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RETROSPECTIVELY ANALYSIS OF CLINICAL/PATHOLOGICAL AND PROGNOSTIC FEATURES OF SUBTYPES OF BREAST CANCER

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ABSTRACT

Aims: Breast cancer is the most common type of cancer among all women across the world, with an incidence of 25.2%. Of all the cancer cases, breast cancer comes second in line after lung cancer. By 6.4% it marks fifth place as the reason for cancer-related-deaths. Therefore new studies on breast cancer are required. We aimed to retrospectively analyze clinical, pathological and prognostic features of cases that were divided into four subgroups based on their hormone receptor and HER-2 conditions.

Method: Records of GATA-Oncology Clinic patients who have been diagnosed with breast cancer within years of 2008-2014, were inspected retrospectively. Cases were divided into four subgroups based on their hormone receptor and HER-2 conditions. Missing records were primarily gathered by electronic recording system, also still-missing-information about the patients were provided via phone calls. Collected data has been evaluated with SPSS 15,0.

Results: While demographics such as family history and menopausal state were not different among 4 subgroups, triple negative patients tended to have a lower body-mass index and mean age (p=009, p=0.041, respectively). Only 12 patients had advanced disease at diagnosis. A total of 168 patients received chemotherapy. Progression occurred in 41 patients (21.9%) from early phase breast cancer cases that were taken to adjuvant chemotherapy program. Family history had a significant association with recurrence in breast cancer patients (p=0.026). Menopausal state, lymphovascular invasion, lymph node state and stage were not associated with progression. Independent prognostic factors were not obtained with multivariate analysis for disease-free survival. Advanced stage breast cancer patients had a higher tendency to metastasis. Triple negative patients had more drug resistance towards systemic treatment than other subgroups (p<0.001). It has been found that full response to anthracycline + taxane regime was less in triple negative patients.

Conclusion: In conclusion, there were some differences within our subgroups. Patients of these subgroups should be followed up and treated with different strategies. All subgroups, especially triple negative group, were in need of new effective therapy strategies.

Keywords: Breast cancer, HER2, estrogen receptors, progesterone receptors, disease-free survival

INTRODUCTION

Breast cancer is the most common type of cancer among all women across the world, with an incidence of 25.2%. Of all the cancer cases, breast cancer comes second in line after lung cancer. According to data acquired in 2012, it marks the fifth place as a reason for cancer-related-deaths, by 6.4%. In Turkey, breast cancer is the most common type of cancer among women. Every year, 30.000 women lose their lives to breast cancer in Turkey. With efficient screening and newly developed treatment methods in the last few years, there has been a significant decrease in breast cancer mortality (1). A good understanding of this tumour's characteristics has an important role in developing new treatment methods for breast cancer. Breast cancer has a heterogeneous histological structure. Many characteristics of this cancer have been revealed, determining different behaviour and responses to various types of treatment. Confirmed prognostic factors are tumour diameter, tumour grade, patient's

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age, axillary lymph node metastasis and the condition of hormone receptors. In recent years, lymphovascular invasion and the status of "Human Epiderman Growth Factor Receptor-2" (HER-2) have also been put forward as crucial prognostic factors (2). During the management of breast cancer cases, the following histopathologic parameters , condition of hormone receptors (estrogene receptor [ER]/progesterone receptor [PR]) and HER2 overexpression/ amplification bears importance. While HER-2 positiveness is an unfavourable prognostic factor, hormone receptor negative (ER-, PR-) and HER-2 negative (HER2-) tumours line up among the breast cancers with the worst prognosis. There have been an increasing number of studies reporting that these tumours, referred as "triple" negative group, have differences compared to other breast cancer types (3). Triple negative breast cancer (TNBC) is a heterogeneous tumour group with aggressive clinical behaviour, making up 10-20% of all breast cancer cases (4, 5). A more thorough understanding of tumour characteristics is necessary to develop new treatment methods, while hormone receptor negativity and HER-2 negativity limit treatment options.

The aim of this study is to present the demographic, clinic, pathologic differences and responses to treatment of the four breast cancer subtypes, which were formed according to their hormone receptors and HER-2 status. In case of possible differences, different treatment and follow-up strategies could be applied to these patient groups in clinical practice. Moreover, possible differences will allow for further clinical and laboratory researches.

MATERIAL AND METHODS

The study is based on 187 patients with breast cancer, who were diagnosed in Gülhane Military Medical Academy , Department of Medical Oncology clinics between 2008 and 2014. Cases were divided into 4 subgroups, according to their hormone receptor and HER-2 status [(in order ER±, PR±, HER2±) Group I (-,-,-), Group II (-,-,+), Group III (-,+,+), Group IV (+,+,+)]. Age, body mass index, date of diagnosis, family history, menopausal status, surgical history, radiotherapy history, chemotherapy history, relapse, last follow-up date and status; tumour's lymphovascular invasion status, grad (according to Scharf-Bloom-Richardson's grad), histopathology, hormone receptor status, HER-2 status, tumour size, amount of lymph nodes, status of metastasis, and tumour phase of all cases were determined.

The data was obtained by scanning the hospital's electronic records and via phone calls. The study was planned according to Helsinki Decleration, patient's bill of rights and ethics. Approval was obtained from Gülhane Military Medical Academy Ethics Committee, before the study.

World Health Organization's response to treatment criteria have been used to interpret the breast cancer cases. In a time period, which is a minimum of 4 weeks, complete response suggests a complete recovery from the tumour; whereas partial response implies that there is more than 50% of regression in the sum of biggest diameters of measurable lesions, and no new lesions appearing; stable disease means there is less than 50% of regression or less than 25% of increase in the sum of biggest diameters, but no new lesions appearing; and no response means there is more than 25% of increase in any diameter of the lesion and/or appearance of new lesions.

In the disease-free survival analysis, the dependant variable was the time spent until progression; the independent variables were family history, menopausal status, lymphovascular invasion, histologic grade, histopathological classification, HER-2 status, tumour size, amount of lymph nodes, metastasis, tumour stage and group.

Follow-up time was determined by considering the amount of time between the date of diagnosis and last follow-up or death. Survival rates were estimated by the Kaplan-Meier method. With log-rank test, the histopathological, clinical and treatment characteristics with prognostic importance related to survival were identified. Factors with a possible relevance to progression were searched by one variable analysis. The correlation of non-parametric variables with each other was searched with Ki-square test. The comparison of parametric variables between groups was accomplished by student's test. Statistical analyzes were performed by using SPSS 15.0, while $p<0.05$ was chosen statistically significant.

RESULTS

187 patients who visited our policlinics of Medical Oncology Department between years 2008 and 2014

were evaluated. These 187 patients were divided into 4 subgroups, 17 (9.1%) of them belonged to triple negative Group I (-,-,-), 21 (11.2%) belonged to Group II (-,-,+), 100 (53.5%) belonged to Group III (+,+,-), 49 (26.2%) belonged to Group IV (+,+,+).

Demographic characteristics

Mean follow-up time was 25 months (between 0,2 and 69 months). Median age of all patients included in this study was 50 (between 17 and 91). Age-specific incidence of breast cancer subtypes is presented in Figure 1.

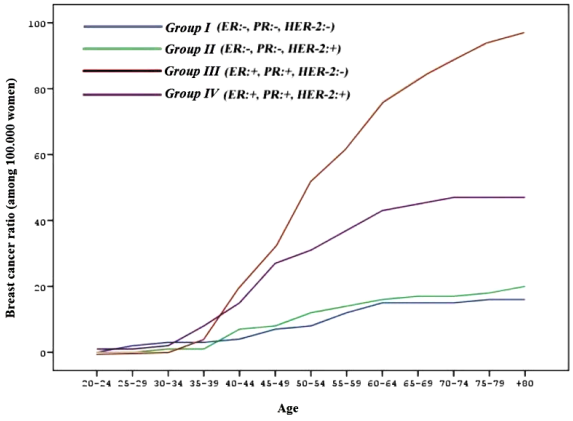

Figure 1: Age-specific incidence of breast cancer subtypes

77 patients (41.2%) were premenopausal, and 107 patients (57.2%) were postmenopausal. Mean body mass index was 27.2 ± 5.3 kg/m2 (mean ± standard deviation). 81 patients had a family history of breast cancer. No detailed information was obtained from the corresponding registry of their family members with breast cancer.

Comparative demographic results of the patients according to their HER-2 and hormone receptor status are given in Table 1.

Table 1. Demographic characteristics of breast cancer sub-groups.

	Group I (-,-,-)	Group II (-,-,+)	Group III (+,+,-)	Group IV (+,+,+)	P value
Age [year, median (min-max)]	n:16 55 (27-75)	n:20 54 (34-93)	n:97 54 (35-85)	n:47 48 (22-74)	0,041[a]
Body mass index (kg/m2, mean ± sd)	n:15 25,9 ± 5,1	n:17 29,0 ± 6,3	n:73 28,8 ± 5,0	n:38 25,7 ± 4,8	0,009[a]
Family history	n:17	n:21	n:100	n:49	
Present	9 (%52,9)	8 (%38,1)	41 (%41)	23 (%43,1)	0,716[b]
Non-present	8 (%47,1)	13 (%61,9)	59 (%59)	26 (%56,9)	
Menopausal status	n:17	n:20	n:99	n:48	
Premenopausal	7 (%41,2)	7 (%35)	37 (%37,4)	26 (%54,2)	0,241[b]
Postmenopausal	10 (%58,8)	13 (%65)	62 (62,6)	22 (%45,8)	

Description: n: Amount of eligible patients for assigned data, a: student-t test, b: Ki-square, min: minimum, max: maximum, sd: standard deviation

Tumour characteristics

75 patients (40.1%) were T1, 84 patients (44.9%) were T2, 10 patients (5.3%) were T3 and 8 patients (4.3%) were T4. 80 patients were listed as N0, 53 were N1, 24 were N2 and 14 patients were N3. Of the 152 patients which were evaluated for histologic grade, 11 (5.9%) were grade 1, 70 (37.4%) were grade 2 and 71 (38%) were grade 3. For the analysis of lymphovascular invasion, records of 172 patients were acquired.

Invasion was detected in 46 (24.6%) patients, while 126 (67.4%) patients did not have invasion. Among the 177 patients which were histopathologically classified, 21 (11.2%) had lobular invasive cancer, while other 156 (83.4%) had invasive ductal cancer. For staging, data for only 61 patients could be found, and 1 patient (0.5%) was stage 0, 13 patients (7%) were stage 1, 19 (10.2%) were stage 2 and 12 (6.4%) were stage 4.

Patient subtypes based on hormone receptor and HER-2 levels were compared. For the measurable parameters student-t test was used and for the non-parametric tests Ki-square was consulted. Patient distribution in lymph node status was significantly different (p=0.075). All four subgroups had similar characteristics (p>0.05) in tumour size, histologic grad, lymphovascular invasion, stage and histopathologic classifications. The comparison results of subgroups based on hormone receptor and HER-2 status are presented in Table 2.

Table 2. Characteristics of tumour during diagnosis in breast cancer subgroups

	Group I (-,-,-)	Group II (-,-,+)	Group III (+,+,-)	Group IV (+,+,+)	P value[a]
Lymphovascular invasion	n:17	n:21	n:88	n:46	
Present	5 (%29,4)	8 (%38,1)	23 (%26,1)	10 (%21,7)	0,563
Not present	2 (%70,6)	13 (%61,9)	65 (%73,9)	36 (%78,3)	
Histologic grad	n:12	n:16	n:83	n:41	
Grad 1	1 (%8,3)	1 (%6,3)	8 (%9,6)	1 (%2,4)	0,152
Grad 2	2 (%16,7)	5 (%31,3)	42 (%50,6)	21 (%51,2)	
Grad 3	9 (%7,5)	10 (%62,5)	33 (%39,8)	19 (%46,3)	
Histopathologic classification	n:17	n:18	n:94	n:48	
Lobular invasive cancer	12 (%11,8)	1 (%5,6)	12 (%12,8)	6 (%12,5)	0,855
Invasive ductal cancer	5 (%88,2)	17 (%94,4)	82 (%87,2)	42 (%87,5)	
Tumour size	n:16	n:17	n:98	n:46	
T1	7 (%43,8)	4 (%23,5)	43 (%43,9)	21 (%45,7)	
T2	7 (%43,8)	10 (%58,8)	51 (%52)	16 (%34,8)	0,163
T3	1 (%6,3)	2 (%11,8)	2 (%2)	5 (%10,9)	
T4	1 (%6,3)	1 (%5,9)	2 (%2)	4 (%8,7)	
Lymph node	n:15	n:16	n:96	n:44	
N1	8 (%53,3)	7 (%43,8)	44 (%45,8) 32	21 (%47,7)	
N2	6 (%40)	4 (%25)	(%33,3) 15 (%	11 (%25)	0,075
N3	0 (%0)	5 (%31,3)	25,6)	4 (%9,1)	
N4	1 (%6,7)	0 (%0)	5 (%5,2)	8 (%18,2)	
Stage	n:6	n:7	n:34	n:14	
Stage0	0 (%0)	0 (%0)	1 (%2,9)	0 (%0)	
Stage1	2 (%33,3)	1 (%14,3)	9 (%26,5)	1 (%7,1)	0,737
Stage2	1 (%16,7)	1 (%14,3)	11 (%32,4)	6 (%42,9)	
Stage3	2 (%33,3)	4 (%57,1)	6 (%17,6)	4 (%28,6)	
Stage4	1 (%16,7)	1 (%14,3)	7 (%20,6)	3 (%21,4)	

n: Number of patients evaluated for corresponding data, a: Ki-square.

Surgical Treatment

44 patients (23.5%) were treated with protective surgery (lumpectomy). 5 patients from Group I (29.4%), 5 from Group II (23.8%), 24 from Group III (24%) and 10 from Group IV (20.4) were treated with protective surgery. While 60 patients (32.1%) underwent mastectomy, 53 patients (28.3%) had MRM+ALND (Modified radical mastectomy + axillary lymph node dissection).

Adjuvant Treatment

Adjuvant chemotherapy was given to 166 patients. Adjuvant treatment planning differed later on, depending on variable practice.

123 patients received adjuvant radiotherapy to the chest wall and axillary area. Comparative results of different treatment methods before progression depending on hormone receptor and HER-2 status are given in Table 3.

Table 3. Treatment method before progression

	Group I (-,-,-)	Group II (-,-,+)	Group III (+,+,-)	Group IV (+,+,+)
Chemotherapy	n:16	n:18	n:84	n:48
Anthracycline based regime	5/(2S+2P+1R)	2/(2P)	28/(2N+7S+15P+4R)	8/(3S+4P+1R)
Anthracycline + Taxane regime	11/(3S+8P)	6/(1S+4P+1R	54/(7N+14S+28P+5R)	20/(6S+11P+3R)
Taxsane + Transtuzumab	--	10/(2C+5P+3R)	--	20/(1N+4S+15P)
Other regimes	0	0	2/(2P)	0
Radiotheraphy	n:17	n:21	n:100	n:49
Yes	13	15	61	34
No	4	6	39	15
Surgery	n:12	n:19	n:100	n:51
L	5	5	24	10
M	2	8	30	20
MRM+ALND	3	4	32	14
L and M	0	0	0	2
L and MRM+ALND	1	2	6	2
M and MRM+ALND	1	0	7	2
L, M and MRM+ALND	0	0	1	1

n: Number of patients evaluated for corresponding data, N: Nonresponse, S: Stabile, P: Partial response, R: Full response, L: Lumpectomy, M: Mastectomy, MRM+ALND: Modified radical mastectomy + axillary lymph node dissection.

Clinical progress

Factors for progression

Progression was noted in 41 patients (21.9%) of our study group. Factors responsible for progression were investigated with one variable analysis. A significant relationship between family history and progression was detected (p=0.026). Histological grade had a tendency to be related to progression (p=0.069). Menopausal status (p=0.123), lymphovascular invasion (p=0.491), histopathologic classification (p=0.888), HER-2 status (p=0.333), tumour size (p=0.935) and lymph node status (p=0.652) had no relationship with progression. Even though the progression of Stage 0/1 patients was 14.3% and progression of Stage 2/3/4 patients was 36.6%, no significant relationship was found between these two values (p=0.121), probably because the number of patients was not enough. For the same reason, we could say that we could not find a significant relationship between groups (minimum 14.3%, maximum 35.3% progression, p=0.108). Chemotherapy regimes had no effect on progression (p=0.754). That said, taxane-based regimes were used on more advanced stages (p=0.006). Detailed risk factors for progression are provided in Table 4.

Table 4. Risk factors related to progression

Factor	Progression status Present	Nonpresent	P value[a]
Family history			
Yes	24 (%29,6)	57 (%70,4)	0,026
No	17 (%16)	89 (%84)	
Menopausal status			
Premenopausal	21 (%27,3)	56 (%72,7)	0,123
Postmenopausal	19 (%17,8)	88 (%82,2)	
Lymphovascular invasion			
Present	8 (%17,4)	38 (%82,6)	0,491
Nonpresent	28 (%22,2)	98 (%77,8)	
Histologic grad			
Grad 1	2 (%18,2)	9 (%81,8)	
Grad 2	21 (%30)	49 (%70)	0,069
Grad 3	10 (%14,1)	61 (85,9)	
Histopathologic classification			
Lobular invasive cancer	5 (%23,8)	16 (%76,2)	0,888
Invasive ductal cancer	35 (%22,4)	121 (%77,6)	
HER-2 status			
Negative	23 (%19,7)	94 (%80,3)	0,333
Positive	18 (%25,7)	52 (%74,3)	
Tumour size			
T1/T2	34 (%21,4)	125 (%78,6)	0,935
T3/T4	4 (%22,2)	14 (%77,8)	
Lymph node status			
N0/N1	27 (%20,3)	106 (%79,7)	0,652
N2/N3	9 (%23,7)	29 (%76,3)	
Stage			
0/1	2 (%14,3)	12 (%85,7)	0,121
2/3/4	17 (%36,2)	30 (%63,8)	
Group			
Group I	6 (%35,3)	11 (%64,7)	
Group II	3 (%14,3)	18 (%85,7)	0,108
Group III	17 (%17)	83 (%83)	
Group IV	15 (%30,6)	34 (69,4)	

a: One variable analysis.

Disease-free survival results

Mean value of time until progression was 22 months (between 0.2 and 69 months). Family history, menopausal status, lymphovascular invasion, histologic grad, histopathologic classification, HER-2 status, tumour size, lymph node status and stage were analyzed with log-rank test as prognostic factors which effect disease-free survival. A strong relationship was noted between metastasis and disease-free survival (p=0.01), (Figure 2). Mean survival time of patients with metastasis was 26 months (95% GA, 17.73-33.72), distinctly shorter than mean survival time of patients without metastasis (52 months, 95% GA, 47.08-57.10). The

relationship of probable prognostic factors with disease-free survival is shown in details in Table 5.

Table 5. Evaluation of prognostic factors related to disease-free survival

Factor	Mean disease-free life time (month)[a]	P value[b]
Family history		
Yes	48 (%95CI. 40,74-54,21)	0,244
No	53 (%95CI. 46,06-58,93)	
Menopausal status		
Premenopausal	48 (%95CI. 40,90-54,67)	0,244
Postmenopausal	52 (%95CI. 45,43-58,42)	
Lymphovascular invasion		
Yes	56 (%95CI. 47,49-64,07)	0,874
No	49 (%95CI. 44,29-54,70)	
Histologic grad		
Grad 1	45 (%95CI. 33,86-55,89)	0,234
Grad 2	47 (%95CI. 40,00-53,49)	
Grad 3	56 (%95CI. 49,11-63,67)	
Histopathologic classification		
Lobular Invasive Canser	47 (%95CI. 32,68-61,03)	0,813
Invasive Ductal Canser	50 (%95CI. 45,14-55,76)	
HER-2 status		
Negative	51 (%95CI. 44,47-56,56)	0,411
Positive	41 (%95CI. 36,24-46,33)	
Tumour size		
T1/T2	49 (%95CI. 44,28-54,67)	0,742
T3/T4	54 (%95CI. 41,56-65,81)	
Lymph node		
N0/N1	50 (%95CI. 44,54-56,45)	0,961
N2/N3	52 (%95CI. 43,47-60,26)	
Metastasis		
Present	26 (%95CI. 17,73-33,72)	0,001
Nonpresent	52 (%95CI. 47,08-57,10)	
Stage		
0/1	27 (%95CI. 21,60-32,99)	0,397
2/3/4	39 (%95CI. 31,00-47,92)	
Group		
Group I	39 (%95CI. 24,05-53,74)	
Group II	47 (%95CI. 39,39-54,05)	0,200
Group III	53 (%95CI. 46,37-59,68)	
Group IV	39 (%95CI. 32,59-45,24)	

a: Kaplan-Meier, b:log-rank, CI: Confidence interval.

Factors with a p value of 0.15 or lower underwent multivariate analysis with cox-regression test. The only independent prognostic factor related to disease-free survival was designated as metastasis (p=0.001). HER-2 status (p=0.411), group (p=0.200) and stage (p=0.397) were not confirmed as independent prognostic factors.

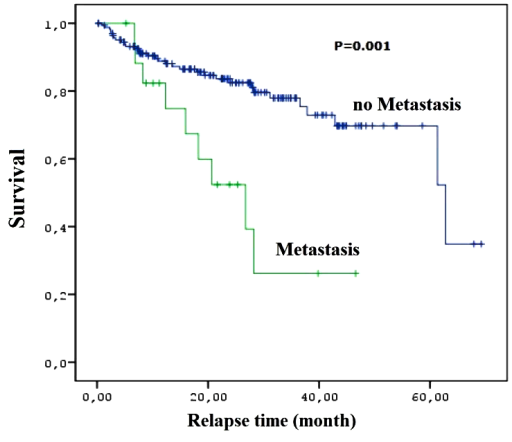

Figure 2. Survival graph, showing the relationship of metastasis and disease-free survival

In conclusion, the aim of our study in Gülhane Military Medical Faculty was to develop strategies according to proven differences of breast cancer subtypes by retrospectively analyzing their clinical, pathologic and prognostic characteristics.

We achieved these results in our study;

1. Group IV (ER:+, PR:+, HER-2:+) patients had a lower median age.

2. Group II (ER:-, PR:-, HER-2:+) patients had a higher mean body mass index.

3. Group I (ER:-, PR:-, HER-2:-) (triple negative) patients had more lymph node N1, N2 status.

4. In breast cancer patients, family history was an independent factor related to progression. Group was not related to progression.

5. In breast cancer patients, metastasis was an independent factor related to disease-free survival. Group was not related to disease-free survival.

6. Group III (ER:+, PR:+, HER-2:-) patients had more resistance to taxane-group cytotoxic medication.

DISCUSSION

Breast cancer is a common health problem and its incidence increases continuously. Nevertheless, a decrease in mortality in developed countries has been noted in the last 30 years, due to regular screening programs and the developments in adjuvant treatment programs for early stage patients. Recently, advancements in targeted therapy has also made it useful against some breast cancer subtypes.

The group called "triple negative" do not benefit from these up-to-date hormonal and trastuzumab-based targeted therapies. In contrast to hormone receptor positive breast cancers, this group has a worse prognosis and limited treatment options (3). For this reason the researchers tend towards finding new treatment methods for this subgroup. To illustrate, half of the "triple" negative breast cancer cases are also EGFR-1 positive, which indicates that this receptor may be a specific target for the treatment (7-9). Furthermore, there is not enough study on HER-2 positive patients, which make up 15-30% of hormone receptor negative breast cancers (5-10% of all breast cancers).

HER-2 positivity, playing an important role in tumour growth, proliferation and metastasis; can worsen the course of hormone receptor negative breast cancers. There are few comparative studies which help us comprehend the clinical and pathologic characteristics of "triple" negative, hormone receptor negative and HER-2 positive patients (10, 11). In these studies, the results of survival analysis and cytogenetic characteristics have been evaluated, but their responses to systemic therapy, demographic characteristics and clinical behaviour were not compared with each other. In our study, we compared the breast cancer subtypes in terms of demographic characteristics, tumour characteristics and their response to therapy.

In hormone receptor negative patients the status of HER-2 can be a marker for carcinogenesis, metastasis ability and medicine resistance. For instance, while in "triple" negative breast cancer cases the insufficiency of DNA repairing related to BRCA-1 mutation renders these patients more vulnerable to DNA damaging agents like cisplatine, HER-2 positive patients benefit from antracyclins and paclitaxels more than HER-2 negative patients (12-15). Therefore, in hormone receptor negative patients the HER-2 status (except from treatment agents like trastuzumab or lapatinib which target HER-2) may be a determining factor for adjuvant and metastatic treatment of breast cancer.

In our study with a small number of patients there was no significant relationship between triple negative breast cancer and family history; however some studies support that while evaluating hereditary breast cancer cases, which make up 10%, it is important to take a detailed family history, especially in "triple" negative patients. Same studies also suggest that a genetic consultation service should be part of the routine follow-up and treatment course for "triple" negative patients and their relatives (15, 16).

In A. Jemal et al. 's study (5) with large numbers of patients, the mean age of hormone receptor positive and HER-2 negative patients was smaller than the mean age of other subgroups. In our study with a smaller sample size, the mean age of hormone receptor positive and HER-2 positive patients was lower than other subgroups, with a statistical significance.

"Triple" negative breast cancers are also related to high tumour grad; but in our research no significant correlation between "triple" negative breast cancers and high tumour grad was confirmed (3). Liu et al. (10) proved that basal type breast cancers have a higher grad than HER-2 positive breast cancers, in their study comparing the subtypes of hormone receptor negative breast cancers. Additionally, basal type breast cancers make up 30% of "triple" negative breast cancers , and the tumour grad of "null type triple" breast cancers was found similar with HER-2 positive breast cancers.

Progression rate among all groups was determined as 21.9%. In our patients the progression rate was significantly higher than current known literature. The most important reason behind this is that breast cancer in our patients was diagnosed merely during symptomatic stage. None of our patients could be diagnosed early with screening methods during asymptomatic stages.

It is not clear whether there is a relationship between resistance to chemotherapy agents and HER-2. Some experimental studies put forward that HER-2 could develop a resistance against anthracyclines, taxanes, 5-flourourasile and cisplatine. The fact that clinical studies also prove the usage of trastuzumab on HER-2 positive patients to increase the sensitivity to chemotherapy agents, stands for a relation between HER-2 and medicine resistance. In some other studies, no relationship between HER-2 and chemotherapy could be indicated (17). Even though in our study we could not find a significant difference, many clinical studies point that anthracyclines and paclitaxels are more effective on HER-2 patients than other medicines (12-15). These studies reveal that many treatment regimes are less effective of HER-2 positive patients than HER-2 negative patients. These studies also indicate that in adjuvant treatment if trastuzumab is administered together with cytotoxic agents, the results become better (18). In our study we could not put forward any result about this due to lack of data. In addition, even though trastuzumab is known as an active medicine independent from hormone receptor status, the negativity of hormone receptors can cause some partial resistance (19).

Ethics Committee Approval: This study was approved by Scientific Researches Committee of Gulhane Military Medical Academy of Medicine.
Informed Consent: Written informed consent was obtained from the participants of this study.
Conflict of Interest: The authors declared no conflict of interest.
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