Joint Committee on Cancer, AJCC), and ovarian cancer according to the FIGO classification (Fédération Internationale de Gynecologie et d'Obsterique).

Treatment outcomes were investigated by collecting data on surgical and oncological treatments and were defined by overall survival (OS). Overall survival is defined as the period from the diagnosis of the disease to death from the tumor or from some other cause.

Categorical variables were presented as percentages. We used the Kaplan-Meier method to estimate overall survival. We used Excel 2007, Microsoft Corp., for data collection and processing, and ORIGIN 2016, OriginLab Corporation, for Kaplan-Maier analysis.

RESULTS

Our cohort consists of 15 patients with a confirmed pathogenic variant of the *BRCA1* and/or *BRCA2* genes who were diagnosed with breast and ovarian cancer. The median age of patients at the time of breast cancer diagnosis was 53 years. The youngest patient was 33 years old, and the oldest was 67 years old. The median age of the patients at the time of diagnosis of ovarian cancer was 56 years. The youngest patient was 41 years old, and the oldest was 66 years old. Table 1 shows the clinical characteristics of 15 patients with HBOC in the study.

Breast cancer was diagnosed in stage IA (T1N0M0) in 5 patients (33%), in 8 patients (53%) in stage II (5 in stage IIA: T2N0M0, and 3 in stage IIB: T2N1M0), and in 2 patients (14%) in stage III (both

Table 1.

Clinical characteristics of patients diagnosed with hereditary breast and ovarian cancer, n=15.

Clinical parameter	n (%)
Age at diagnosis of breast cancer, years* median (range)	53 (33-67)
Age at diagnosis of ovarian cancer, years median (range)	56 (41-66)
Breast cancer – AJCC stage [a, *]	
I	5 (33)
II	8 (53)
III	2 (14)
IV	0
Ovarian cancer – FIGO stage [b]	
I-II	1 (7)
III-IV	14 (93)

* for 4 patients with bilateral breast cancer, the data of the first diagnosed breast cancer are presented

[a] FIGO – french. *Federation Internationale de Gynecologieet d'Obsterique*

[b] AJCC – *American Joint Committee on Cancer*

Table 2.

Pathohistological characteristics of breast cancer in patients with hereditary breast and ovarian cancer

Breast cancer characteristic	n (%)
Histology	
invasive NOS	12 (80)
lobular	2 (13)
other	1 (7)
Grade	
grade 1	1 (7)
grade 2	2 (13)
grade 3	12 (80)
ER and PR[a] status	
ER+, PR+	7 (46,5)
ER+, PR-	1 (7)
ER-, PR+	0
ER-, PR-	7 (46,5)
HER2[b] status	
positive	1 (7)
negative	14 (93)
Ki 67 index status	
≤20%	1 (7)
>20%	14 (93)
Immunophenotype	
Luminal A	1 (7)
Luminal B	6 (40)
Triple negative	7 (46)
HER2 positive (luminal)	1 (7)

* for 4 patients with bilateral breast cancer, the data of the first diagnosed breast cancer are presented

[a] ER, PR – estrogen receptor, progesterone receptor

[b] HER2 – Human epidermal growth factor receptor 2

in stage IIIA: T1N2M0, and T2N2M0). Two-thirds (67%) of all breast cancer patients had negative lymph nodes. None of the patients was initially diagnosed with metastatic breast cancer (stage IV).

Table 3.

Types of BRCA1 and BRCA2 mutations in patients with hereditary breast and ovarian cancer from Dalmatia

Patients	Gene	Mutation – nucleotide change	Mutation – protein change	Mutation - type
1	*BRCA1*	c.1252G>T	p.Glu418Ter	nonsense
2	*BRCA1*	c.5266dup	p.Gln1756fs	frameshift
3	*BRCA1*	c:843_846del	p.Ser282fs	frameshift
4	*BRCA1*	c.5266dup	p.Gln1756fs	frameshift
5	*BRCA1*	c.5266dup	p.Gln1756fs	frameshift
6	*BRCA1*	c.5266dup	p.Gln1756fs	frameshift
7	*BRCA2*	c.5073dup	p.Trp1692fs	frameshift
8	*BRCA1*	c.5266dup	p.Gln1756fs	frameshift
9	*BRCA1*	c.5266dup	p.Gln1756fs	frameshift
10	*BRCA2*	c.9371A>T	p.Asn3124Ile	missense
11	*BRCA1*	c.1252G>T	p.Glu418Ter	nonsense
12	*BRCA1*	c:843_846del	p.Ser282fs	frameshift
13	*BRCA2*	c.6641dup	p.Tyr2215fs	frameshift
14	*BRCA1*	c.5503C>T	p.Arg1835Ter	nonsense
15	*BRCA1*	c.1508del	p.Lys503fs	frameshift

Four patients were diagnosed with bilateral breast cancer, so in this analysis, we processed the data of the first diagnosed breast cancer.

The primary site of ovarian, fallopian tube, and peritoneal cancer in most patients was the ovary (67%) and all cancers were high-grade serous histologic type (100%). Most ovarian cancers were diagnosed at FIGO stages III and IV (93%).

The most common histological subtype of breast cancer was invasive no otherwise specified (NOS) carcinoma grade 3 (80%). Hormone receptors (estrogen and/or progesterone receptors) were positive in 53% of cases. HER2 receptor status was negative in 93% of cases. The proliferation index Ki67 above 20% was defined in 93% of patients. In our cohort, 46% of patients had triple-negative breast cancer, and 47% had a luminal, mostly luminal B immunophenotype. Table 2 shows the pathohistological characteristics of breast tumors in 15 patients.

According to the results of the analysis of mutations in the BRCA1 or BRCA2 genes from the blood of patients, the BRCA1 gene mutation predominates (80%, 12 patients). The most common BRCA1 mutation detected in six patients (50%) was the frameshift mutation c.5266dup (p.Gln1756fs). Mutations in the BRCA1 gene present in 2 patients were: c.1252G>T (p.Glu418Ter) and c.843_846del (p.Ser282fs). We detected 3 patients

Table 4.

Positive family history in patients with hereditary breast and ovarian cancer

Patients	Gene mutation	Age of patients at diagnosis breast cancer/ ovarian cancer (years)	Positive family history
1	*BRCA1*	58/60	Mother - colon cancer; three sisters - breast cancer
2	*BRCA1*	47/63 - metachronous bilateral breast cancer	mother - breast cancer
3	*BRCA1*	53 - synchronous breast and ovarian cancer	mother and grandmother - uterine cancer
4	*BRCA1*	47/63	father, cousin - gastric cancer; sister - metastatic cancer of unknown primary site
5	*BRCA1*	37/50 - metachronous bilateral breast cancer	mother, grandmother, aunt - breast cancer
6	*BRCA1*	56/64	mother - lung cancer
7	*BRCA2*	59/47	grandmother - breast cancer; sister - ovarian cancer; second-degree relatives on the fathers site - prostate cancer
8	*BRCA1*	67/56	daughter - breast cancer
9	*BRCA1*	33/44 - metachronous bilateral breast cancer	father - colon cancer; grandmothers sister - breast cancer
10	*BRCA2*	44/56	grandfather - lung cancer
11	*BRCA1*	55/48	sister - breast cancer
12	*BRCA1*	37/48	unknown
13	*BRCA2*	66 - synchronous breast and ovarian cancer	two sisters - breast cancer; brother - prostate cancer
14	*BRCA1*	58/62 - metachronous bilateral breast cancer	sister - breast cancer
15	*BRCA1*	38/41	negative

Table 5.
Immunophenotypes of bilateral breast cancer in four patients with hereditary breast and ovarian cancer

	The first diagnosis of breast cancer		The second diagnosis of breast cancer	
	Year of diagnosis, site of cancer	Immunophenotype	Year of diagnosis, site of cancer	Immunophenotype
Patient 1	1999, right breast	luminal B	2001, left breast	triple negative
Patient 2	2005, right breast	luminal B HER2+	2014, left breast	triple negative
Patient 3	2002, right breast	triple negative	2017, left breast	triple negative
Patient 4	2016, left breast	luminal B	2020, right breast	triple negative

Table 6.
Surgical and medical treatment applied in patients with hereditary breast and ovarian cancer

	n (%)
Breast cancer – surgical treatment	
mastectomy	8 (53)
wide local excision	7 (47)
Breast cancer – adjuvant chemotherapy	
yes	14 (93)
no	1 (7)
Breast cancer – adjuvant radiotherapy	
yes	9 (60)
no	6 (40)
Breast cancer – adjuvant hormonal therapy	
yes	9 (60)
no	6 (40)
Ovarian cancer – surgical treatment	
primary cytoreduction	13 (87)
interval cytoreduction	2 (13)
Ovarian cancer – platinum-based chemotherapy	
adjuvant	13 (87)
neoadjuvant	2 (13)
Ovarian cancer – olaparib	
first line	3 (13)
therapy od recurrence	5 (33)

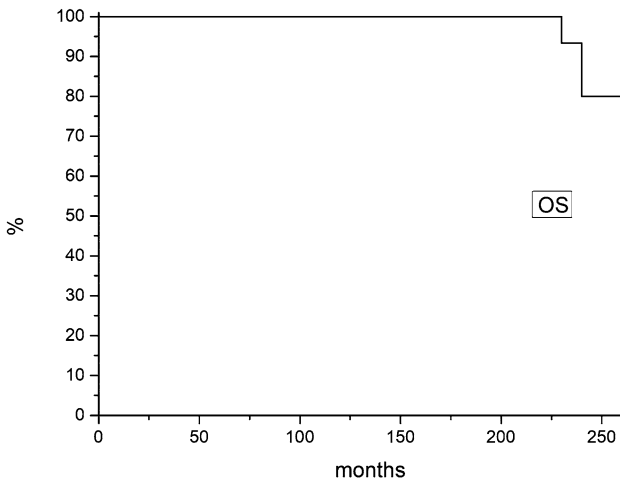

Figure 1. Kaplan-Meier curve of overall survival (OS) of 15 hereditary breast and ovarian cancer (HBOC) patients diagnosed, treated and monitored at University Hospital of Split from 1999 to 2021. The median OS of patients with HBOC was not reached.

(20%) with *BRCA2* mutations: c.5073dup (p.Trp 1692fs), c.9371A>T (p.Asn3124Ile), and c.6641dup (p.Tyr2215fs). Table 3 shows the detected BRCA1/2 mutations.

Almost all patients had a positive family history of malignant diseases in their first- and second-degree relatives (87%, 13 patients). Breast cancer was confirmed in relatives of nine patients with hereditary breast and ovarian cancer (60%). Ovarian cancer, as well as prostate cancer, were present in relatives of two patients (13%). Table 4 shows the family history related to malignant diseases.

In our cohort, four patients developed metachronous bilateral breast cancer. All had a detected *BRCA1* mutation and a positive family history of breast cancer, and later (range 4-18 years), they developed ovarian cancer. The most common *BRCA1* mutation (c.5266dup) was detected in three patients. Table 5 shows the immunophenotype in four patients with metachronous bilateral breast cancer.

Breast and ovarian cancers were diagnosed synchronously in two patients. One patient with triple-negative breast cancer had a *BRCA1* mutation (c.843_846del), while another patient with a luminal B/HER2-negative immunophenotype had a *BRCA2* mutation (c.6641dup). Tables 4 and 5 list

the characteristics of synchronous breast and ovarian cancer.

Patients with ovarian cancer were treated with primary cytoreduction and platinum-based chemotherapy in 87% of cases. In our study population, seven patients (46.7%) were treated with or are still receiving the PARP inhibitor olaparib. Two patients receive olaparib in first-line treatment, and five patients in maintenance therapy after a good response to platinum-based chemotherapy. In all patients, breast cancer was initially treated surgically; mastectomy and wide local excision were carried out in equal proportions. Depending on the stage and immunophenotype of breast cancer, adjuvant chemotherapy was prescribed for 93% of patients and adjuvant radiotherapy and hormone therapy for 60%. Table 6 shows the method of treatment for the patients included in the trial.

The median overall survival of 15 patients with hereditary breast and ovarian cancer in our sample was not reached. Figure 1 shows the Kaplan-Mayer curve of overall survival. Outcomes at the end of follow-up are: 1 patient (6%) was lost to follow-up; 3 patients (20%) died due to ovarian cancer recurrence (the median time for ovarian recurrence was 24 months); 4 patients (27%) are alive and receiving therapy due to disease recurrence; and 7 patients (47%) are alive too, in remission.

DISCUSSION

Hereditary breast and ovarian cancer patients are prone to the development of malignant neoplasms in multiple organs, including the breast, ovary, and fallopian tube, and less often the prostate, pancreas, and skin(5). HBOC is most commonly characterized by pathogenic germline mutations in the *BRCA1* and *BRCA2* genes(3,5,6). Germline mutations of several other genes, including *CHEK2*, *BRIP1*, *BARD1*, *ATM*, *RAD51C*, *RAD51D*, and *PALB2*, can increase the lifetime risk of breast and/or ovarian cancer(6). An Indian retrospective study investigated the genetic background of patients with familial breast and ovarian cancer. The researchers confirmed that in addition to BRCA1/2 mutations, there are mutations of other genes with different penetrances involved in the process of homologous recombination that are important in the development of the disease(19).

Systematic analysis of BRCA genes from the blood of ovarian cancer patients began in 2016, when the Croatian Health Insurance Fund approved the drug olaparib, a PARP inhibitor, for BRCA-mutated ovarian cancer recurrence after response to platinum-based chemotherapy. BRCA testing became a reflex for all patients with platinum-sensitive relapses. After a detailed analysis of the medical histories of the tested patients with ovarian cancer, we found 15 patients from Dalmatia with breast and ovarian cancer.

Patients with HBOC are diagnosed at an earlier age than patients without the BRCA mutation. In our cohort, the median age of the BRCAm breast cancer patients was 53 years, and 56 years for the BRCAm ovarian cancer patients. Our results are comparable to those of other races and nations. In a Vietnam analysis, the median age for HBOC patients was 51 years. Patients with *BRCA1* mutations were diagnosed earlier (median age 48 years) in comparison with patients with *BRCA2* mutations (median age 61 years)(20). Powell et al. reported that ovarian cancer was diagnosed 8-10 years later in BRCA2m carriers than in BRCA1m carriers(21). An Italian researchers showed an analysis of 270 patients with synchronous and metachronous BRCAm and BRCAwt breast and ovarian cancer. Breast cancer was diagnosed at an earlier age than ovarian cancer ($P<0.001$). The median age of patients with first-diagnosed breast cancer was 48 years (range 28-83), and for first-diagnosed ovarian cancer, 54 years. Patients with synchronous breast and ovarian cancer had a median age of 60 years(6). In the Turkish retrospective study, HBOC patients were diagnosed at an earlier age, with a median age of 44 years(22). A retrospective Sicily study showed that the median age of HBOC patients with a confirmed *BRCA1* mutation was 48 years for breast cancer and 53 years for ovarian cancer, and for patients with a *BRCA2* mutation, it was 50 years for breast cancer and 57 years for ovarian cancer(23).

In our study, breast cancer was most often diagnosed as a localized disease with equally represented high-grade triple-negative and luminal immunophenotypes. In an Italian study, HBOC patients with first-diagnosed breast cancer most often had a luminal immunophenotype. Hormone receptor status was positive in 62.5% of patients, and HER2 status was negative in 89.6% of patients. A triple-negative immunophenotype was

recorded in 32.4% of patients. Metachronous carcinomas were recorded in 10% and synchronous in 9% of the patients(6). In a sample of Turkish patients with HBOC, Atci et al. confirmed a higher incidence of triple-negative breast cancer immunophenotype (56.1%), grade 3 (65.9%), and positive lymphovascular invasion (78%) in BRCA1m carriers compared to BRCA2m carriers. BRCA1m carriers had lower expression of estrogen and progesterone receptors (41.5% and 36.6%) than BRCA2m carriers (62.2% and 51.4%). HER2 status was positive in 3 patients (7.3%) with the *BRCA1* mutation and in 6 patients with the *BRCA2* mutation (16.2%)(22). The immunophenotype of breast cancer in Indian patients with HBOC was specific. Luminal immunophenotype was most common in 55% of patients, but HER2-positive immunophenotype was more common than triple-negative (30% vs. 15%)(19).

The primary site of the disease in our patients with high-grade serous ovarian, fallopian tube, and peritoneal cancer was the ovary (67%). They were mostly diagnosed in FIGO stages III and IV (93%). The Italian researchers also showed that serous histology of ovarian cancer (76%) of high grade (92.2%) and FIGO stage III-IV (75.7%) was most commonly detected in the BRCA-mutated population(6). Among the Slavic peoples, the characteristics of ovarian cancer in HBOC syndrome are the same. It is most often a serous, with a smaller proportion of endometrioid, high-grade histological type of cancer, diagnosed in advanced FIGO stage III and IV(24-35).

In our study population, which included 15 patients from Dalmatia, 80% (12 patients) had confirmed BRCA1 mutations. The most frequently recorded *BRCA1* mutation was c.5266dup (50% of patients, 6 patients). Three patients with metachronous bilateral breast cancer had the most common *BRCA1* mutation, c.5266dup. This is the first report about the status and types of BRCA1/2 mutations in Croatian patients from Dalmatia with HBOC. A large Italian study about synchronous and metachronous breast and ovarian cancers confirmed BRCA mutations in 112 patients. *BRCA1* mutations were present predominantly in 64% of patients, *BRCA2* mutations in 28%, and simultaneous BRCA1/2 mutations in 3% of all patients. This analysis did not define the type of BRCA mutation(6). The most common BRCA1/2 mutation defined by testing 163 Moroccan patients with HBOC was the *BRCA2* mutation, c.1310_1313del, presented in 33% of the patients(36). The BRCA1 c.211dup was the most common mutation among patients with HBOC in Tunisia, with a participation rate of 16.6%. It is interesting that one of the relatively frequent *BRCA1* gene mutations in the Tunisian study population was c.5266dup, which was defined as the most common in our population (37, 38). In a smaller study population from Saudi Arabia, the most common mutation was the *BRCA1* gene mutation, c.4136_4137del, recorded in 7 patients(39). In the Lebanese population of patients with HBOC, the specific and most frequent mutation of the *BRCA1* gene is c.131G>T(40). Then, in Jordan, a type of *BRCA1* mutation, c.2254_2257del, was found in 8 patients and defined as the most common(41). In Qatar, the mutation c.4787C>A was confirmed as the most common mutation of the *BRCA1* gene in 6 patients(42). In Palestine, the most common mutation was the *BRCA2* mutation, c.2482del, found in 7 patients(43). The *BRCA1* gene mutation, c.66_67del, was defined in nine Iranian patients and published as the most common genetic aberration in hereditary breast and ovarian cancer(44). The first report on the type of BRCA1/2 mutations in Vietnamese patients was published in the journal Genes last year. Le and a coworker presented a detailed analysis of 33 Vietnamese patients with HBOC. BRCA mutations were proven in 12 patients (27.3%), with a predominance of BRCA1 mutations (75%, 9 patients)(20). In a Turkish retrospective study of 75 BRCAm patients with HBOC, an almost equal ratio of *BRCA1* and *BRCA2* mutations was recorded (54.6% vs. 45.4%) (22). The most common *BRCA1* mutation in an Indian retrospective study was c.5137+1G>A (19). The most common *BRCA1* mutation among Sicilian patients with HBOC and their families was c.4964_4982del, and the most common *BRCA2* mutation was c.1238del(23). The dominant BRCA1/2 mutations in HBOC patients in Russia were two variants of *BRCA1* (c.68_69del and c.5266dup) and *BRCA2* (c.5946del)(31). The most common mutation in Russia, c.5266dup (most common in Croatia), was also recorded in other Slavic nations such as Litva, Latvia, Poland, Belarus, the Czech Republic, Slovenia, and northern Greece(24-33). This type of BRCA1 mutation was recorded as the second most frequent in the Jewish population(45).

We showed a relatively high frequency of positive family histories of malignant diseases in first- and second-degree relatives (87%, 13 patients). Among Turkish patients with BRCA-mutated tumors, a positive family history of breast cancer (34.4%) and ovarian cancer (1.4%) was recorded(22). Similar results were reported by researchers in Belarus. Among 36 patients with breast cancer, 10 had relatives with breast cancer and 4 had relatives with ovarian cancer. Breast and ovarian cancer were recorded in a second-degree relative of one patient(27). The relatively low frequency of a positive family history of breast and ovarian malignancies among patients with BRCA-mutated HBOC in Latvia is interesting. More precisely, 71.4% of patients with breast cancer and 87.5% of patients with ovarian cancer did not have or did not report first- or second-degree relatives with breast and ovarian cancer (24). Positive family history among BRCA1/2 mutation carriers in the Sicilian study population ranged between 18 and 33%(23).

Treatment of BRCAm patients with breast cancer depends on the stage of the disease and the immunophenotype of the cancer. Our patients were initially treated surgically, and according to their immunophenotype, they received adjuvant chemotherapy, mostly anthracycline-based, and anti-hormone therapy. Patients with ovarian cancer were mostly treated with primary cytoreduction and platinum-based chemotherapy. Two patients receive olaparib in first-line treatment and five in maintenance therapy after a response to platinum-based chemotherapy due to disease recurrence. Italian patients with breast and ovarian cancer were similarly treated. However, they did not present data on PARP inhibitor therapy for ovarian and breast cancer because, at that time, it was not prescribed in daily clinical practice(6).

The median overall survival of patients with HBOC in our study was not reached. This outcome can be explained by the relatively small number of patients, the early stage of breast cancer in the majority of patients, and the introduction of PARP inhibitors in maintenance therapy for ovarian cancer patients. The prognosis of BRCA1/2 mutation carriers with HBOC has been investigated through large cohorts and meta-analyses(3). A large pooled analysis of 16 studies, with 1325 BRCA1m breast cancer patients and 8855 BRCAwt patients from multicenter prospective cohort studies in the United Kingdom, showed no statistically significant difference in overall survival between the two cohorts(46,47). A large meta-analysis of 33 studies with ovarian cancer patients showed statistically significantly longer OS exclusively in BRCA1 mutation carriers. Another clinical study involving more than 600 BRCAm ovarian cancer patients showed a benefit in 3-year OS compared with BRCAwt patients. However, in both analyses, there was no benefit in long-term 10-year OS(48). The most common cause of death in the Italian study was ovarian cancer (70.5%), followed by less common breast cancer (7.6%), and reasons unrelated to cancer (8.6%). Median overall survival for BRCAm and BRCAwt patients was equal (88.2 vs. 86.7 months)(6).

The main limitations of our study are the retrospective design and the small number of patients. However, the value of this report is contained in the analysis of data from daily clinical practice through years of detection, treatment, and follow-up of patients with HBOC. Clinical characteristics of patients, pathohistological characteristics of tumors, as well as treatment outcomes in our study population are comparable to the data of a large number of studies and meta-analyses published in the literature, respecting the characteristics of different nations and races. In this report, we present for the first time the status and types of BRCA mutations in Croatian women from Dalmatia with HBOC. Based on the BRCA status, we can individualize the prognosis, treatment, and follow-up of BRCA-mutated patients, especially today when we can use PARP inhibitors in early high-risk and metastatic breast cancer and in the first-line treatment and treatment of ovarian cancer recurrence.

CONCLUSION

Our retrospective analysis confirmed similar clinical and patohistological characteristics and treatment outcomes in our patients with HBOC in comparison with patients from different geographic regions. For the first time, we reported the status and type of BRCA mutations in patients with HBOC in Dalmatia. This report presents a useful database for timely screening programs and preventive measures, genetic testing, and help in defining a treatment strategy with targeted therapies.

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Sažetak

NASLJEDNI KARCINOM DOJKE I JAJNIKA - ISKUSTVA KLINIČKOG BOLNIČKOG CENTRA SPLIT

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Cilj: Istražiti kliničke osobitosti, patohistološke karakteristike tumora, način i ishode liječenja bolesnica s nasljednim karcinomom dojke i jajnika koje su dijagnosticirane, liječene i praćene u Kliničkom bolničkom centru Split od listopada 1999. do travnja 2021. godine.

Metode: Podatci su prikupljeni retrospektivno iz povijesti bolesti 15 bolesnica. Uključivali su dob bolesnica kod dijagnoze bolesti, obiteljsku anamnezu za zloćudne bolesti, histološki podtip, gradus, imunofenotip karcinoma dojke, stadij bolesti, status i tip *BRCA* mutacija, osobitosti kirurškog i onkološkog liječenja, specifičnosti metakrono nastalih bilateralnih karcinoma dojke, specifičnosti sinkrono nastalih karcinoma dojke i jajnika te ishod liječenja kroz ukupno preživljenje.

Rezultati: Medijan dobi bolesnica u trenutku dijagnoze raka dojke bio je 53 godine, a za karcinom jajnika 56 godina. Pozitivna obiteljska anamneza potvrđena je u 13 (87%) bolesnica. Karcinom jajnika je kod svih bolesnica bio seroznog papilarnog histološkog podtipa visokog gradusa i najčešće dijagnosticiran u FIGO stadiju III i IV. Karcinom dojke je najčešće dijagnosticiran u stadiju IA i IIA, jednake zastupljenosti trostruko negativnog i luminalnog imunofenotipa. Najčešća mutacija je bila *BRCA1* c.5266dup. Medijan ukupnog preživljenja naših bolesnica nije dosegnut.

Zaključak: Kliničke osobitosti bolesnica, patohistološke karakteristike tumora kao i ishodi liječenja u našoj studijskoj populaciji su usporedivi s izvješćima iz literature, respektirajući specifičnosti različitih naroda i rasa.

KLJUČNE RIJEČI: *karcinom dojke i jajnika; BRCA mutacije; ishodi*