

# Comparison of clinicopathological features and treatments between pre- and postmenopausal female breast cancer patients – a retrospective study

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## Abstract

**Introduction:** To find out if there are clinical and biological differences in breast cancer characteristics of premenopausal and postmenopausal women. For this reason, we investigated the differences in terms of the clinicopathological features and treatment methods of premenopausal and postmenopausal breast cancer patients in our study.

**Material and methods:** In this study, the files of 428 patients who were operated due to breast cancer between 1 January 2007 and 31 December 2017 in Ankara Atatürk Training and Research Hospital were examined retrospectively. The age, tumour size, tumour grade, oestrogen receptor, progesterone receptor, HER2 score, Ki-67 proliferation index, perineural invasion, and lymphovascular invasion were investigated.

**Results:** In patients with premenopausal breast cancer, the tumour diameter was larger ( $p = 0.047$ ) and the lymph node metastasis was higher ( $p < 0.001$ ). Oestrogen receptor (OR) expression ( $p = 0.002$ ), progesterone receptor (PR) expression ( $p = 0.014$ ), negative human epidermal growth factor receptor 2 (HER2) expression ( $p = 0.038$ ), and Ki-67 expression ( $p = 0.017$ ) were higher in the premenopausal group. In the premenopausal group, breast conserving surgery ( $p = 0.004$ ), chemotherapy ( $p = 0.007$ ), radiotherapy ( $p = 0.008$ ), and endocrine therapy ( $p = 0.025$ ) were higher than in the postmenopausal group.

**Conclusions:** Premenopausal and postmenopausal female breast cancer patients have significant differences in tumour size, tumour grade, axillary lymph node metastasis, hormone receptor status, HER2 expression, and treatment modalities.

**Key words:** breast cancer, hormone receptor, premenopausal, postmenopausal, breast-conserving surgery.

## Introduction

In recent years, the incidence of breast cancer has increased all over the world. In 2012, the incidence of breast cancer in Asian countries was reported as 27 per 100,000 women and 92 per 100,000 women in the United States [1]. The incidence of breast cancer in Turkey was 31.9 per 100,000 in 2002, and 43 per 100,000 in 2014. The most common type of cancer among women in Turkey, seen with a rate of 24.9%, is breast cancer [2]. According to the World Health Organisation, in 2016 the incidence of breast cancer was 1.7 million and resulted in 535,000 deaths worldwide [3]. Breast cancer diagnosis is recommended by breast self-examination, ultrasonography (USG), and mammography. Factors such as prolonged exposure to the oestrogen effect (early menarche, nulliparity, and late menopause), older age at first live birth, obesity, alcohol use, and long-term consumption of high-fat diets increase

serum oestrogen levels and increase breast cancer risk [4-6]. Exposure to radiation also increases breast cancer risk [7]. Factors protecting from breast cancer include short duration of oestrogen effect, moderate exercise, longer lactation duration, and breastfeeding [8]. The protective effect of multiparity decreases along with postmenopausal breast cancer; breastfeeding is an important factor in reducing the risk of breast cancer in the postmenopausal period [9].

The age of menopause varies between the ages of 45 and 55 years in Turkey. The mean age is  $47 \pm 4.2$  years [10]. There are clinical and biological differences in patients with premenopausal and postmenopausal breast cancer. Premenopausal tumours peak in early life whereas postmenopausal tumours peak in later life [11]. It is estimated that the incidence of hormone receptor-positive breast cancer is affected by the menopausal transition [12]. Immunohistochemical status of

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oestrogen receptors (OR), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) are among the factors that influence breast cancer treatment options and prognosis [13, 14]. There is an inverse relationship between OR, PR expression, and Ki-67 mitotic proliferation index [15]. OR, PR, HER2 receptor level, Ki-67 proliferation index, and some risk factors also determine treatment selection and prognosis [16]. Although there are studies reporting that breast cancer hormone receptors are affected by menopause, there are still discussions about this subject. Therefore, whether premenopausal and postmenopausal patients with breast cancer may differ between clinicopathological features and treatment modalities should be investigated.

The aim of this study is to develop treatment strategies, to improve the prognosis of patients, and to gain valuable insights into the effects of menopause. For this reason, we compared the differences between premenopausal breast cancer patients and postmenopausal patients in terms of clinicopathologic features and treatment methods.

## Material and methods

The files of 428 patients who underwent surgery for breast cancer between January 1, 2007 and December 31, 2017 were reviewed retrospectively in the Atatürk Training and Research Hospital. Age of the patients, type of surgery, lateralisation of the tumour, and pathology report were obtained from the archive. Preoperative and postoperative laboratory examinations, pathological examination results, oestrogen and progesterone receptor positivity grade, HER2, and Ki-67 status were retrospectively recorded from the HBYS program. Tumour location, differentiation grade, lymphovascular invasion, perineural invasion, and lymph node metastasis, the patients' treatment regimens, surgical types, and axillary lymph node dissection procedures, follow-up protocols of patients, whether the cancer is recurrent or not, and five-year survival periods were also recorded.

## Ethical consideration

The study was commenced after obtaining written consent from the Yildirim Beyazit University Medical Faculty Clinical Research Ethical Evaluation Commission (decision no. 191, 11 July 2018) at the hospital where the study would be conducted.

## Statistical analysis

The data obtained from the study were evaluated in the SPSS program (version 25.0; SPSS, Chicago, IL,

USA). In the evaluation of descriptive statistics, number, percentage, mean, standard deviation values were used. The differences in the demographic, clinical, and pathological characteristics and in treatments between the two groups were analysed using Student's t-test in the case of quantitative variables and  $\chi^2$  tests in the case of categorical variables.

## Results

In our study, the mean age of the patients during diagnosis of breast cancer was  $56.16 \pm 12.71$  years, the mean age of the premenopausal patients was  $46.84 \pm 6.44$  years (minimal age: 19 years, maximal age: 55 years), and the mean age of the postmenopausal patients was  $66.02 \pm 9.96$  years (minimal age: 44 years, maximal age: 96 years). Premenopausal patients between 47-52 years of age and postmenopausal patients were between 58-65 years of age were found to develop a breast cancer peak.

There was no significant difference between the groups in terms of tumour histology ( $p = 0.795$ ) (Table 1). In 22.55% of the premenopausal patients, the tumour diameter was  $< 2$  cm, in 56.17% the tumour diameter was 2-5 cm, and in 21.28% of the patients the tumour size was greater than 5 cm. In postmenopausal patients these figures were, respectively, 22.8%, 64.77%, and 12.43%. In premenopausal patients, the number of patients with tumor diameter greater than 5 cm was significantly higher than postmenopausal patients ( $p = 0.047$ ). The axillary lymph node in 76.60% of premenopausal patients and in 57.51% of postmenopausal patients was positive. Lymph node involvement was significantly higher in the premenopausal group ( $p < 0.001$ ).

We found that patients in the premenopausal group had a higher likelihood of positive expression of OR than patients in the postmenopausal group (55.8% vs. 44.2%,  $p = 0.002$ ). For patients in the premenopausal group PR was more likely to show positive expression than for those in the postmenopausal group (52.7% vs. 40.9%,  $p = 0.014$ ). It was also found that the probability of OR and PR showing double positive expression in the premenopausal group (Table 2) was higher than in the postmenopausal group (53.61% vs. 30.05%,  $p < 0.0001$ ). OR+ and PR- were significantly higher in the postmenopausal group than in the premenopausal group (15.32% vs. 24.87%  $p = 0.013$ ). Similarly, OR- and PR+ were significantly higher in the postmenopausal group than in the premenopausal group (4.25% vs. 12.95%,  $p = 0.001$ ). OR- and PR- were found to be significantly higher in the postmenopausal group than in the premenopausal group (28.08% vs. 43%,  $p < 0.001$ ). HER2 positivity was significantly higher in the postmenopausal group than in the group premenopausal (11.91% vs. 19.17%  $p = 0.038$ ). Ki67 expression

**Table 1.** Pathological characteristics of the tumours

Characteristics	Premenopausal		Postmenopausal		Total		p-value
	n	%	n	%	n	%	
Tumour histology							
Carcinoma <i>in situ</i>	7	2.98	7	3.63	14	3.27	0.795
Invasive carcinoma	211	89.79	172	89.12	383	89.49	
Other carcinomas	17	7.23	14	7.25	31	7.24	
Tumour size							
< 2 cm	53	22.55	44	22.80	97	22.66	0.047
2-5 cm	132	56.17	125	64.77	257	60.05	
> 5 cm	50	21.28	24	12.43	74	17.29	
Axillary lymph nodes metastasis							
Negative	55	23.40	82	42.49	137	32.01	< 0.001
Positive	180	76.60	111	57.51	291	67.99	
Tumour grade							
I	26	11.06	41	21.24	67	15.65	0.001
II	120	51.06	105	54.40	225	52.57	
III	89	37.87	47	24.35	136	31.78	

$\chi^2$  test

**Table 2.** Immunohistochemical marker characteristics of the tumours

Characteristics	Premenopausal		Postmenopausal		Total		p-value
	n	%	n	%	n	%	
OR+/PR+							
Yes	126	53.61	58	30.05	184	42.99	< 0.001
No	109	46.39	135	69.95	244	57.01	
OR+/PR-							
Yes	36	15.32	48	24.87	84	19.63	0.013
No	199	84.68	145	75.13	344	80.37	
OR-/PR+							
Yes	10	4.25	25	12.95	35	8.18	0.001
No	225	95.75	168	87.05	393	91.82	
OR-/PR-							
Yes	66	28.08	83	43.01	149	34.81	0.001
No	169	71.92	110	56.99	279	65.19	
HER2+							
Yes	28	11.91	37	19.17	65	15.19	0.038
No	207	88.09	156	80.83	363	84.81	
Triple negative							
Yes	51	21.7	42	21.76	93	21.73	0.988
No	184	78.3	151	78.24	335	78.27	
Ki-67+							
Yes	78	33.19	44	22.8	122	28.5	0.017
No	157	66.81	149	77.2	306	71.5	

$\chi^2$  test

was significantly higher in the premenopausal group than in the postmenopausal group (33.19% vs. 22.8%,  $p = 0.017$ ).

Chemotherapy, radiotherapy, and endocrine therapy for the premenopausal disease were more frequent-

ly performed (Table 3). Chemotherapy treatment was found to be higher in the premenopausal group than in the postmenopausal group (83.83% vs. 73.06%,  $p = 0.007$ ). Radiotherapy was used more frequently in the premenopausal group than in the postmenopausal

**Table 3.** Treatments of the patients with breast cancer

Characteristics	Premenopausal		Postmenopausal		Total		p-value
	n	%	n	%	n	%	
Chemotherapy							
Yes	197	83.83	141	73.06	338	78.97	0.007
No	38	16.17	52	26.94	90	21.03	
Radiotherapy							
Yes	53	22.55	26	13.47	79	18.46	0.008
No	182	77.45	167	86.53	317	81.54	
Endocrine therapy							
Yes	71	30.21	40	20.73	111	25.93	0.025
No	164	69.79	153	79.27	317	74.07	
Anti-HER2 therapy							
Yes	19	8.09	9	4.66	28	6.54	0.149
No	216	91.91	184	95.34	400	93.46	
Type of surgery							
Type of surgery modified Radical mastectomy	183	77.87	147	76.17	330	77.10	0.004
Breast-conserving surgery	22	9.36	6	3.11	28	6.54	
Simple mastectomy and other	30	12.77	40	20.72	70	16.36	

χ<sup>2</sup> test

group (22.55% vs. 13.47%,  $p = 0.008$ ). Endocrine therapy was used more frequently in the premenopausal group than in the postmenopausal group (30.21% vs. 20.73%,  $p < 0.025$ ). There was no significant difference in anti-HER2 treatment (8.09% vs. 4.66%,  $p = 0.149$ ). Breast-conserving surgery was performed more frequently in the premenopausal group (9.36% vs. 3.11%,  $p = 0.004$ ). While 90% of premenopausal patients undergoing breast-conserving surgery completed their five-year lifespan, 88% of postmenopausal patients completed their five-year lifespan.

## Discussion

Differences in some risk factors between premenopausal women with breast cancer and postmenopausal women were identified. Patients with premenopausal breast cancer constituted 54.9% of all patients in our study. Similar rates were found in studies conducted in Asia, at 54.3-54.55% [17, 18].

We found the mean age of the patients with breast cancer to be 58 ±12.69 years in our study. Age is an important factor affecting breast cancer development. Younger women have been reported to have larger breast cancer tumour size, higher HER-2/EGFR expression, and worse prognosis [19, 20]. In our study, the number of patients with breast cancer greater than 5 cm was higher in the premenopausal group. In addition, HER-2 expression in the premenopausal group was higher than in the postmenopausal group. Young premenopausal women have been reported to have a larger breast tumour di-

ameter, higher-grade breast cancer, and more negative tumour receptors [21]. In our study, in patients with premenopausal breast cancer, the number of patients with a tumour diameter greater than 5 cm was found to be higher than in the postmenopausal group. In premenopausal patients, tumour grade was higher than in the postmenopausal group. The OR-PR receptor status is the most important indication that will guide endocrine treatment to be administered to the patient. It is also an important factor that affects the prognosis of breast cancer [22, 23]. In our study, OR positivity was high in both premenopausal women and postmenopausal women. OR positivity was 68.94% in the premenopausal group and 54.92% in the postmenopausal group; Feng *et al.* found 59% in the premenopausal group and 55% in the postmenopausal group in their study [17]. In the premenopausal group, OR+ PR+ patients were at a higher rate, whereas in the postmenopausal group OR- PR- patients were higher. There was a negative correlation between OR+ expression and overexpression of HER-2. OR+ has been reported to be associated with a better prognosis [24]. We achieved similar results in our study. In our study, 97% of premenopausal patients with OR+ and anti-HER2 treatment and 95% of postmenopausal patients completed five-year survival. Studies have shown that HER2 expression of breast cancer cells in premenopausal women is lower than in postmenopausal women [25-27].

In women with premenopausal breast cancer, axillary lymph node metastasis was significantly higher than in postmenopausal women. The presence of lymph

node involvement is an important factor in follow-up of breast cancer recurrence [20]. As the surgical approach, the most common technique in both groups was modified radical mastectomy surgery. Breast-conserving surgery was significantly more common in premenopausal woman than in postmenopausal women (9.36% vs. 3.11%,  $p = 0.004$ ). In recent years, sentinel lymph node biopsy has been performed in our clinic during operation. Breast-conserving surgery, simple mastectomy, or modified radical mastectomy have been performed according to the results. After a simple mastectomy and breast-conserving operations, axillary lymph node dissection was performed. Mastectomy and breast-conserving operations were reported as 87.6% and 93.2%, respectively, in five-year recurrence-free survival studies [28]. Chemotherapy was used more in the premenopausal group because the risk of tumour recurrence is higher in patients with premenopausal breast cancer. It has been reported that chemotherapy is the most widely used adjuvant therapy in breast cancer treatment, and it significantly reduces the risk of breast cancer recurrence [22]. LHRH agonists or laparoscopic bilateral salpingo-oophorectomy are recommended for the treatment of breast cancer patients who are premenopausal hormone receptor positive and 40-49 years old [29]. Postoperative adjuvant radiotherapy decreases local recurrence and increases the survival rate in patients who have undergone breast-conserving surgery or who have had lymph node involvement after mastectomy [30].

## Conclusions

In conclusion, premenopausal and postmenopausal female breast cancer patients have significant differences in tumour size, tumour grade, axillary lymph node metastasis, hormone receptor status, HER2 expression, and treatment modalities. Breast cancer is larger in premenopausal women and tends to develop lymph node metastasis. Chemotherapy, endocrine therapy, and radiotherapy treatments are used more frequently than in postmenopausal women.

## Disclosure

The authors report no conflict of interest.

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