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# The study of genetic and clinicopathological characterisation of Turkish bilateral breast cancer patients

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**ABSTRACT**

**Introduction.** Although bilateral breast cancers are a rare condition in the general population, the incidence has increased significantly in *BRCA1* and *BRCA2* gene carrier breast cancer patients. Besides the genetic susceptibility, many risk factors such as age, first breast cancer diagnosis age, lifestyle, and environmental factors may be effective in the development of this type of cancer. This study aimed to determine *BRCA1/2* gene carriage in patients with bilateral breast cancer and to find out the risk factors that may lead to contralateral cancer formation.

**Material and methods.** From 2016 to 2018, in Turkey, we grouped 31 women diagnosed with bilateral breast cancer synchronously and metasynchronously. Analysis of *BRCA1* and *BRCA2* genes of these women evaluated for clinical and pathological tumour characteristics was performed using the NGS technique.

**Results.** No significant difference was found between the metachronous (MBBC) and synchronous (SBBC) groups in terms of clinical and pathological tumour characteristics. MBBC patients' age at first diagnosis of breast cancer was lower than SBBC. Also, there was a statistically significant relationship between chronic diseases and MBBC cancers ($\chi^2$ = 11.519; p = 0.001). In our study, disease-related variants were found only in three patients, and two of these variants were identified the first time in the literature.

**Conclusion.** The risk of bilateral breast cancer of BRCA1/2 carriers increases when the first breast cancer is diagnosed at a young age and there is a significant family history of cancer. MBBC is associated with chronic diseases, and large-scale research will contribute to clarifying this relationship.

**Key words:** *BRCA*, bilateral breast cancer, metachronous, synchronous, chronic disease

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## Introduction

Breast cancer is the most common type of cancer in women all over the world and is one of the first causes of deaths due to female sex cancers [1]. Although this type of cancer is mostly seen in the unilateral breast, approximately 2% to 11% of all events are bilaterally detected, and the second most common malignancy in breast cancer patients is located in the contralateral breast [2]. The development of diagnostic, screening, and treatment techniques in cancer and increased survival of cancer patients are thought to lead to the more frequent observation of bilateral breast cancer. However, the causes of invasive or in situ histological types of lobular breast cancer, gene mutation, early detection of breast cancer, and a history of radiation exposure in previous cancer treatment are thought to increase the risk of BBC development [3, 4]. While the risk of BBC developmental cumulative incidence is 3.4% in 10 years in patients with unilateral breast cancer, this rate increases to 13–40% in women with *BRCA* mutation [5, 6]. BBC patients, according to the time elapsed between the detection of tumors in both breasts (although many authors have not yet reached a consensus), can be grouped as synchronous (SBBC) or meta-synchronous (MBBC) [7–10]. The number of studies investigating the clinical and pathological characteristics of both groups is not sufficient in the literature. In this study, we aimed

**Table 1. Age parameters of SBBC and MBBC groups**

| Variable | Synchronous (n = 14) | | Metasynchronous (n = 17) | | Statistical analysis* Probability |
|---|---|---|---|---|---|
| | $\overline{X} \pm$ S.S. | Median [Min–Max] | $\overline{X} \pm$ S.S. | Median [Min–Max] | |
| Age (years) | 52.93 ± 8.75 | 54.5 [39.0–67.0] | 54.29 ± 8.91 | 53.0 [42.0–73.0] | t = –0.428 p = 0.672 |
| Age at first ca dia. (years) | 48.43 ± 8.83 | 49.5 [36.0–66.0] | 40.88 ± 9.47 | 40.0 [19.0–61.0] | T = 2.276 **p = 0.030** |
| Age at sec ca dia. (years) | 48.64 ± 8.78 | 49.5 [36.0–66.0] | 51.94 ± 8.61 | 49.0 [40.0–67.0] | t = –1.053 p = 0.301 |

*Independent Samples t-test (T-table value) statistics were used to compare the measurement values of two independent variables in the normal distribution data

to evaluate the demographic and clinical characteristics, pathological details of tumours, and *BRCA1/2* mutation status of patients we grouped as MBBC and SBBC.

## Methods

We performed this study in 31 patients who were diagnosed with bilateral breast cancer and referred to the genetics department of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between June 2016 and January 2018 in order to clarify the genetic aetiology. All patients who participated in the study were in accordance with the National Comprehensive Cancer Network (NCCN) guidelines for BRCA1/BRCA2 test standards [11]. Of the patients' demographic characteristics, background and family history, age at first and second cancer diagnosis, tumour-node-metastasis (TNM) staging, oestrogen receptor (ER)/progesterone receptor (PR), C-erbB-2 status, etc. were obtained from the patients themselves, their medical records, and the electronic database of the hospital during genetic counseling. Bilateral breast cancer of patients was grouped into SBBC or MBBC based on the interval between the first and contralateral tumours ($\leq$ 12 and > 12 months, respectively) [12]. All patients included in the study were informed about this study and gave written, informed consent for publication. The independent Ethics Committee of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital approved this descriptive case series study (Document No. 2020-02/536).

Genetic materials obtained from peripheral blood samples of patients were tested by next-generation sequencing methods to detect germline variants of *BRCA1* and *BRCA2* genes. In the genetic analysis of the patients, the Oncomine™ BRCA Research Assay commercial kit was used, and this analysis was performed on the Ion S5™ System (Ion Torrent™) platform. In this analysis, all exonic regions and the part up to 20 base pairs of exon-intron boundaries were examined. The sequence results were compared

with the human genome of hg19, and Ion Reporter Software Version 5.4 (Thermo Fisher Scientific) was used for bioinformatics analysis. The in silico analysis for the gene variants was performed using SIFT, Poly-Phen2, DANN, PROVEAN, GERP, MPC, Mutation Assessor, Fathmm, and Mutation Taster. In this study, genomic changes were identified according to ACMG criteria [13].

SPSS (IBM SPSS Statistics 24) was used for all statistical calculations. Independent sample t-test (t-table value) and Mann-Whitney U test (Z-table value) statistics were used to compare the measurement values of two independent variables. $\chi^2$ cross tables were used in the study of the relations of the two qualitative variables. A p-value less than or equal to 0.05 was considered statistically significant.

## Results

Of the 31 patients who were treated and followed up for bilateral breast cancer between January 2016 and December 2017, 14 (45.16%) presented with SBBC and 17 (54.84%) were diagnosed with MBBC, and all of them underwent *BRCA1/2* genes analyses. The median age of all patients was 53 (range 39–73 years) years, SBBC patients were 49.5 (range 36–66) years old, and MBBC patients were 40 (range 1–61) years old. There was a statistically significant difference between breast cancers in terms of breast cancer diagnosis age (t = 2,276; p = 0.030). The time interval between cancers, breast CA first diagnosis age of metasynchronised patients was statistically significantly lower than synchronised patients (Tab. 1).

In terms of the 31 bilateral breast cancer patients, patient demographics and tumour-related general factors are shown in Table 2. In the assessment of smoking status, women who smoked at least 10 cigarettes a day for 10 years or more were included in the positive group. Chronic diseases were recognised as conditions requiring periodic monitoring and supportive care (hypertension, diabetes mellitus, goiter, familial Mediterranean

**Table 2. Baseline patient demographics and clinical details**

| Characteristic | n (%) | Characteristic | n (%) | Characteristic | n (%) |
|---|---|---|---|---|---|
| **Level of education** | | **Age at first labour** | | **Mass size (left)** | |
| Elementary school | 9 (29.0) | Nulliparity | 1 (3.2) | ≤ 2 cm | 9 (49.9) |
| High school | 15 (48.4) | < 20 | 3 (9.7) | 2–4 cm | 6 (33.4) |
| University | 7 (22.6) | 20–30 | 23 (74.2) | Multifocal | 3 (16.7) |
| | | > 30 | 4 (12.9) | | |
| **Working condition** | | **First breast ca laterality** | | **Mass size (right)** | |
| Yes | 7 (22.6) | Left | 11 (35.6) | ≤ 2 cm | 9 (45.0) |
| No | 24 (77.4) | Right | 10 (32.2) | 2– ≤ 4 cm | 7 (35.0) |
| | | Bilateral | 10 (32.2) | > 4 cm | 2 (10.0) |
| | | | | Multifocal | 2 (10.0) |
| **Residence** | | **Time between cancers** | | **Metastasis (at the first diagnosis)** | |
| Rural | 7 (22.6) | Simultaneously | 10 (32.2) | | |
| City | 24 (77.4) | Simultaneously – ≤ 1 year | 4 (13.0) | None | 22 (71.0) |
| **Smoking** | | 1 year – ≤ 5 years | 3 (9.6) | Axillar | 7 (22.6) |
| Yes | 7 (22.6) | 5 years – ≤ 10 years | 3 (9.6) | Bone | 1 (3.2) |
| No | 24 (77.4) | More than 10 years | 11 (35.6) | Lung | 1 (3.2) |
| **BMI** | | **The first breast ca diagnosis** | | **Metastasis (at the contralateral breast diagnosis)** | |
| Normal | 9 (29.0) | | | | |
| Overweight | 13 (42.0) | Palpable mass | 14 (41.1) | None | 28 (90.4) |
| Obese | 9 (29.0) | Swelling and disfigurement | 7 (20.6) | Lung | 2 (6.5) |
| **Menarche age** | | Nipple discharge | 2 (5.9) | Lung and bone | 1 (3.1) |
| < 12 | 3 (9.7) | Routine check | 11 (32.4) | | |
| 12–14 | 26 (83.8) | | | | |
| > 14 | 2 (6.5) | | | | |
| **Menstrual periods** | | | | **Histopathology (left)** | |
| Regular | 28 (90.3) | **The second breast ca diagnosis** | | Ductal carcinoma in situ | 2 (7.1) |
| Irregular | 3 (9.7) | Palpable mass | 5 (15.6) | Invasive ductal carcinoma | 18 (64.3) |
| | | Swelling and disfigurement | 2 (6.2) | | |
| **Relation between diagnosis and menopause** | | Routine check | 25 (78.2) | Invasive lobular carcinoma | 5 (17.8) |
| Pre-menopausal | 16 (51.6) | | | Mixed invasive carcinoma | 1 (3.6) |
| After menopause | 15 (48.4) | | | Musinoz carcinoma | 1 (3.6) |
| | | | | Metaplastic carcinoma | 1 (3.6) |
| **Breast feeding duration** | | **Number of relatives with cancer** | | | |
| No | 2 (6.5) | | | **Histopathology (right)** | |
| ≤ 1 year | 20 (64.5) | 1 | 8 (44.4) | | |
| 1–2 years | 7 (22.5) | 2 | 5 (27.8) | Ductal carcinoma in situ | 1 (3.4) |
| More than 2 years | 2 (6.5) | 3 | 3 (16.7) | Lobular carcinoma in situ | 1 (3.4) |
| | | 4 and more | 2 (11.1) | | |
| **Chronic disease/Surgical history** | | **Relative with breast and over Ca** | | Invasive ductal carcinoma | 20 (69.0) |
| Yes | 19 (61.3)/17 (54.8) | Breast | 17 (85) | Invasive lobular carcinoma | 6 (20.8) |
| No | 12 (38.7)/14 (45.2) | Over | 3 (15) | Invasive apocrine carcinoma | 1 (3.4) |

fever, asthma, etc). Surgical history group; appendectomy, cholecystectomy, haemorrhoidectomy, etc. Patients undergoing surgeries were included. In the evaluation of cancer history in relatives, all cancers diagnosed in many organs such as breast, ovary, colon, and brain were included. Relatives diagnosed with breast and ovarian cancer were grouped separately. Metastasis status was determined in all patients after both the initial diagnosis and one-year follow-up. When calculating BMI (kg/m$^2$), 25.0–29.9 was considered as overweight, 30 and over as

obese, and 18.5–24.9 as healthy. While patients were mostly diagnosed with the first breast cancer because of a palpable mass complaint, the second breast cancer was diagnosed in many patients during their routine checks. The most common breast cancer histopathological type of both breasts was invasive ductal carcinoma, and the mass size was ≤ 2 cm.

For *BRCA1* and *BRCA2* gene analysis, the accession numbers of these genes were accepted as NM_007294.3 (*BRCA1*) and NM_000059.3 (*BRCA2*), respectively. Genomic changes in *BRCA1* and *BRCA2* were detected in only nine (29%) of 31 patients (Tab. 3). Seven of these gene changes were in the *BRCA2* (77.8%) gene, and two were in the *BRCA1* (22.2) gene and were heterozygous contitions. Of these genomic changes, two were pathogenic, one was probably pathogenic, and the remaining seven were variants of uncertain significance (VUS).

In these genes, two variants which were not reported in the literature and classified as pathogenic by us were detected. The variants NM_007294.3 (*BRCA1*): c.2131_2132delAA (p.Lys711Valfs*6) in patient P28 and NM_000059.3 (*BRCA2*):c.1773_1776delTTAT (p.Ile-591Metfs*22) in patient P13 were formed in the exonic regions of the genes. These variants caused a loss of function in the gene by means of the frameshift mutation mechanism. Various insilico predictive analysis programs support that these variants have a deleterious effect on the gene or gene product. The variant c.8954-5a > G, detected in the *BRCA2* gene of P14, was previously reported as a likely pathogenic variant in the literature [14, 15]. P13 and P14 patients were grouped as MBBC, and P28 patients were grouped as SBBC. These three patients had their first breast cancer diagnosis in their 40s and their cancer was first detected in the right breast. These patients had numerous cancerous relatives. Patients first consulted a doctor for a palpable mass in the right breast. After the analysis, these three patients were diagnosed with hereditary breast and ovarian cancer syndrome (HBOC) associated with BRCA1 and BRCA2 and were given genetic counseling. Because BRCA disease-related variants were seen in a small number of patients in our sample, it was not possible to compare them statistically with others in this group.

VUS variants were detected in *BRCA1/2* genes of the remaining six patients, two of which were reported in the literature [16–19]. The variants detected in patients P2, P23, P24, and P26 had not been previously reported in the literature. Among the patients with VUS variant, P9 was remarkable because she was diagnosed as Hodgkin's disease when she was 32 years old. In this patient, two separate VUSs were detected: NM_000059.3 (*BRCA2*):c.3310A > C (p.Thr1104Pro) and NM_000059.3 (*BRCA2*):c.3503T > A (p.Met1168Lys).

The patient was 54 years old, was first diagnosed with MBBC in the left breast, and her family cancer history was not significant for HBOC. In patients with other VUSs, breast cancer was diagnosed almost exclusively in the left breast (except P24) and grouped as MBBC. In addition to giving genetic counseling to these patients, it was also planned to reevaluate all VUSs determined according to ACMG once every six months. In 10 (58.8%) patients with MBBC, the first cancer was detected in the left breast. The first application of patients in this group was usually due to a mass complaint addressed in the breast.

As a result of the comparison of demographic data of the patients grouped as SBBC and MBBC, a statistically significant relationship was found in the breast where the cancer was first localised ($\chi^2 = 18.850$; p = 0.000). There was also a statistically significant relationship between the time interval of cancers and chronic disease ($\chi^2 = 11.519$; p = 0.001) (Tab. 4). There was no significant relationship between the two groups in the other demographic data. In addition, histopathological data of tumors in both breasts were compared but no statistically significant result was obtained in the groups. We performed a statistical analysis of the number of children and the number of relatives with cancer variables by grouping according to the first diagnosis age of the patients as ≤ 40 years and > 40 years. The result was not statistically significant (p > 0.05).

## Discussion

The NCCN guideline recommends the analysis of *BRCA1* and *BRCA2* genes in individuals with bilateral breast cancer [20]. In detecting multiple primer breast cancer of patients, the diagnostic criteria that Warren and Gates first determined in 1932 were used. These criteria include the following: that each tumour is malignant, it has its own pathological features and its own metastatic pathway and the diagnosis of metastatic or recurrent tumours can be excluded, and tumours occur in different parts or organs and are not continuous with each other [21].

In this study of *BRCA1/2* gene analysis findings, demographic characteristics of 31 patients with bilateral breast cancer were investigated, and disease-causing gene variants were identified in three patients. In this way, the aetiology of the disease became clear in these patients. Of these gene variants, the frameshift ones were first described in our patient in the literature. These patients were diagnosed as HBOC and therefore were given genetic counseling. In addition, genetic counseling was given to six patients in whom the VUS variants were identified. VUS classification means that there is insufficient or conflicting evidence regarding a molecular alteration's role in the disease, and hence a periodic

**Table 3. *BRCA1* and *BRCA2* gene analysis results and details**

| Patient ID | Gene | Nucleotid change/ AA change | Exon/ intron | Function | ACMG scoring | Age | Age at first/second diagnosis | First diagnosis location in breast | SBBC/ MBBC | Background | Cancer history on relatives | | | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | 1° | 2° | 3° | |
| P13 | BRCA2 | c.1773_1776delTTAT (p.Ile591Metfs*22) | Exon 10 | Frameshift | PAT | 57 | 40/52 | RIGHT | MBBC | Thrombosis, Steatosis hepatis | 2 Lung, 1 Stomach, 1 Larynx | 2 Lung, 1 Breast | 2 Lung, 1 Breast, 1 Endometrium, 1 Brain | Novel |
| P14 | BRCA2 | c.8954–5A > G (p.?) | Intron22 | Splice Acceptor | L.PAT | 61 | 43/61 | RIGHT | MBBC | Ovarian cyst, Diabetes | 1 Breast | 2 Breast | 1 Endometrium, | De Garibay et al. (2014), Santos et al. (2014) |
| P28 | BRCA1 | c.2131_2132delAA (p.Lys711Valfs*6) | Exon 10 | Frameshift | PAT | 43 | 40/41 | RIGHT | SBBC | – | 1 Ovary | – | 2 Breast, 1 Ovary, 1 Leukaemia | Novel |
| P2 | BRCA1 | c.694G > T (p.Asp232Tyr) | Exon 10 | Missense | VUS | 43 | 38/42 | LEFT | MBBC | Haemorrhoid, Hypertension | 1 Breast | 1 Stomach | 1 Lung, 1 Breast, 1 Stomach | Novel |
| P7 | BRCA2 | c.9364G > A (p.Ala3122Thr) | Exon 25 | Missense | VUS | 61 | 45/59 | LEFT | MBBC | Tonsillectomy, Steatosis hepatis | – | – | – | Tavtigian et al. (2008), Tazzite et al. (2012) |
| P9 | BRCA2 | c.3310A > C (p.Thr1104Pro)/ c.3503T > A (p.Met1168Lys) | Exon 11 | Missense | VUS | 65 | 54/64 | LEFT | MBBC | Hodgkin's disease (Diagnosis: 32), Hypertension | 1 Brain | – | – | DE Silva et al. (2011), Karbassi et al. (2016) |
| P23 | BRCA2 | c.1160T > C (p.Val387Ala) | Exon 10 | Missense | VUS | 42 | 19/40 | LEFT | MBBC | Haemorrhoid, Goitre | 1 Melanoma | 1 Colon | – | Novel |
| P24 | BRCA2 | c.8474C > T (p.Ala2825Val) | Exon 19 | Missense | VUS | 61 | 39/39 | SAME | SBBC | Cholecystectomy, Appendectomy, FMF, Glaucoma | – | 3 Breast | 1 Breast | Novel |
| P26 | BRCA2 | c.670G > A (p.Asp224Asn) | Exon 8 | Missense | VUS | 49 | 40/47 | LEFT | MBBC | Hypertension, Goitre, Myomectomy | – | 1 Prostate | 1 Endometrium, 1 Breast, 1 Colon | Novel |

**Table 4. Significant parameters of SBBC and MBBC groups**

| Variable | SBBC (n = 14) | | MBBC (n = 17) | | Statistical analysis* Probability |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **First Ca** | | | | | |
| Right | 3 | 21.4 | 7 | 41.2 | $\chi^2 = 18.850$ |
| Left | 1 | 7.2 | 10 | 58.8 | **p = 0.000** |
| Simultaneous | 10 | 71.4 | | | |
| **Chronic disease** | | | | | |
| No | 10 | 71.4 | 2 | 11.8 | $\chi^2 = 11.519$ |
| Yes | 4 | 28.6 | 15 | 88.2 | **p = 0.001** |

*$\chi^2$ cross tables were used to examine the relationships between the two qualitative variables

re-evaluation of the VUS identified in patients in the genetic test was planned.

Although there are many studies in the literature regarding the increase in breast cancer risk in individuals carrying *BRCA1/2* gene mutations, there are fewer reports that determine this risk in contralateral breast cancer. In BRCA carriers, the risk of developing breast cancer until the age of 70 years is approximately 50–87%. These carriers have a 32–64% risk for the development of contralateral breast cancer. In the literature some authors claim that the overall risk for contralateral MBBC is approximately 0.5%, and this risk may reach up to 3% of women with BRCA1/2 carriers, and even a 10-year risk of 13–40% can be reached [22, 23]. In another study, 10-year contralateral breast cancer risk in BRCA1 carriers was reported to be 24%, and the same risk for BRCA2 carriers was 19% [6]. The unquestionable joint consequence obtained as a result of research in the literature is that BBC risk increases in carrier women with disease-related variants of the *BRCA1/2* genes. Weitzel et al. searched women in detecting the first breast cancer diagnose age. And they determined that the diagnosis age of first cancer for BRCA1 and BRCA2 was on average 38.6 and 43.6 years old, respectively. In their study, they also examined the time interval between the two cancer diagnoses and found an average of 5.1 years for BRCA1 carriers and 5.2 years for BRCA2 carriers [24]. In another study, individuals with the *BRCA1* mutation were shown to have a 1.6-fold risk of contralateral breast cancer compared to those with *BRCA2* mutations [23]. Rogozińska-Szczepka et al. determined that the age at first diagnosis of bilateral cancer with BRCA carriers and BRCA non-carriers was at the age of 42 and 49 years, respectively [25].

The importance of the first diagnosis age in breast cancer was emphasised in a study conducted by Metcalfe et al., who found that 'women diagnosed with breast cancer under the age of 40 had a 42% risk of developing contralateral breast cancer for 15 years and an annual risk of 2.8%. The same risk decreased to 19% in women who had their first diagnosis after

50 years of age and the annual risk was 1.3%' [6]. Graeser et al. conducted a similar study in relatives of *BRCA1* mutation carriers and found that 'those who received first diagnosis with breast cancer younger than 40 years of age had an increased 25-year contralateral breast cancer risk compared to those older than 50 years (63% and 20%, respectively). The annual risk ratios were 2.5% in the young group and 0.8% in the other group' [23].

In our study, we first examined 31 patients demographically. We then grouped all patients as SBBC and MBBC and compared them for tumour characteristics. Fourteen of the patients (45.16%) were grouped as SBBC, and 17 (54.84%) were grouped as MBBC. The median age was 53 years for all patients, 49.5 years for SBBC patients, and 40 years for MBBC patients, and all values were the same as those in the literature [26]. 32.4% of the patients were diagnosed with first breast cancer and 78.2% with second breast cancer during routine controls. For this reason, the fact that both healthy and breast cancer women are subject to routine checks plays an important role in the early diagnosis and determination of treatment options for this disease. In the literature, it has been illustrated that young patients are vulnerable to MBCC [7].

There was a statistically significant relationship between chronic disease and MBBC in our patient group (p = 0.001). The mean age of first and second cancer diagnosis in the MBCC group was 40 and 49 years, respectively. The time interval between the two cancer diagnoses was 11 years (35.6) or more. It was found that 10 (71.4%) of the patients with SBBC had no chronic disease and 15 (88.2%) patients with MBBC had a chronic disease. Among these diseases, goitre, hypertension, diabetes mellitus, migraine, and some inflammatory diseases such as Behcet's disease and familial Mediterranean fever can be considered. All these diseases require periodic monitoring, medical supportive care, and/or drug therapy. In order to investigate this relationship in more detail, it is important to divide chronic diseases into subgroups in larger

patient groups and to question the relationship between the time of diagnosis of these subgroups and the duration of diagnosis of first and second breast cancer. In fact, chronic diseases diagnosed after the treatment of cancer, which is itself a kind of chronic disease, may be triggered by the long-term side effects of this treatment. Also, a chronic disease in the organism may provide a basis for facilitating the development of contralateral breast cancer due to itself and/or treatment. In the literature, a study showing an increased relationship of MBCC compared to SBBC in chronic diseases has not been published. The results of this study, which was carried out for the first time in a small group of patients in Turkey, should be confirmed in a large number of patient groups, and the underlying cause of this condition should be discovered.

In our patient groups, following the literature, there was a statistically significant difference between breast cancers in terms of breast cancer diagnosis age (p = 0.030). An aspect of the time interval between cancers was that the breast cancer first diagnosis age of MBBC patients was statistically lower than that of SBBC patients. A clear difference was not found between the tumour characteristics of both groups clinicopathologically [12].

## Conclusion

Women with bilateral breast cancer who have a *BRCA* mutation carrier receive their first breast cancer diagnosis at an early age and have a remarkable family history of cancer. MBBC patients receive their first diagnosis at an earlier age than those with SBBC. For the first time in the literature, this study demonstrated a significant association between MBBC with chronic diseases and SBCC. Increasing the number of patients and conducting larger-scale studies will help clarify the uncertainties in the relationship between chronic diseases and MBBC.

## Ethical compliance

The independent Ethics Committee approved this study.

## Conflicts of interest

The authors declare to have no conflict of interest.

## References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
2. Soerjomataram I, Louwman WJ, de Vries E, et al. Primary malignancy after primary female breast cancer in the South of the Netherlands, 1972–2001. Breast Cancer Res Treat. 2005; 93(1): 91–95, doi: 10.1007/s10549-005-4016-2, indexed in Pubmed: 16184464.
3. Intra M, Rotmensz N, Viale G, et al. Clinicopathologic characteristics of 143 patients with synchronous bilateral invasive breast carcinomas treated in a single institution. Cancer. 2004; 101(5): 905–912, doi: 10.1002/cncr.20452, indexed in Pubmed: 15329896.
4. Cook LS, White E, Schwartz SM, et al. A population-based study of contralateral breast cancer following a first primary breast cancer (Washington, United States). Cancer Causes Control. 1996; 7(3): 382–390, doi: 10.1007/BF00052945, indexed in Pubmed: 8734833.
5. Lu W, Schaapveld M, Jansen L, et al. The value of surveillance mammography of the contralateral breast in patients with a history of breast cancer. Eur J Cancer. 2009; 45(17): 3000–3007, doi: 10.1016/j.ejca.2009.08.007, indexed in Pubmed: 19744851.
6. Metcalfe K, Gershman S, Lynch HT, et al. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2011; 104(9): 1384–1392, doi: 10.1038/bjc.2011.120, indexed in Pubmed: 21487411.
7. Hartman M, Czene K, Reilly M, et al. Incidence and prognosis of synchronous and metachronous bilateral breast cancer. J Clin Oncol. 2007; 25(27): 4210–4216, doi: 10.1200/JCO.2006.10.5056, indexed in Pubmed: 17878475.
8. Hartman M, Czene K, Reilly M, et al. Genetic implications of bilateral breast cancer: a population based cohort study. Lancet Oncol. 2005; 6(6): 377–382, doi: 10.1016/S1470-2045(05)70174-1, indexed in Pubmed: 15925815.
9. Kuo WH, Yen AMF, Lee PH, et al. Incidence and risk factors associated with bilateral breast cancer in area with early age diagnosis but low incidence of primary breast cancer: analysis of 10-year longitudinal cohort in Taiwan. Breast Cancer Res Treat. 2006; 99(2): 221–228, doi: 10.1007/s10549-006-9194-z, indexed in Pubmed: 16544057.
10. Jobsen JJ, van der Palen J, Ong F, et al. Bilateral breast cancer, synchronous and metachronous; differences and outcome. Breast Cancer Res Treat. 2015; 153(2): 277–283, doi: 10.1007/s10549-015-3538-5, indexed in Pubmed: 26268697.
11. Beck AC, Yuan H, Liao J, et al. Rate of BRCA mutation in patients tested under NCCN genetic testing criteria. Am J Surg. 2020; 219(1): 145–149, doi: 10.1016/j.amjsurg.2019.06.012, indexed in Pubmed: 31255259.
12. Ozturk A, Alco G, Sarsenov D, et al. Synchronous and metachronous bilateral breast cancer: A long-term experience. J BUON. 2018; 23(6): 1591–1600, indexed in Pubmed: 30610782.
13. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee. 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(5): 405–424, doi: 10.1038/gim.2015.30, indexed in Pubmed: 25741868.
14. de Garibay GR, Acedo A, García-Casado Z, et al. Capillary electrophoresis analysis of conventional splicing assays: IARC analytical and clinical classification of 31 BRCA2 genetic variants. Hum Mutat. 2014; 35(1): 53–57, doi: 10.1002/humu.22456, indexed in Pubmed: 24123850.
15. Santos C, Peixoto A, Rocha P, et al. Pathogenicity evaluation of BRCA1 and BRCA2 unclassified variants identified in Portuguese breast/ovarian cancer families. J Mol Diagn. 2014; 16(3): 324–334, doi: 10.1016/j.jmoldx.2014.01.005, indexed in Pubmed: 24607278.
16. Tazzite A, Jouhadi H, Nadifi S, et al. BRCA1 and BRCA2 germline mutations in Moroccan breast/ovarian cancer families: novel mutations and unclassified variants. Gynecol Oncol. 2012; 125(3): 687–692, doi: 10.1016/j.ygyno.2012.03.007, indexed in Pubmed: 22425665.
17. Tavtigian SV, Byrnes GB, Goldgar DE, et al. Classification of rare missense substitutions, using risk surfaces, with genetic- and molecular-epidemiology applications. Hum Mutat. 2008; 29(11): 1342–1354, doi: 10.1002/humu.20896, indexed in Pubmed: 18951461.
18. De Silva S, Tennekoon KH, Karunanayake EH, et al. Novel sequence variants and common recurrent polymorphisms of BRCA2 in Sri Lankan breast cancer patients and a family with BRCA1 mutations. Exp Ther Med. 2011; 2(6): 1163–1170, doi: 10.3892/etm.2011.337, indexed in Pubmed: 22977638.
19. Karbassi I, Maston GA, Love A, et al. A standardized DNA variant scoring system for pathogenicity assessments in mendelian disorders. Hum Mutat. 2016; 37(1): 127–134, doi: 10.1002/humu.22918, indexed in Pubmed: 26467025.
20. Goetz MP, Gradishar WJ, Anderson BO, et al. NCCN Guidelines Insights: Breast Cancer, Version 3.2018. J Natl Compr Canc Netw.

2019; 17(2): 118–126, doi: 10.6004/jnccn.2019.0009, indexed in Pubmed: 30787125.

21. Warren S, Gates O. Multiple primary malignant tumors. Am J Cancer. 1932; 16: 1358.

22. Narod SA. Bilateral breast cancers. Nat Rev Clin Oncol. 2014; 11(3): 157–166, doi: 10.1038/nrclinonc.2014.3, indexed in Pubmed: 24492834.

23. Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2009; 27(35): 5887–5892, doi: 10.1200/JCO.2008.19.9430, indexed in Pubmed: 19858402.

24. Weitzel JN, Robson M, Pasini B, et al. A comparison of bilateral breast cancers in BRCA carriers. Cancer Epidemiol Biomarkers Prev. 2005; 14(6): 1534–1538, doi: 10.1158/1055-9965.EPI-05-0070, indexed in Pubmed: 15941968.

25. Rogozińska-Szczepka J, Utracka-Hutka B, Grzybowska E, et al. BRCA1 and BRCA2 mutations as prognostic factors in bilateral breast cancer patients. Ann Oncol. 2004; 15(9): 1373–1376, doi: 10.1093/annonc/mdh352.

26. Sim Y, Tan VKM, Sidek NAB, et al. Bilateral breast cancers in an Asian population, and a comparison between synchronous and metachronous tumours. ANZ J Surg. 2018; 88(10): 982–987, doi: 10.1111/ans.14773, indexed in Pubmed: 30141242.