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ORIGINAL ARTICLE

Do we know properly young age breast cancer patients: a double centre study

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ABSTRACT

Background: According to American Cancer Society, an estimated 268,600 new cases of invasive breast cancer was diagnosed among women, and nearly 50,000 women were under age 50 years. Therefore, the identification of young age breast cancer patients can have a collosal impact on treatment, and medical follow-up. The present study aimed to understand the young age breast cancer pathophysiology and redound new BRCA variants to literature.

Methodology: This was a double-centre study performed in the Medical Genetics Department of Kahramanmaras Necip Fazıl City Hospital. In this study, sixty female patients, who are under 45 years old, diagnosed with primer breast cancer in the oncology clinic of the same hospital and Kahramanmaraş Sütçü İmam University were included. The patients were selected for BRCA mutation testing based on NCCN Guideline Version 3.2019 BRCA1/2 Testing Criteria. Relatives who meet the same criteria from the same family were not included to prevent repetition. Patients with known other cancer syndromes were also excluded.

Results: We found that Luminal-B type breast cancer was the most frequent subtype ($p < 0.001$), patients with Luminal-A subtype breast cancer had significantly smaller tumor size and smaller grade than those had other subtypes of breast cancer at diagnosis stage ($p = 0.03$ and $p < 0.001$, respectively). Regarding tumor localization, the breast carcinomas were mostly localized in the right breast (53.3%). Two patients (3.3%) had *BRCA1* pathogenic mutation and five patients (8.3%) had *BRCA2* pathogenic mutation. Additionally, we found two new variations in *BRCA2* gene (c.478_488delGTATGTGGGAG and c.8830 A>T (rs4987047). All *BRCA1/2* MLPA results were normal.

Conclusion: The incidence of young age breast cancer varies among countries, and it is higher in developing countries. Understanding of young age breast cancer cases will be helpful to provide suitable treatment options and will help to reduce the death rate of these patients.

Keywords: Young age breast cancer, *BRCA1, BRCA2.*

Introduction

Breast cancer (BC) is the most common cancer type seen among women in the World, with a 12.5% lifetime risk (1,2). BC is the primary cause of cancer-related deaths in developing countries and the second main cause in developed regions. Therefore, it is important to manage this situation as clinicians and governments. BC is a multifactorial and heterogeneous disease (To date, four clinically relevant BC subtypes have been identified, including TNBC, Luminal A, Luminal B, and HER2) (1,3). This means that several risk factors can be caused (4). Although it can affect both women and men, it is predominantly seen in women during their sixth decade of life. However, 6-10%(1) of cases present in women younger than 45 years old. This type of breast cancer named as hereditary breast cancer and generally occurs because of hereditary mutations seen in several types of tumor suppressor genes or protooncogenes. And it is generally inherited in an autosomal dominant manner from a family member. Early reports showed that the majority of hereditary breast cancers occur because of germline mutations in *BRCA1* and *BRCA2* genes.

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The risk of developing breast cancer in *BRCA1* and *BRCA2* mutation carriers by the age of 70 is 45%-87%, respectively (2,5-7). But of course, other genes cause breast cancer at a young age.

According to American Cancer Society, an estimated 268,600 new cases of invasive breast cancer was diagnosed among women, and nearly fifty thousand women were under age 50 years (8), so the identification of genetic mutations in young age breast cancer patients can have a colossal impact on treatment, and closer medical follow-up. Screening and prevention for other family members are also beneficial as a public health issue. Therefore, several different guidelines have been published. The latest version of the *BRCA*-related breast and/or over cancer syndrome guideline was published on January 18, 2019 (9).

The incidence of young age breast cancer varies among countries. The estimated rate of this group is higher in Turkey (it is one of the young-aged-countries) than in Europe or the USA. Therefore it is important to diagnose and maintain the young age diagnosed patients because it can be a projection for countries located near our region and have a similar population.

Subjects and Methods

This was a double-centre study performed in the Medical Genetics Department of Necip Fazıl City Hospital located in Kahramanmaras, where nearly 1.5 million people live, in Turkey. In this study, 55 ≤45-year-old female patients diagnosed with primer breast cancer in the oncology clinic of the same hospital, and five ≤45-year-old female patients diagnosed with primer breast cancer in the oncology clinic of Kahramanmaras Sutçu Imam University (between 2017 and 2020) were included. This study has an ethical permission from the regional ethics committee at the Kahramanmaras Sutcu Imam University with a 44/2020 approval number. Breast cancer diagnosis was determined by pathological test results (Molecular subtypes of breast cancer were grouped into based on 13th International Breast Cancer Conference criteria (10)). The patients were selected for *BRCA* mutation testing based on NCCN Guideline Version 3.2019 *BRCA1/2* Testing Criteria. Relatives who meet the same criteria from the same family were not included to prevent repetition. Patients with known other cancer syndromes were also excluded. Breast cancer diagnosis was confirmed with pathological tests from tumor tissues.

For germline mutation detection, DNA was isolated from the peripheral blood of patients and the whole exons and exon-intron junctions of *BRCA1* and *2* genes were sequenced on Illumina Miseq NGS platform. The data were analysed by Integrative Genomics Viewer, Ensemble, DB- Single Nucleotide Polymorphism Database, Mutation Taster, PolyPhen-2, Varsome, HGMD

Table 1. *Statistical results according to molecular subtypes.*

		Molecular subtypes *n* (%)				
	Total	**Luminal A**	**Luminal B**	**Luminal B HER2+**	**Triple Negative**	***p***
Total[1]	60 (100.0%)	22 (36.7%)	24 (40.0%)	4 (6.7%)	10 (16.7%)	<0.001
Diagnosis Age (Mean ± SD)	37.38 ± 5.47	37.95 ± 3.88	36.00 ± 5.56	37.75 ± 8.62	39.30 ± 6.88	0.37
Localisation						0.12
Left	28 (46.7%)	9 (40.9%)	14 (58.3%)	3 (75.0%)	2 (20.0%)	
Right	32 (53.3%)	13 (59.1%)	10 (41.7%)	1 (25.0%)	8 (80.0%)	
T						0.03
T1	9 (15.0%)	8 (36.4%)	1 (4.2%)	-	-	
T2	44 (73.3%)	12 (54.5%)	21 (87.5%)	3 (75.0%)	8 (80.0%)	
T3-4	7 (11.7%)	2 (9.1%)	2 (8.3%)	1 (25.0%)	2 (20.0%)	
N						0.30
N0	14 (23.3%)	8 (36.4%)	3 (12.5%)	1 (25.0%)	2 (20.0%)	
N1	20 (33.3%)	7 (31.8%)	10 (41.7%)	1 (25.0%)	2 (20.0%)	
N2	10 (16.7%)	3 (13.6%)	2 (8.3%)	1 (25.0%)	4 (40.0%)	
N3	16 (26.7%)	4 (18.2%)	9 (37.5%)	1 (25.0%)	2 (20.0%)	
M						0.73
M0	52 (86.7%)	20 (90.9%)	19 (79.2%)	4 (100.0%)	9 (90.0%)	
M1	8 (13.3%)	2 (9.1%)	5 (20.8%)	-	1 (10.0%)	
Grade						<0.001
Grade 1-2	37 (61.7%)	22 (100.0%)	12 (50.0%)	1 (25.0%)	2 (20.0%)	
Grade 3	23 (38.3%)	-	12 (50.0%)	3 (75.0%)	8 (80.0%)	

(The Human Gene Mutation Database) databases. *BRCA1* (NG_005905.2 and NM_007294) and *BRCA2* (NG_012772.3 and NM_000059) sequences from the National Center for Biotechnology Information (NCBI) database (http://www.ncbi.nlm.nih.gov) were used as reference sequences. All variations were confirmed by Sanger sequencing. We performed *BRCA1* and *BRCA2* MLPA analysis for patients who do not have any pathogenic mutation in their *BRCA1/2* whole exons and exon-intron junctions sequence analysis. MLPA studies for *BRCA1* and *BRCA2* genes were performed with MRC Holland SALSA MLPA KIT P087 (39 probe) and MRC Holland SALSA MLPA KIT P077 (39 probe), respectively. The Statistical Package for the Social Sciences was used for the statistical analysis. Descriptive analyses were presented using means, standard deviations, and proportions. Numeric variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/ Shapiro Wilk's test) to determine whether or not they are normally distributed. Mann-Whitney U test, Kruskal-Wallis test and Chi-square and Fisher's Exact test was used to compare variables in different groups. Bonferroni correction was used to adjust for multiple comparisons. The statistical significance level of alpha was accepted as $p < 0.05$.

Results

A total of 60 patients were included in this study. The average age was 40.5 years old (range: 28-62 years). The average diagnosis age was 37.38 years old (range: 28-45). When the histological tumor type was considered, there were invasive ductal carcinomas in 58 (96.6%) patients, medullary carcinoma in 1 patient (1.6%), and mixt type in 1 patient (1.6%). Forty-six patients had ER+ (76.6%), 15 patients had HER2+ (25%), 41 patients had PR+ (68.3%). Nine patients (15%) had first-degree relatives with breast carcinomas. Eight patients (13.3%) had second-degree relatives with breast carcinomas. Thirteen patients (21.6%) had at least one family member who has a cancer type excluding breast cancer. Seventeen patients (28.3%)

Table 2. *Statistical results according to family cancer status.*

		Family cancer history *n* (%)		
	Total	**No**	**Yes**	***p***
Total[1]	60 (100.0%)	20 (33.3%)	40 (66.6%)	
Diagnosis Age (Mean±SD)	37.38 ± 5.47	36.85 ± 5.26	37.65 ± 5.62	0.58
Localisation				0.06
Left	28 (46.7%)	13 (65.0%)	15 (37.5%)	
Right	32 (53.3%)	7 (35.0%)	25 (62.5%)	
T				0.21
T1	9 (15.0%)	4 (20.0%)	5 (12.5%)	
T2	44 (73.3%)	12 (60.0%)	32 (80.0%)	
T3-4	7 (11.7%)	4 (20.0%)	3 (7.5%)	
N				0.91
N0	14 (23.3%)	4 (20.0%)	10 (25.0%)	
N1	20 (33.3%)	8 (40.0%)	12 (30.0%)	
N2	10 (16.7%)	3 (15.0%)	7 (17.5%)	
N3	16 (26.7%)	5 (25.0%)	11 (27.5%)	
M				0.71
M0	52 (86.7%)	18 (90.0%)	34 (85.0%)	
M1	8 (13.3%)	2 (10.0%)	6 (15.0%)	
Grade				0.85
Grade 1-2	37 (61.7%)	12 (60.0%)	25 (62.5%)	
Grade 3	23 (38.3%)	8 (40.0%)	15 (37.5%)	
Mol. Subtypes				0.86
Luminal A	22 (36.7%)	6 (30.0%)	16 (40.0%)	
Luminal B	24 (40.0%)	9 (45.0%)	15 (37.5%)	
Luminal B HER2+	4 (6.7%)	1 (5.0%)	3 (7.5%)	
Triple negative	10 (16.7%)	4 (20.0%)	6 (15.0%)	

had more than one family member who has cancer other than themselves. However, 20 patients (33.3%) had no family history. Regarding the characteristics of the molecular subtypes, 22 patients (36.7%) had LUMINAL-A, 24 patients (40%) had Luminal-B, 4 patients (6.7%) had Luminal-B HER2+, 10 patients (16.7%) had Triple Negative type cancer. According to the statistical analysis, Luminal-B type breast cancer was significantly more frequent than other subtypes ($p < 0.001$) in our study.

In terms of the tumor localization, the breast carcinomas were localized in the right breast in 32 (53.3%) patients and the left breast in 28 patients (46.7%). While there is not a significant difference regarding tumor localisation between molecular subtypes, there is a nearly meaningful result for family cancer history status. We found that patients with positive family cancer history had mostly right-breast tumors and patients who did not have a family cancer history mostly had a left-breast tumor at diagnosis stage ($p = 0.06$). We found that 9 patients had T1 level, 44 patients had T2 level, 6 patients had T3 level and 1 patient had T4 level tumor size. After performing advanced statistical analysis, we found that patients with Luminal-A subtype breast cancer had significantly smaller tumor size than those who had other subtypes of breast cancer at diagnosis stage ($p = 0.03$). However, there is not difference between patients with family history and patients with no family history regarding tumor size at the diagnosis stage.

In our study, there were 8 patients (13.3%) who had distant metastasis, and 46 patients (76.6%) had lymp node invasion at the time of diagnosis. There is not a difference among cancer molecular subtypes and family history status regarding both parameters. Thirty-six patients had grade 2 (60%), 23 patients (55%) had grade 3 and 1 patient (1.6%) had grade 1 tumors. After statistical analysis, it was shown that patients with Luminal-A subtype breast cancer had significantly smaller grade at the time of diagnosis ($p < 0.001$). However, there is not a difference regarding grade status at the time of diagnosis between patients who had a family history and patients who did not. All information is summirized in Table 1 and Table 2. The presence of a pathogenic mutation in *BRCA1* and *BRCA2* genes was seen in seven patients (11.6%). Two patients (3.3%) had BRCA1 pathogenic mutation and five patients (8.3%) had BRCA2 pathogenic mutation. All these BRCA mutations are accepted as pathogenic in current guidelines. The average cancer diagnosis ages of the patients with *BRCA1/2* positivity were 34.2 years old (range: 29-43 years). One of patients who have *BRCA1* mutation has brain metastasis (the type of tumor was triple negative in this patient) and the other patient has opposite breast metastasis(the type of tumor was Luminal-b in this patient), regarding patients who have *BRCA2* mutation, there is not any metastasis in the follow-up studies (three of them had Luminal-a and two of them had Luminal-b type tumor).

Additionally, we found two new variations in *BRCA2* gene by sequence analysis. The first one was heterozygote eleven base deletion (c.478_488delGTATGTGGGAG). The second variation was heterozygote single base change (c.8830 A>T (rs4987047). All fifty-three *BRCA1/2* MLPA results were normal in our study.

Discussion

The American Cancer Society estimates that breast cancer will affect 276,480 women in the United States alone in 2020 (11). Although in 2019, breast cancers among women under 40 years constituted only 4% of all age groups, the American data shows, that it is the most commonly diagnosed cancer type among women aged 20-49. It is also the major cause of death in the group of patients aged 30-49 (4, 12). Maintaining an accurate and complete cancer registry program can only be done with accurate data collected from accurate sources. Understanding of young age breast cancer cases will be helpful to provide suitable treatment options and will help to reduce the death rate of these patients. In the current study, we evaluated the patients with breast cancer diagnosed under 45 years old. Similar to other studies performed in the past, we found that the IDC is the most frequent histologic cancer type among our patients. Compared with breast cancer in older patients, breast cancer in young women usually displays different molecular subtypes that have more aggressive progression. Similar to other studies (13-15), we have shown that Luminal B is the more frequent subtype among young age breast cancer, and it is also significantly meaningful. Although, family history is one of the strongest risk factors in young age breast cancer patients, nearly 10% of them had no family history (16,17). In our study, one-third of the patients had no family history. This can be because of the fact that we did not include more than one patient from the same family.

In our study, we found that right breast cancer is more frequent than the left one. This is opposite to the literature published in recent years (18-20). However, a current study found that right breast cancer is more frequent in patients diagnosed with breast cancer under age 40 (21). According to our study, there is not a significant difference regarding tumor localisation among molecular subtypes but we found that patients with positive family cancer history had mostly right-breast tumor and patients who did not have a family cancer history mostly had a left-breast tumor at first diagnosis stage. This finding was nearly meaningful ($p = 0.06$). According to our study, patients had mostly T2 stage breast cancer (73.3% of all patients) at the first diagnose. This finding is similar to other studies(22,23). Similar to other studies (13,24), we found that the tumor size and the tumor grade were smaller in luminal-a subtype than other molecular subtypes and this finding is significantly meaningful ($p = 0.03$). However, there is not difference regarding these two parameters between patients with family history and patients with no family history.

With regards to the lymph node invasion, another prognostic parameter although other studies showed that this parameter is seen more frequently in Luminal-b

subtype, a more aggressive form, in our study, we could not find a difference between molecular subtypes regarding this parameter. Similarly, we could not find a difference in terms of lymph node invasion for family history status. This can be because of the fact that the number of patients was limited. In young patients with breast carcinomas, the *BRCA* mutation prevalence is higher, ranging from 5.9 to 23% (25-30). This difference can be seen because of the lack of the exact definition of the "young age", regional differences, environmental factors and ethnicity. In one study, the *BRCA1/2* mutation prevalence in the Turkish population was reported as 14% (31) In another study, the *BRCA1/2* positivity was 19% in the breast carcinoma patients with first-degree relatives having breast carcinoma histories. In these patients, the BRCA1 positivity was 9.5% and the *BRCA2* positivity was 9.5%. In patients with breast carcinoma histories in their second-degree relatives, the *BRCA1* mutation prevalence was 12.5% (25). A recent study conducted in Turkey showed that the *BRCA1/2* mutation positivity prevalence was 19% for high-risk young age (under 40 years old) population (25). In our study, 11.6% of all patients had either *BRCA1* or *BRCA2* germline mutation. This difference between our study and the previous studies can be because of the fact that including different age groups as well as including only high-risk population in their studies. Therefore, it is hard to say that the exact prevalence of *BRCA1/2* germline mutation rate for patients with breast cancer diagnosed under 45 years old, in Turkey before. In our study, we found two new variations in *BRCA2*. The first one was heterozygote eleven base deletion (c.478_488delGTATGTGGGAG). Although there is not a concrete evidence regarding it is a pathogenic variant, in the current Mutation Taster database, it is suggested as disease-causing variation for breast cancer. This patient has a mother and sister with breast cancer but we do not know whether they have the same germline variation. The second variation was heterozygote single base change (c.8830 A>T (rs4987047). This variation is accepted as benign in Clinvar and Varsome database, while Mutation Taster accepts it as disease-causing, Sorting Intolerant From Tolerant database accepts it as deleterious variation, and PolyPhen database accepts is probably damaging. In HGMD database, this variation can not be associate completely with breast cancer. Although our patient has this variation, her sister (this patient was not included in our study) with the same breast cancer type does not have the same germline variation. Large genomic rearrangements in *BRCA1* and *BRCA2* are responsible for 4–28% of all germline *BRCA* mutations (32). However, most of the previous studies included high-risk group breast cancer patients. Therefore, there is not a relevant result regarding the prevalence of *BRCA* large genomic alterations. In our study, we did not found any large genomic rearrangement by MLPA method. This is probably because of limited patient population and needs to be improved. Another scenario is that all these BRCA negative patients can have another mutated gene that can cause breast cancer. For example, high-penetrance genes such as *RAD51D, PTEN TP53*, *CDH1*, *STK11*, and *RAD51C*. Low-moderate penetrance *ATM*, *CHEK2*, *BRIP1*, and *PALB2* gene variants also can be responsible for hereditary breast cancer (33). Panel tests are not common in routine because of their costs, but by the help of improving technology, their costs have been decreasing. We think that new methods and finding new genes will change our understanding of young age breast cancer in the future.

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Ethical approval
This study was approved by the regional ethics committee at the Kahramanmaras Sutcu Imam University with approval number: 44/2020.

Consent to participate
Informed consent was obtained from the patients.

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