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Comparison of Premenopousal and Postmenopausal Breast Cancer Cases in Terms of Demographic and Prognostic Factor

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Abstract Breast cancer is the second most common type of cancer in the world and it is the most frequently seen cancer type in women. In early stages involving small and monocenter tumors, surgical treatment with breast conserving surgery followed by radiotherapy is the most preferred treatment regimen. Similar to the size of the tumor, several prognostic factors determine survival in breast cancer patients. This study was conducted to evaluate prognostic factors and their relationship to the menopausal status of the patients. University Ataturk Training and Research Hospital, Izmir, Turkey with 573 patients diagnosed with breast cancer between January 2006 and December 2012. Patient age, menopausal status, tumor location surgical treatment information, treatment regimen was gathered using the registry system of the hospital. Male breast cancer patients and patients with insufficient data were excluded. The mean (±SD) age of the study population was determined as 55.9 (±12.9). Most of the patients (65.3%) included in the study were identified as post-menopausal (n=199). Post-menopausal women were detected with larger tumors (p=0.048), at a later stage (p=0.037), with higher KI-67 index (p=0.015) and received more adjuvant hormone therapy (p=0.036) when compared to the pre-menopausal women. Multi-centered studies are needed to evaluate prognostic factors and their relationship to the menopausal status of the patients in order to plan more precise personal treatment regimens.

Keywords: *breast cancer, KI-67, menopausal status*

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1. Introduction

Breast cancer is the second most common type of cancer in the world and it is the most frequently seen cancer type in women. According to the data of Globocan project of International Agency for Research on Cancer, 1.6 million patients were diagnosed breast cancer in 2012 [1]. The incidence of breast cancer varies among countries. It has a high incidence in developed North and West European countries and the USA, excluding Japan [2]. In the United States, 211240 new patients were diagnosed with breast cancer and 40410 of them died in 2005 [3]. The increase of breast cancer in societies with low incidence rate is significantly higher than the increase in societies with high incidence of breast cancer. Thus, the gap between the breast cancer incidences of women who live the western and eastern countries is expected to close within years [4]. In analogy to other developing countries, the breast cancer incidence rapidly keeps increasing in Turkey as well [5,6,7]. The incidence of breast cancer in Turkey, which was 24/100.000 in 1992, doubled and reached up to the level of 50/100.000 in 2008 [8]. Tumor stage at the time of diagnosis of the disease is the most important factor in determining prognosis. The success rate in breast cancer cases diagnosed at early stage can be up to 90% [8].

In order for the early diagnosis of the disease, the factors causing the delay caused by the patients and the health system should be analyzed and the risk and prognostic factors should be tried to be determined with the studies to be performed. Age has been identified as an important risk factor in breast cancer. It was found that the disease was seen more frequently in women over 30 years of age [9]. Many prognostic factors such as tumor size, environment, nutrition and genetics have been identified in breast cancer. Similar studies continue to investigate different prognostic factors. Due to the different characteristics of prognostic factors, the differences in

courses and biological behaviors of premenopausal and postmenopausal breast cancer patients should be analyzed separately [10].

In the present study, the prognostic factors such as age, gender, tumor size, lymph node metastasis, histopathologic type and steroid hormone receptor as well as cerb B2 gene and Ki-67 proliferative index were analyzed and their relationship with menopausal status was analyzed. The study is thought to contribute to the literature and the prognostic factors in breast cancer.

2. Materials and Methods

This study was designed as a retrospective observational study and 573 patients who applied to Izmir Katip Çelebi University Atatürk Training and Research Hospital General Surgery Clinic between the dates of January 01, 2006 and December 31, 2012 and diagnosed with breast cancer were involved in it. The patient records were accessed by using the PROBEL hospital information management system of our hospital. A database was created by recording the data of the cases such as age, menopausal status, tumor side and clock-face distribution, surgical treatment regimen, primary tumor magnitude, state of axillary lymph node metastasis, TNM stage, steroid hormone receptor status, c-erbB2 gene status, KI-67 proliferation index rate, adjuvant chemotherapy (CT), radiotherapy (RT) and hormonal therapy (HRT) uptake rate and the statistical analysis was performed. Patients with inadequate file information (n=54) and male breast cancer patients (n=6) were not included in the statistical analysis.

2.1. Statistical Methods

Statistical Package for the Social Sciences (SPSS) 21 program was used in the analysis of the data. Pearson Chi-Square tests were used in the comparison of the categorical data and Gamma correlation test was used for analyzing the correlations between the variables. Logistic regression test was used to determine the cause and effect relation of categorical response variable with explanatory variables in binary and multiple categories. The categorical data was expressed with numbers (n) and percentages (%). The data was analyzed in 95% confidence level and the cases with p value less than 0.05 was accepted as statistically significant in the analyses performed.

3. Results

It was observed that 34.7% of 573 breast cancer patients (n=199) included in the study were in the premenopausal and 65.3% were in the postmenopausal period. The mean (±SD) age of the study population was determined as 55.9 (±12.9) and it was seen that the age range varied between 21 and 92 years. When the ages of pre- and postmenopausal groups were evaluated separately, it was determined that the mean age in the premenopausal group was 42.7 (±5.40) and the youngest and oldest patients were at the ages of 21 and 53 respectively. While the mean age in the postmenopausal group was 63.0 (±9.7), the minimum and maximum ages were 40 and 92, and it attracted attention that the number of patients in this group (n=374) was two times more than the premenopausal group (n=199) (Table 1).

Table 1. Evaluation of the mean ages of the groups involved in the study

Groups	Age	
	Mean (±SS)	Minimum - Maximum
Premenopausal (n=199)	42.67 (±5.40)	21 - 53
Postmenopausal (n=374)	62.97 (±9.72)	40 - 92
General (N=573)	55.92 (±12.86)	21 – 92
Age	Frequency (n)	Percentage (%)
(20-35)	21	3.7%
(36-50)	202	35.3%
(51-65)	213	37.2%
66≤	137	23.9%

The most common disease was Invasive Ductal Carcinoma (IDC) with 451 (78.7%) patients and Invasive Lobular Carcinoma (ILC) was the second most common disease with 41 patients (7.2%). The others were Mix (IDC+ILC) (5.9%) and Ductal Carcinoma In-situ (DCIS) (5.4%) (Table 2).

Table 2. Distribution of the patients according to their histopathological types

PATHOLOGY	Frequency (n)	Percentage (%)
Invasive Ductal Carcinoma (IDC)	451	78.7
Invasive Lobular Carcinoma (ILC)	41	7.2
Mix (IDC+ILC)	34	5.9
Ductal Carcinoma In-situ (DCIS)	31	5.4
Paget's Disease	3	0.5
Lobular Carcinoma In-situ (LCIS)	3	0.5
Metaplastic Carcinoma	3	0.5
Inflammatory Carcinoma	2	0.3
Phyllodes Tumor	2	0.3
Other	2	0.3
Carcinosarcoma	1	50.0
Salivary Gland	1	50.0
Malign Mesenchymal Carcinoma	1	0.2

There was no statistically significant difference in the probability of incident in the premenopausal and postmenopausal periods between patients with right breast cancer (281) and patients with left breast cancer (279) (P=0.954) (Table 3).

Breast cancer was seen most frequently in the Upper Outer region of the breast with 364 patients. There was no statistically significant difference in the incidence of cancer in the Upper Outer region between premenopausal (34.6%) and postmenopausal (65.4%) periods (P=0.583) (Table 3).

With 286 patients, mostly the stage 2 breast cancer was detected. It was found that the TNM classification did not create a difference in premenopausal and postmenopausal periods (P=0.037) (Table 3).

In postmenopausal cases with breast cancer, the rate of application to hospital in stage IV was found to be 12.95 times higher than in premenopausal cases. Furthermore, the incidence of T4 in postmenopausal cases with breast cancer was 4.35 times higher than premenopausal cases (Table 3).

Table 3. Distribution of the cases by groups, tumor side and clock-face distribution, surgical procedure implemented, tumor size, lymph node metastasis, TNM stage

		Premenopausal			Postmenopausal			Total	p *
		Frequency (n)	Column percentage (%)	Line percentage (%)	Frequency (n)	Column percentage (%)	Line percentage (%)		
Side	Right	98	34.9	49.2	183	65.1	48.9	281	0.954
	left	96	34.4	48.2	183	65.6	48.9	279	
	Synchronicity	5	38.5	2.5	8	61.5	2.1	13	
	Total	199			374			573	
Clock-face Distribution	Upper Outer	126	34.6	63.3	238	65.4	63.6	364	0.583
	Upper Inner	26	38.8	13.1	41	61.2	11	67	
	Bottom Outer	20	35.7	10.1	36	64.3	9.6	56	
	Bottom Inner	15	38.5	7.5	24	61.5	6.4	39	
	Central	12	27.9	6	31	72.1	8.3	43	
	Occult	0	0	0	4	100	1.1	4	
	Total	199			374			573	
Tumor Size	Tis	15	42.9	7.6	20	57.1	5.4	35	0.048
	T1	57	31.7	28.8	123	68.3	33.4	180	
	T2	108	37.8	54.5	178	62.2	48.4	286	
	T3	13	41.9	6.6	18	58.1	4.9	31	
	T4	5	14.7	2.5	29	85.3	7.9	34	
	Total	198			368			566	
Lymph node metastasis	N0	87	36.7	47	150	63.3	44.1	237	0.445
	N1	84	34	45.4	163	66	47.9	247	
	N2	14	37.8	7.6	23	62.2	6.8	37	
	N3	0	0	0	4	100	1.2	4	
	Total	185			340			525	
TNM Stage	Stage 0	15	40.5	7.5	22	59.5	5.9	37	0.037
	Stage I	40	31.3	20.1	88	68.8	23.5	128	
	Stage II	118	37.6	59.3	196	62.4	52.4	314	
	Stage III	25	33.8	12.6	49	66.2	13.1	74	
	Stage IV	1	5	0.5	19	95	5.1	20	
	Total	199			374			573	

Table 4. Distribution of the cases by groups, steroid receptor status, cerb B2 gene status, KI-67 proliferation index and statuses of receiving adjuvant KT, RT and HRT

		Premenopausal			Postmenopausal			Total	p *
		Frequency (n)	Column percentage (%)	Line percentage (%)	Frequency (n)	Column percentage (%)	Line percentage (%)		
Steroid receptor status	Negatif (-)	47	36.7	27.5	81	63.3	23.7	128	0.348
	Pozitif (+)	124	32.2	72.5	261	67.8	76.3	385	
	Total	171			342			513	
Cerb B2 gene status	Negatif (-)	136	32.9	84	278	67.1	87.4	414	0.269
	Pozitif (+)	26	39.4	16	40	60.6	12.6	66	
	Total	162			318			480	
KI- 67 proliferation index	≤15	62	27.9	53.9	160	72.1	68.7	222	0.015
	(15-45)	26	47.3	22.6	29	52.7	12.4	55	
	≥45	27	38	23.5	44	62	18.9	71	
	Total	115			233			348	
Adjuvant HRT	Absent	57	42.2	28.6	78	57.8	20.9	135	0.036
	Present	142	32.4	71.4	296	67.6	79.1	438	
	Total	199			374			573	
Adjuvant KT	Absent	66	30	33.2	154	70	41.2	220	0.06
	Present	133	37.7	66.8	220	62.3	58.8	353	
	Total	199			374			573	
Adjuvant RT	Absent	44	36.4	22.1	77	63.6	20.6	121	0.671
	Present	155	34.3	77.9	297	65.7	79.4	452	
	Total	199			374			573	

Table 5. Distributions of surgical procedures implemented according to TNM stage

Surgical Procedure	TNM Stage						Total	p *
	Early Stage (Stage 0 + I + II) (n=479) (83.6%)			Late Stage (Stage III + IV) (n=94) (16.4%)				
	N	(Column %)	(Line %)	N	(Column %)	(Line %)		
Breast Conserving Surgery (BCS)	301	62.8	92	26	27.7	8	327	<0.001
Modified Radical Mastectomy (MRM)	151	31.5	74.4	52	55.3	25.6	203	<0.001
Simple Mastectomy (SM)	20	4.2	74.1	7	7.4	25.9	27	0.180
Excision	7	1.5	50	7	7.4	50	14	<0.001
Radical Mastectomy (RM)	0	0	0	2	2.1	100	2	-

* Chi-Square Test.

Table 6. Evaluation of risk factors

	Postmenopausal		95% C.I for Odds Ratio	
	P Value	Odss Ratio	Lower Limit	Upper Limit
TNM Stage(Stage IV)	0.018	12.95	1.562	107.416
Tumor Size(T4)	0.013	4.35	1.362	13.896
HRT(Present)	0.037	1.52	1.025	2.263
KI-67(≤15)	0.007	2.31	1.263	4.237

Multiple Logistic Regression (Method: Enter), CI: Confidence Interval.

With 385 patients, the positive steroid receptor status was detected most. There was no statistically significant difference in the steroid receptor statuses between premenopausal and postmenopausal periods (P=0.348) (Table 4).

With 414 patients, the Cerb B2 gene status was detected most. There was no statistically significant difference in the Cerb B2 gene statuses between premenopausal and postmenopausal periods (P=0.269) (Table 4). With 222 patients, the KI- 67 proliferation index was detected most and this value was not found statistically significant (P=0.036) (Table 4).

Considering the TNM stages, it was seen that 479 (83.6%) of 573 patients with breast cancer were in the early stages (Stages 0-I-II) and 94 (16.4%) were in the late stages (Stages III-IV). Breast Conserving Surgery (BCS) was preferred rather in the early stages and this surgical procedure was implemented 62.8% (n=301) of the early stage breast cancer patients and 27.7% (n=26) of the late stage patients (p<0.001). It was determined that 74.1% (n=20) of the patients implemented Simple Mastectomy (SM) were in the early stages (Stages 0. 1 and 2A) and 25.9% were in the late stages (Stages 2B, 3 and 4), and a statistically significant difference was not found between the early and late stage groups in 27 breast cancer patients who were implemented SM (p=0.180). Modified Radical Mastectomy was implemented 203 patients in total and this procedure was preferred mostly (74.4%, n=151) in the early stage cases (p<0.001). Excision was implemented in 14 patients in total and preferred equally in the early and late stages of breast cancer (%50; n=7). Radical mastectomy (RM) was not preferred for the early stage patients and it was implemented only for 2 patients in late stages (Table 5).

When the early and late stage breast cancer patients involved in the study are analyzed among themselves, it was seen that BCS (62.8%) was preferred mostly in the early stage patients and MRM (55.3%) in the late stage patients (Table 5). Patients were categorized as ≤15, 15-45 and≥45 according to their proliferation indexes and these groups were classified as per their premenopausal and post-menopausal states. Similarly, the most frequent category in the pre- and post-menopausal groups was ≤15 (72.1% for premenopausal and 68.7% for postmenopausal). However, when categories were analyzed within themselves, the number of patients in the postmenopausal group was higher for all categories (p=0.015). Patients were evaluated according to adjuvant hormonal therapy (HRT) and it was determined that the majority of both premenopausal and postmenopausal groups received hormonal therapy (71.4% for premenopausal, 79.1% for postmenopausal group). While the rate of the patients who received HRT in the premenopausal group was 32.4%, it rose up to 67.6% in the postmenopausal group and it was determined that the differences between these distributions were statistically significant (*p*=0.036) (Table 6).

A statistically significant difference was not observed when tumor localization (side), clock-face distribution, lymph node metastasis, steroid receptor status, Cerb B2 gene status, adjuvant KT and adjuvant RT status are compared separately between two groups (p>0.005).

The risk factors examined in the study were examined, and it was determined that the rate of TNM Stage IV patients were 12.95 times, the rate of patients with T4 tumor size were 4.35 times, the rate of patients receiving HRT treatment was 1.52 times, and the rate of patients with KI-67 proliferation index of ≤15 was 2.31 times more than the rate of patients in the premenopausal group, and that this difference was statistically significant (P<0.05) (Table 6).

4. Discussion

In this study (*), it was determined that the rate of application of the postmenopausal patients with breast cancer in stage IV was 12.95 times higher than the premenopausal patients (**), the incidence of T4 in postmenopausal patients with breast cancer was 4.35 times higher than premenopausal patients (***) the rate of KI-67

to be ≤15 in the postmenopausal patients with breast cancer was 2.31 times higher than the premenopausal patients (****) the rate of receiving adjuvant HRT therapy in postmenopausal patients with breast cancer was 1.52 times higher than premenopausal patients and the most important risk factor was TNM.

Breast cancer is a heterogeneous disease group with different clinical behavior, radiological and pathological features and biopsy potential. This heterogeneity carries with it the need to put every breast cancer case into its appropriate and right place in this wide spectrum. And this is only possible with the recognition and assessment of the parameters based on morphology as well as molecular indicators, which are prognostic parameters not based on morphology, defined until today, and by developing individual treatment plans for each patient and providing personalized treatment [10].

Breast cancer is a heterogeneous disease caused by the progressive accumulation of epigenetic and genetic changes and influenced by hereditary and environmental risk factors [11]. Uncontrolled cell proliferation due to breast cancer exhibits alterations such as signs of genomic instability and disappearance of certain epithelial properties. Therefore, knowing the molecular mechanisms causing to carcinogenesis and determination of appropriate treatment methods are of capital importance. The overall objective of breast cancer researches is to identify prognostic and predictive changes [12]. In this study, the most common disease was IDC with 451 patients (78.7%), while ILC was the second most common disease with 41 patients (7.2%). No statistically significant difference was found between patients with right breast cancer (281) and those with left breast cancer (279). The incidence of right or left breast cancers in premenopausal and postmenopausal periods was not statistically significant.

Nouh et al. reported that the rate of axillary lymph node metastasis decreased in patients between the ages of 40-60 [13]. Kondov et al. emphasized that axillary lymph node metastases are associated with tumor size, and that the proportion of lymph node metastasis in patients with Ki67 is significantly higher [14]. Çakır et al. compared the rates of axillary lymph node metastasis in monocenter tumors, multicenter tumors, or patients with breast involvement in the study they performed on 267 patients. As a result of the study, compared to monocenter tumors, breast tumors with nipple involvement or multiple foci show a significantly higher incidence of axillary lymph node metastasis which is a predictor of a poor prognosis [15]. Snell et al., evaluated the progesterone receptor expression in the lymph node metastasis in the study they performed on 229 patients with metastatic lymph node and determined that the patients could benefit more from the adjuvant tamoxifen [16]. In the present study, a statistically significant difference was not seen between the groups in the analysis of lymph node metastases of premenopausal and postmenopausal breast cancer patients, and it was determined that the most frequent involvements were NO (47.0%) in the premenopausal and N1 (47.9%) in the postmenopausal group. The high ratio of NO may arise from patients to get early diagnosis thanks to high accessibility and efficient use of screening programs in Izmir province and its surroundings.

Benson compiled breast cancer screenings, prevention methods, systemic treatments, some of the important studies presented in the case of breast cancer, metastatic breast cancer in the first part, extended endocrine therapy and the prognostic importance of the BRCA 1/2 gene in a study where the speeches made in the 36th Saint Antonio Breast Cancer Symposium in 2016 were compiled. He discussed the anti-HER2-directed therapies, the effect of radiotherapy on implant and otology valve-based reconstruction, biological risk predictors for ductal carcinoma in situ (DCIS), a series of subjects such as long-term effects of diet oil, and the modification of the aromatase inhibitors on the endothelial cell function in his study [17].

The most important factor in the choice of treatment protocol to be applied and determining the prognosis of breast cancer is the status of the axillary lymph nodes. Thus, axillary dissection is important in the correct staging of the breast cancer and determining the adjuvant treatment to be implemented the metastatic involvement determined in the histological examination of axillary lymph nodes is the most powerful prognostic factor for patients with breast cancer [17]. In our study, the most frequent tumor stage in premenopausal and postmenopausal groups was the same and it was the Stage II tumors in both groups. However the incidence rate of advanced stage tumors in the postmenopausal group was higher comparing to the premenopausal group. Similar results were obtained also in the comparison made in the common age group involving only the patients in the 40-53 age group. As is the case with tumor size, the increase of advanced stage breast cancer incidence rate in the postmenopausal group may arise from lack of self-examination, decreasing of body awareness and lack of compliance with screening programs in postmenopausal period. It was determined that breast cancers were seen most frequently in the Upper Outer region of the breast the rate of application of the postmenopausal patients with breast cancer in stage IV was 12.95 times higher than the premenopausal patients. In addition, the incidence of T4 in postmenopausal patients with breast cancer was 4.35 times higher than premenopausal patients. The positive steroid receptor was determined most. The rate of KI-67 to be ≤15 in the postmenopausal patients with breast cancer was 2.31 times higher than the premenopausal patients. Therefore, an increasing rate of early stage breast cancer diagnosis and improvement of prognosis can be expected in future with the increasing efficiency of screening programs and public awareness activities

In conclusion, In this study, TNM staging was determined as the most important risk factor and it was seen that the Stage IV applications were higher in the postmenopausal period comparing to the premenopausal cases. In addition, it was seen that the rates of T4 incidence, KI-67 ≤ 15 and receiving HRT were higher in the postmenopausal group.

Age, gender, tumor size, lymph node metastasis, histopathological type, steroid hormone receptor, cerb B2 gene, KI-67 proliferative index were analyzed in many studies as prognostic factors, but the relationship between these parameters and menopausal status was not analyzed in previous studies. Multicenter studies are needed for the

relationship between prognostic factors and menopausal status in line with the personalized treatment plan.

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