ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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COMPARISON OF THE EFFECTS OF CLINICOPATHOLOGICAL AND RADIOLOGICAL FINDINGS ON SURVIVAL IN WOMEN YOUNGER THAN 40 YEARS AND OLDER THAN 55 YEARS OF AGE WITH BREAST CANCER

40 YAŞ ALTI VE 55 YAŞ ÜSTÜ MEME KANSERLİ KADINLARIN KLİNİKOPATOLOJİK VE RADYOLOJİK BULGULARININ SAĞ KALIM ÜZERİNE ETKİLERİNİN KARŞILAŞTIRILMASI

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Öz

Amaç
Meme kanserli kadınların tümörleri, yaşla birlikte gelişen hormonal değişikliklere bağlı olarak klinik ve biyolojik farklılıklar göstermektedir. Bu nedenle bu çalışmada meme kanserli hastaların <40 yaş ve ≥55 yaşlarının radyolojik ve klinikopatolojik özelliklerini karşılaştırdık.

Gereç ve Yöntem
10 yıllık dönemde üç merkezde meme kanseri nedeniyle opere edilen 40 yaş altı 92 hasta ve 55 yaş ve üzeri 322 hasta olmak üzere toplam 759 hastanın dosyaları geriye dönük olarak incelendi ve Östrojen Reseptör (ER), Progesteron Reseptör (PR), İnsan Epidermal Büyüme Faktörü 2 (HER2) ,Lenfovaskuler İnvazyon (LVI) durumu, Aksiller Lenf Nodu Metastazı (ALNM) varlığı, multifokalite, Duktal Karsinoma İnsitu (DCIS) veya Lobuler Karsinoma İnsitu (LCIS) varlığı, tümör boyutu, tümör histopatolojik tipi, tümör derecesi ve skoru kaydedildi.

Bulgular
40 yaşın altındaki hastalarda tümörün memenin üst-iç ve alt-iç kadranlarında daha az yerleştiği, multifokalitenin ise daha sık görüldüğü, büyük bir çoğunluğunun dens meme yapısına sahip olduğu, tümörün histolojik derecesinin yüksek olduğu, LVI ve LNM'nin daha sık görüldüğü, daha düşük ER reseptör pozitifliği ve daha yüksek Ki-67 proliferasyon indeksine sahip olduğu saptandı (sırasıyla p<0.001, p<0.001, p<0.001, p<0.001, p=0.021, p=0.039, p=0.001 ve p<0.001). 55 yaşının altındaki hastalarda tümörlerde multifokalitenin ve meme dokusunun yoğunluğunun daha az olduğu görüldü (sırasıyla p=0.002, p<0.001). 40 yaş altı hastalarda moleküler alt tiplerden luminal B ve TN daha fazla görülürken 55 yaş üzeri hastalarda luminal A alt tipi daha fazla görüldü (sırasıyla p<0.001, p=0.001).

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Sonuç
<40 yaş ile 55 yaş ve üzeri hastalar arasında klinikopatolojik farklılıklar doğrulandı. 40 yaşın altındaki hastalarda meme kanseri için olumsuz prognostik faktörler ortaya çıktı.

Anahtar Kelimeler: Lenf nodu metastazı, Lenfovasküler invazyon, Meme kanseri, Meme yoğunluğu, Moleküler alt tip

Abstract

Objective
Tumors of women with breast cancer show clinical and biological differences depending on the hormonal changes that develop with age. Therefore, in this study, we compared the radiologic, and clinicopathological features of breast cancer patient's < 40 age and ≥55 age.

Material and Method
The files of a total of 759 patients, including 92 patients under 40 aged, and 322 patients 55 aged and over who were operated on for breast cancer over a 10-year period in three centres were retrospectively reviewed and Estrojen Reseptor (ER), Progesteron Reseptor (PR), Human epidermal growth factor receptor 2 (HER2), Lymphovascular invasion (LVI) status, presence of axillary lymph node metastasis (ALNM), multifocality, presence of Ductal Carsinoma İnsitu (DCIS) or Lobular Carsinoma İnsitu (LCIS), tumor size, tumor histopathological type, grade, and score were recorded.

Results
In patients under the age of 40, the tumor is less localized in the upper-inner and lower-inner quadrants of the breast, multifocality is more common, most of them have dense breast structure, the histological grade of the tumor is higher, LVI and LNM are more common. It was found that they had ER receptor positivity and higher Ki-67 proliferation index ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.021$, $p=0.039$, $p=0.001$ and $p<0.001$, respectively). It was observed that the multifocality and density of breast tissue were lower in tumors in patients under 55 years of age ($p = 0.002$, $p <0.001$, respectively). Luminal B and TN were more common among molecular subtypes in patients under 40 years of age, while luminal A subtype was more common in patients over 55 years of age ($p<0.001$, $p=0.001$, respectively).

Conclusion
Clinicopathological differences between <40 aged, and 55 aged and over patients were confirmed. Adverse prognostic factors for breast cancer at the age of under 40 patients were revealed.

Keywords: Breast cancer, Breast density, Lymph node metastasis, Lymphovascular invasion, Molecular subtype

Introduction

Breast cancer is the most common type of cancer in women. It ranks second among women deaths due to cancer (1). According to the International Cancer Research Agency 2018 statistics; 2.1 million patients were newly diagnosed with breast cancer (2). Among breast cancer risk factors; many factors are blamed such as; female gender, advanced age, family history, personal breast disease or cancer history, inherited genes that increase cancer risk, exposure to radiation, early menarche, late menopause, obesity, postmenopausal hormone therapy, never conceiving, and conceiving at an advanced age (3,4). Clinicopathological parameters used in breast cancer management and treatment which tumor size, axillary lymph node metastasis (ALNM), histological grade, lymphovascular invasion (LVI), estrogen receptor (ER), and progesterone receptor (PR) from hormone receptors, and human epidermal growth factor receptor 2 (HER2) status are the most important prognostic factors (5-7). Breast cancer is a heterogeneous disease and 5 different molecular subtypes have been defined. These molecular subtypes consist of: luminal A, luminal B, HER2-enriched, triple-negative (TN) and basal-like groups (8, 9). Breast cancers of premenopausal and postmenopausal women have clinical and biological differences (10).

Since the menopausal status of the patients was not known, the patients were evaluated in two different ways to investigate the clinicopathological changes in breast cancer with age. The patients were divided into two groups as under 40 years old and over 40 years old. In addition, they were divided into two groups as under 55 years old and over 55 years old. Both age groups were evaluated within themselves.

Material and Method

1012 patients with invasive breast cancer who were operated in three general surgery clinics between April 1, 2010 and December 31, 2020 were included in the study. Informed consent was obtained from all

individual participants included in the current study.

Inclusion criteria of the patients in the study; older than 18 years, all the examinations performed before the diagnosis were in the patient file, and the mammography examinations before and after the diagnosis were performed, the pathologies of the biopsy and surgery specimen performed in our hospitals, and the patients came for regular polyclinic controls. 253 patients, whose surgical operations were performed in centers in different regions of Turkey and followed up in three centers participating in the study, were excluded from the study due to lack of data or difficulties in obtaining permission from the relevant clinics for ethics committee approval. From the retrospective file scanning of 759 patients whose data could be accessed, the patient's age, ER, PR, HER2, LVI status, presence of ALNM, multifocality, presence of DCIS or LCIS, tumor diameter, tumor histopathological type, grade, and score were recorded. Preoperative imaging reports and surgery reports of the patients were recorded. Besides, the mammography of the patients included in the study were evaluated as double-blind. From the follow-up notes, follow-up findings and overall survival times were calculated and recorded.

When specimens were evaluated immunohistochemically, nuclear staining for ER, PR and Ki-67 index and the presence of membranous staining for HER2 were accepted as positive findings. ER and PR are receptors that stimulate the growth of normal and neoplastic breast epithelium. ER and PR positive tumors are low grade and less aggressive. If the sample contains at least 1% positive invasive tumor nuclei, it is recommended that ER and PR tests be considered positive (11). In this way, the positivity of ER and PR was evaluated in our study. HER2's status was scored as 0, 1+, 2+ and 3+ according to staining intensity and membranous persistence. In cases where HER2 was 2+, DNA fluorescence in situ hybridization (FISH) result was checked. HER2 overexpression indicates aggressive clinical course and poor prognosis. The cases with Ki-67 proliferation index over 14% were accepted as Ki-67 positive.

The patients were divided into two groups as younger than 40 years old and above 40 years old. In addition, they were divided into two groups as under 55 and 55 and above. Both age groups were evaluated within themselves.

Statistical Package for Social Sciences (SPSS) software version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics, frequency and percentages of categorical variables were reported. Using the Chi-square test for categorical variables, we examined the relationship between patient age groups and molecular subtypes, tumor size, histopathological subtype, grade, presence of in situ carcinoma foci, multifocality, presence of LVI and ALNM status. Post-hoc analysis was performed with Bonferroni correction to find out where the significant difference between the groups originated. The significance of the difference between groups was analyzed using the Mann-Whitney U test for non-categorical variables such as ER positivity and Ki-67 proliferation index. The Kaplan-Meier method was used to calculate the mean survival length. Cox proportional hazard regression analysis was performed to estimate breast cancer-specific mortality hazard ratios (HR). If the p value was <0.05, the results were considered statistically significant.

Results

The mean age of the patients was 53.86 ± 12.38 (min: 21 years, median: 52 years and max: 94 years) years. Comparison of clinicopathological parameters of patients under 40 and over 55 years of age is summarized in Table 1. When the patients with breast cancer were evaluated in terms of the location of the tumor in the breast, it detected that the location of breast cancer was significantly less in the upper-inner and lower-inner quadrants in patients under the age of 40 ($p<0.001$). In terms of multifocality, significantly more multifocality was observed in breast cancer in patients under 40 years of age, while multifocality was observed less in patients over 55 years of age ($p<0.001$, $p=0.002$, respectively). When the mammographic breast density was evaluated, it consisted of dense breast tissue in patients under 40 years of age, and non-dense breast tissue in patients 55 years of age and older ($p<0.001$, $p<0.001$, respectively). When evaluated in terms of tumor grade, tumors of patients under 40 were significantly undifferentiated type ($p<0.001$). When evaluated in terms of LVI, LVI was significantly higher in patients under 40 years of age ($p=0.021$). When evaluated in terms of LNM, LNM was significantly higher in patients under 40 years of age ($p=0.039$). ER receptor positivity in patients under 40 years of age was significantly lower than patients aged 40 and over (56.5% vs 70.6%) ($p=0.001$). Ki-67 proliferation index and HER2 positivity were significantly higher in patients under 40 (41.3% vs 25.9%, 25% vs 16%, respectively) ($p <0.001$, $p = 0.033$, respectively). When evaluating in terms of molecular subtypes, luminal B and TN molecular subtypes were more common in patients under the age of 40, while luminal A and HER2-enriched molecular subtypes were less

Table 1 Comparison of clinicopathological parameters of patients under the age of 40 and above the age of 55.

			AGE 40		P Value	AGE 55		P Value
			<40	≥40		<55	≥55	
DIAL	Central	N	4	20	<0.001	14	10	0.262
		%	16.7	83.3		58.3	41.7	
	Upper inner quadrant	N	4	89		47	46	
		%	4.3	95.7		50.5	49.5	
	Upper outer quadrant	N	59	429		290	198	
		%	12.1	87.9		59.4	40.6	
	Lower inner quadrant	N	1	52		25	28	
		%	1.9	98.1		47.2	52.8	
	Lower outer quadrant	N	24	77		61	40	
		%	23.8	76.2		60.4	39.6	
Multifocality	No	N	56	527	<0.001	318	265	0.002
		%	9.6	90.4		54.5	45.5	
	Yes	N	36	140		119	57	
		%	20.5	79.5		67.6	32.4	
DCIS or LCIS presence	No	N	29	240	0.402	148	121	0.291
		%	10.8	89.2		55	45	
	Yes	N	63	427		289	201	
		%	12.9	87.1		59	41	
Microcalcification	No	N	73	510	0.539	329	254	0.246
		%	12.5	87.5		56.4	43.6	
	Yes	N	19	157		108	68	
		%	10.8	89.2		61.4	38.6	
Density	Not dense	N	3	136	<0.001	18	121	<0.001
		%	2.2	97.8		12.9	87.1	
	Normal	N	9	260		130	139	
		%	3.3	96.7		48.3	51.7	
	Dense	N	80	271		289	62	
		%	22.8	77.2		82.3	17.7	
Grade according to Bloom Richardson	Undifferentiated	N	33	155	<0.001	121	67	0.054
		%	17.6	82.4		64.4	35.6	
	Moderately differentiated	N	48	317		196	169	
		%	13.2	86.8		53.7	46.3	
	Differentiated	N	11	195		120	86	
		%	5.3	94.7		58.3	41.7	
LVI	No	N	50	444	0.021	281	213	0.598
		%	10.1	89.9		56.9	43.1	
	Yes	N	42	223		156	109	
		%	15.8	84.2		58.9	41.1	
LNM	No	N	49	429	0.039	263	215	0.063
		%	10.3	89.7		55	45	
	Yes	N	43	238		174	107	
		%	15.3	84.7		61.9	38.1	

Table 1 Continued Comparison of clinicopathological parameters of patients under the age of 40 and above the age of 55.

			AGE 40		P Value ≥55	AGE55		P Value
			<40	≥40		<55	≥55	
Luminal	**Luminal A**	N	30	353	< 0.001	198	185	0.001
		%	7.8	92.2		51.7	48.3	
	Luminal B	N	40	154		128	66	
		%	20.6	79.4		66	34	
	HER2-enriched	N	5	48		24	29	
		%	9.4	90.6		45.3	54.7	
	Triple-negative	N	11	69		54	26	
		%	13.8	86.3		67.5	32.5	
	Normal-like	N	6	43		33	16	
		%	12.2	87.8		67.3	32.7	
Stage	**Stage I**	N	27	271	0.276	169	129	0.426
		%	9.1	90.9		56.7	43.3	
	Stage IIa	N	35	222		143	114	
		%	13.6	86.4		55.6	44.4	
	Stage IIb	N	14	88		58	44	
		%	13.7	86.3		56.9	43.1	
	Stage IIIa	N	13	58		48	23	
		%	18.3	81.7		67.6	32.4	
	Stage IIIb	N	0	2		2	0	
		%	0	100		100	0	
	Stage IIIc	N	3	26		17	12	
		%	10.3	89.7		58.6	41.4	
Surgery technique	**BCS**	N	49	426	0.140	266	209	0.078
		%	10.3	89.7		56	44	
	Mastectomy	N	20	116		90	46	
		%	14.7	85.3		66.2	33.8	
	MRM	N	23	125		81	67	
		%	15.5	84.5		54.7	45.3	
Tracking Status	**Survive**	N	86	602	0.320	404	284	0.047
		%	12.5	87.5		58.7	41.3	
	Death	N	6	65		33	38	
		%	8.5	91.5		46.5	53.5	
Total		N	92	667	57.6	437	322	
%		12.1	87.9			42.4		

common. It was determined that TN subtypes were less common in patients 55 years of age and older, while luminal A and HER2-enriched subtypes were more common (p<0.001, p=0.001, respectively).

When the patients were followed for an average of 5.27 ± 2.34 years (min:1.82 years and max:10.48 years), 6 of the patients under the age of 40 and 38 of the patients above the age of 55 died due to factors, associated with breast cancer. The effects of risk factors on HR in breast cancer are summarized in Table 2. When the patients were evaluated in terms of overall survival, patients aged 55 and over significantly died more (p=0.047). When Cox-Regression analysis was

Table 2 Effects of risk factors on HR in breast cancer

	B	HR	95,0% CI for HR		P Value
			Lower	Upper	
AGE < 40	-0.423	0.655	0.263	1.631	0.363
AGE ≥ 55	-0.522	0.593	0.370	0.952	0.030
Multifocality	-0.605	0.546	0.333	0.895	0.016
LVI	-1.110	0.330	0.206	0.527	<0.001
Ki-67 Proliferation index	-1.119	0.327	0.198	0.537	<0.001
Luminal B & luminal A	-0.971	0.379	0.213	0.672	0.001
TN & luminal A	-1.317	0.268	0.139	0.518	<0.001

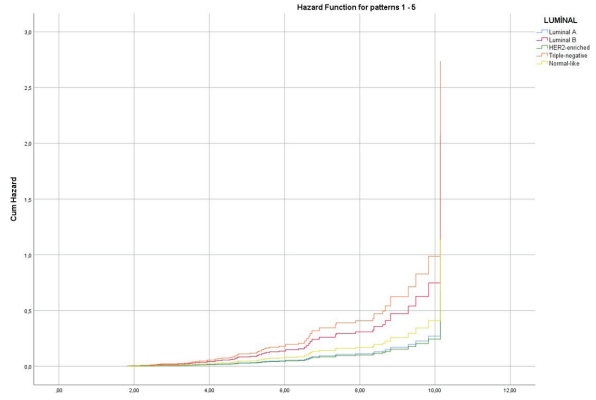

Figure 1:
Chart showing Hazard ratio according to breast cancer subtypes.

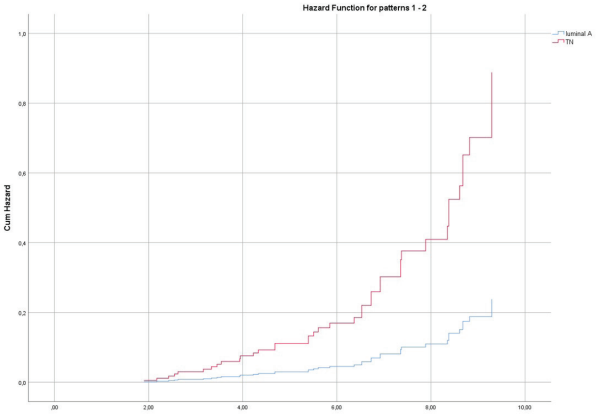

Figure 2:
Graph comparing Luminal A and TN hazard ratio from breast cancer subtypes

performed, HR was significantly higher in patients 55 years of age and older, those with multifocality, those with LVI and those with high Ki-67 proliferation index. Hazard ratio according to breast cancer molecular subtypes are shown in Figure 1. Compared to the luminal A molecular subtype, HR was significantly higher in luminal B, and TN molecular subtypes. The comparison of the HR of luminal A with luminal B and TN molecular subgroups, which are among the breast cancer molecular subtypes, are shown in Figure 2 and Figure 3.

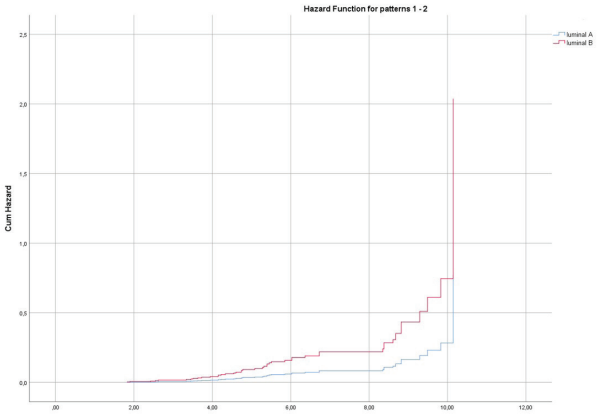

Figure 3:
Graph comparing Luminal A and Luminal B ratio from breast cancer subtypes

Discussion

Breast cancer is most common in the upper outer quadrant of the breast (12, 13). Tumor location in the breast has clinical and prognostic importance. Tumors originating from the inner quadrant of the breast, the

nipple, or the middle part of the breast have worse prognostic outcomes than the upper outer quadrant of the breast (14-16). Kocic B et al. reported that in patients with breast cancer under the age of 40, tumor is most frequently detected in the upper outer quadrant of the breast (17). In our study, tumor was detected most frequently in the upper outer quadrant of the breast. In addition, it was found that in patients under the age of 40, tumor was less common in the lower-inner and upper-inner quadrants of the breast.

Fried G et al. reported that patients under 40 years of age (in the premenopausal period) with multifocal tumors and LVI have a high risk of local recurrence and poor prognosis (18). Foxcroft LM et al. reported multifocality at a rate of approximately 20% in mammography and 33.6% by USG in patients under 40 years of age (19). Appleton DC et al. suspected multifocality in 50% of patients under the age of 40 with preoperative Magnetic Resonance Imaging (MRI) and confirmed the presence of multifocality histologically in 40.5% (20). In our study, 39.13% of patients under the age of 40 had multifocality. Multifocality was 20.99% in patients 40 years and older, and 17.70% and even lower in those 55 years and older. Our study shows that with increasing age, multifocality decreases.

Durhan G et al. reported that 40.2% of patients with breast cancer under the age of 40 have microcalcifications in their mammograms (21). Muttarak M et al. reported that they detected microcalcification at a rate of 28.7% in mammography of patients with breast cancer under the age of 40, with or without breast pathology (22). In another study, Schnejder-Wilk A reported the rate of microcalcified tumors in mammography in patients with breast cancer under 45 years of age as 20.8% (23). In our study, microcalcification was found at a rate of 20.65% where there is breast pathology. Also, there was no significant difference between age groups.

Checka CM et al. reported in their study that there was an inverse relationship between age and breast density (24). In a similar study, Liao YS et al. classified at least 80% of mammograms of patients under the age of 55 as excessively dense or heterogeneously dense breasts (25). In our study, 86.96% of patients with breast cancer under the age of 40 had dense breast tissue, while it was found that dense breast tissue decreased to 19.25% in patients over 55 years old.

Erić I et al. classified the patients with breast cancer under the age of 40 according to the tumor grade, and reported that 16.5% of the patients consisted of grade 1, 54.4% grade 2 and 29.1% grade 3 tumors (26). In another study, Bakkach J et al. reported that the rate of grade 3 patients in patients under the age of 40 was 40.2% (27). In our study, 11.96% of the patients under the age of 40 had grade 1, 52.17% grade 2 and 35.87% grade 3 patients. Tumor grade of patients over 40 years of age consisted of 29.24% grade 1, 47.53% grade 2 and 23.24% grade 3 patients. Our study shows that significantly undifferentiated tumors are seen more frequently in patients with breast cancer under the age of 40.

Bakkach J et al. reported that they detected LVI in 47.7% of patients aged 40 and under (27). In another study, Tvedskov TF et al. reported that LVI and ALNM were seen more (3.6 times) in patients under 40 years old (28). In our study, LVI (45.65% vs 33.43%) in patients under 40 years of age was significantly higher than in patients over 40 years of age.

Eugênio DS et al. reported that luminal B and TN molecular subtypes were observed more frequently in their studies on breast cancer patients under the age of 40 (29). In a similar study, Wang JM et al. reported that luminal B and TN molecular subtype tumors are common in breast cancer patients under the age of 40, and the risk of developing luminal A molecular subtype cancer is increased in patients over 40 years of age (30). In another study, Erić I et al. reported that breast cancers in patients under 40 years of age consist of patients with multicentric localization, TN molecular subtype, more ER negativity and high Ki-67 proliferation index (31). Similarly, in our study, ER receptor positivity was lower and Ki-67 proliferation index was higher in patients under 40 years of age. In addition, luminal B and TN molecular subtypes were found to be more common. We found out that the TN subtypes were less common in patients aged 55 years and older, while luminal A and HER2-enriched subtypes were more common.

Young patients' tumors have a more aggressive biological nature compared to older patients. Tumor nuclear grade and proliferation index are higher, LVI and LNM are more common. In addition, the disease relapses more frequently in younger patients and has a worse prognosis in terms of survival (31, 32). Although HR was high in patients under the age of 40 in our study, the cox-regression test was not significant due to the low number of patients who died in our study. HR was higher in patients 55 years and older due to concomitant chronic diseases. The presence of LVI, multifocality, high Ki-67 proliferation index, and having luminal B and TN molecular subtype tumors were found to cause an increase in HR.

Breast cancer in women under 40 years; it was found that it was less common in the inner quadrants of the breast, and multifocal was higher. While breast density was denser in mammography of patients under 40 years with breast cancer, patients aged 55 and over had lower breast density. Undifferentiated type tumors are more common in patients under the age of 40, and LVI is more common in these patients. It is seen that ER receptor positivity is lower, Ki-67 proliferation index is higher in patients under 40 years of age. When evaluated in terms of molecular subtypes, luminal B and TN molecular subtypes were more common in patients younger than 40 years of age, while molecular subtypes enriched with luminal A and HER2-enriched were more common over 55 years of age. The presence of LVI, multifocality, high Ki-67 proliferation index, luminal B, and TN molecular subtypes increase HR significantly in breast cancer.

Ankara City Hospital, Ankara Numune and Training and Research Hospital and Ankara Atatürk Training and Research Hospital data were included in the study. The authors consist of surgeons working in these three hospitals. Due to the retrospective nature of the study, data on menopause status were not available when patients were diagnosed with breast cancer.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study was found ethically appropriate by the decision of the Ankara City Hospital Ethics Committee, dated 06.01.2021 and numbered 1413. Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Veriler, gizlilik veya diğer kısıtlamalar nedeniyle yalnızca yazarlardan talep edilebilir.

Authors Contributions
BAÖ: Conceptualization; Investigation; Methodology; Writing-original draft

SK: Conceptualization; Methodology; Project administration; Writing-review & editing

BÇ: Formal analysis; Investigation; Validation

MÖY: Formal analysis; Investigation; Visualization

FC: Data curation

CC: Data curation

BK: Editing

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