RESEARCH ARTICLE

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Poor Prognostic Clinicopathological Features of Young Women with Breast Cancer in the MF18-04 Turkish National Breast Cancer Registry Study

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Abstract

Objective: The role of younger age as a prognostic factor in breast cancer remains debated. Despite its association with an aggressive clinical course, there is insufficient research on its etiology. This study aimed to analyze age-related differences in breast cancer diagnosis among Turkish women. **Materials and Methods:** Data from 23,594 patients in the National Breast Cancer Database (NBCD) were analyzed. The demographic, clinical, and pathological characteristics of patients aged ≤40 years were compared with those >40 years. **Results:** The median age was 50 years (range 18–97). Among them, 4,535 patients (19%) were 40 years old or younger, with 84% of this subgroup being over 30 years old. Conversely, 19,059 patients (81%) were older than 40. Patients in the younger age group were less likely to have pathologic T1 disease (41% vs. 47%), N0 disease (49% vs. 55%), and Stage I disease (25% vs. 31%) compared to those over 40 ($p<0.001$). The rates of mastectomy (41% vs. 39%; $p = 0.024$) and axillary dissection (71% vs. 65%; $p = 0.001$) were higher among patients diagnosed at 40 years of age or younger. Multivariate analysis identified significant associations in younger patients, including invasive ductal carcinoma (95% CI, 1.06–1.43), estrogen receptor (ER) negativity (95% CI, 1.26–1.87), PR negativity (95% CI, 1.21–1.75), high histologic grade (95% CI, 1.43–1.87), multifocality/multicentricity (95% CI, 1.26–1.72), T3-T4 tumors (95% CI, 1.06–1.66), and axillary positivity (95% CI, 1.025-1.321). **Conclusions:** Breast cancer diagnosed at ≤40 years is more likely to exhibit aggressive biology, multifocality, or multicentricity presentation, and present at advanced stages. Consequently, younger patients experience higher rates of mastectomy and axillary dissection. These findings suggest a poorer prognosis, highlighting the need for more intensive therapeutic strategies in this population.

Keywords:

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Introduction

In 2020, 2.3 million new breast cancer cases were reported globally, with breast cancer-related deaths reaching approximately 685,000. By 2040, it is projected that new cases will surpass 3 million, and related deaths could alarmingly rise to 1 million [1]. The definition of "young breast cancer" lacks consensus; it generally refers to individuals under 40, although some protocols apply it to those under 35 [2, 3]. In the United Kingdom, only 4% of breast cancer patients are women under 40 [4]. According to 2019 data from the American Cancer Society, the incidence of ductal carcinoma in situ (DCIS) in women under 40 was 2%, while invasive cancer was 4% [5]. In contrast, a study on breast cancer in Türkiye from 2005 to 2015 reported that 16.5% were diagnosed under age 40, with an observed increase over the years [6]. While the median age of breast cancer diagnosis in the USA is 62, in Türkiye, it is significantly earlier at 51.8 years [5, 6].

Young breast cancer patients typically present with more advanced stages, higher grades, and increased rates of hormone receptor negativity at diagnosis [7]. It is undeniable that individuals diagnosed with breast cancer at a young age face distinct social challenges, including fertility concerns, sexual issues, and reintegration into the workforce [8-10]. Rates of psychosocial morbidity are reported to be significantly higher in younger patients compared to their older counterparts. Furthermore, numerous studies indicate that young patients perceive a substantial decline in their overall quality of life [10, 11].

Given the age-specific challenges, diagnosing breast cancer at an early stage in young patients is crucial. Ensuring that their treatment is both personalized and optimized during the planning phase is equally important. The question of whether young age serves as a poor prognostic factor remains debated in breast cancer management. Although breast cancer in young individuals often exhibits an aggressive clinical course, research on its aetiology remains limited.

The Turkish Federation of Breast Diseases Societies (TFBDS) is the largest and sole association of national breast societies in Türkiye. The Turkish National Breast Cancer Registry (NBCR) was implemented on May 1, 2005. This registry was designed as computer software incorporating various clinical parameters. Data on breast cancer patients were collected from multiple centres across Türkiye. Previous analyses of this registry focused on the demographic, clinical, and pathologic characteristics of breast cancer patients overall [6, 12]. The current study aims to evaluate the clinicopathologic differences in breast cancer between patients diagnosed at age 40 or younger and those over 40, based on the updated extensive Turkish patient registry.

Materials and Methods

The Turkish NBCR included 576 parameters capturing the clinicodemographic features of patients with breast cancer. These parameters primarily comprised patient characteristics such as identification details, gender, medical history, and clinical data, alongside information of diagnosis, surgical treatment findings, histopathological features, and oncological treatment modalities, including adjuvant and neoadjuvant chemotherapy as well as hormonotherapy. The database also tracked follow-up information for any recurrence of breast cancer. Ethical approval was granted by the Istanbul Faculty of Medicine Ethics Committee at Istanbul University. This study analyzed data from 23,594 patients diagnosed with breast cancer between January 1998 and January 2019.

Study population

The academic centers participating in the study were affiliated with the TFBDS. This study analyzed various patient characteristics, including age, clinical and pathological stage, tumour size, histological type and grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (*HER-2*) expression, and breast cancer subtype distributions. The data were drawn from a retrospective registry- based dataset. Patients identified as male were excluded from the study.

Invasive cancer histological types were classified using the World Health Organization's classification system, while the modified Scarff-Bloom-Richardson classification was employed for determining histological grade [6, 12]. Breast cancer staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system, which is based on TNM categories. ER, PR, and *HER2* expressions were assessed in core biopsies and/or surgical specimens via immunohistochemistry (IHC) according to ASCO-CAP guidelines [13]. An expression of ER or PR was considered positive if ≥1% of tumor cells showed staining. Tumour subtypes were classified based on the status of ER or PR and *HER2* gene amplification. *HER2* positivity was defined as 3+ on IHC testing, or 2+ on IHC followed by an in situ hybridization test confirming gene amplification.

Tumour subtypes based on immunohistochemical staining were categorized into four groups

1: the *HER2*-negative luminal group (ER and/or PR-positive, *HER2*-negative),

2: the *HER2*-positive luminal group (ER- and/or PR-positive, *HER2*-positive),

3: the non-luminal *HER2*-positive group (ER- and PR-negative, *HER2*-positive), and

4: the triple-negative group (ER-, PR- and *HER2*-negative).

Patients with available Ki-67 score were further classified as follows

• luminal A; ER and/or PR-positive, *HER2*-negative, *Ki67* score <20%,

• luminal B;

ER and/or PR-positive, *HER2*-negative, *Ki67* score ≥ 20%, or

ER and/or PR-positive, *HER2*-positive.

Statistical analysis

The primary objective of this study was to evaluate

the demographic, clinical, and pathologic characteristics of patients categorized into two age groups: ≤40 years and >40 years. Statistical analyses were conducted using SPSS 26 (Statistical Package for Social Sciences; IBM Corp., Armonk, NY, USA). Mean, median, standard deviation and interquartile range values were calculated for continuous variables. Non-parametric continuous variables were analyzed using the Mann-Whitney U test, while parametric continuous variables were assessed using the Student's t-test to examine differences between groups. Associations between categorical variables were evaluated using Pearson's Chi-square test. Logistic regression analysis, employing a forward stepwise method, was conducted to identify significant factors associated with the younger age group of ≤40 years. A p-value of <0.05 was considered to indicate statistical significance.

Results

In this report, breast cancer patients diagnosed between January 1998 and January 2019 were retrospectively evaluated using the NBCR of the TFBDS. A total of 23,594 patients registered in the database were analyzed. Patients were categorized into two age groups: those aged ≤40 years and those >40 years. These groups were compared based on demographic, clinical, and pathological characteristics.

The median age of the study population was 50 years (interquartile range [IQR], 43-60), with a mean age of 51.65 ± 12.6 years. Among the participants, 19.2% (n = 4,535) were aged ≤40, and 80.8% (n = 19,056) were aged >40. Within the ≤40 age group, 12% were under 30 years, while 35% were between 30-35 years, and 53% were between 36–40 years. Figure 1 illustrates the distributions of age groups and their trends over time. In the ≤40 age group, the mean age was 34.9 ± 4.6 years, and the median age was 37 years (IQR 32-38). For the >40 age group, the mean age was 55.6 ± 10.4 years, with a median age of 54 years (IQR 47–63).

The demographic and clinical characteristics of the patients are presented in Table 1. Patients in the younger age group exhibited a higher incidence of symptomatic disease (96.7% vs. 90.2%, p<0.001) compared to their older counterparts. Younger patients were also less likely to present with pathologic T1 (41% vs. 47%), N0 (49% vs. 55%), and stage 1 disease (25% vs. 31%) than those in the over-40 age group (p<0.001). Additionally, the rates of mastectomy (41% vs. 39%, p = 0.024) and axillary dissection (71% vs. 65%, p = 0.001) were greater in the younger age group.

The pathological findings are presented in Table 2. Pathologically, patients in the younger age group demonstrated significantly higher occurrences of invasive ductal carcinoma (76% vs. 73%; p = 0.001), higher histologic grades (54% vs. 42%; p = 0.001), and increased multifocality/multicentricity (19% vs. 15%). Additionally, ER negativity (31% vs. 24%; p = 0.001), PR negativity (38% vs. 35%; p = 0.009), hormone receptor negativity (24% vs. 20%; p = 0.001), and *HER2*-neu positivity (32% vs. 27%; p = 0.001) were more prevalent in this age group. Moreover, these patients had a lower incidence of luminal A disease (23% vs. 33%; p = 0.001) but a higher incidence of luminal-B *HER2*+ (18% vs. 12%; p = 0.001) and triple-negative disease (15% vs. 10%; p = 0.001). A multivariate logistic regression analysis of significant variables revealed that the type of invasive ductal carcinoma (95% CI, 1.06–1.43), ER negativity (CI 95%, 1.26–1.87), PR negativity (CI 95%, 1.21–1.75), high histologic grade (CI 95%, 1.43–1.87), multifocality/multicentricity (CI 95%, 1.26–1.72), T3-T4 tumours (CI 95%, 1.06–1.66), and axillary positivity (CI 95%, 1.025-1.321) were significantly associated with breast cancers in the younger age group (Table 3).

Table 4 presents the associations between the *Ki67* score and various clinicopathological variables. The mean *Ki67* score observed was 29.66 ± 24.47/20 (range 1–95). Patients belonging to the younger age group, as well as those with clinical and pathological nodal positivity, pathologic T3-4, and clinical and pathological Stage III-IV disease, exhibited higher *Ki67* scores. Additionally, patients with invasive ductal pathology, poor histologic grade, unifocal tumours, ER- or PR-negative, *HER2*-positive, or triple-negative tumours also had significantly

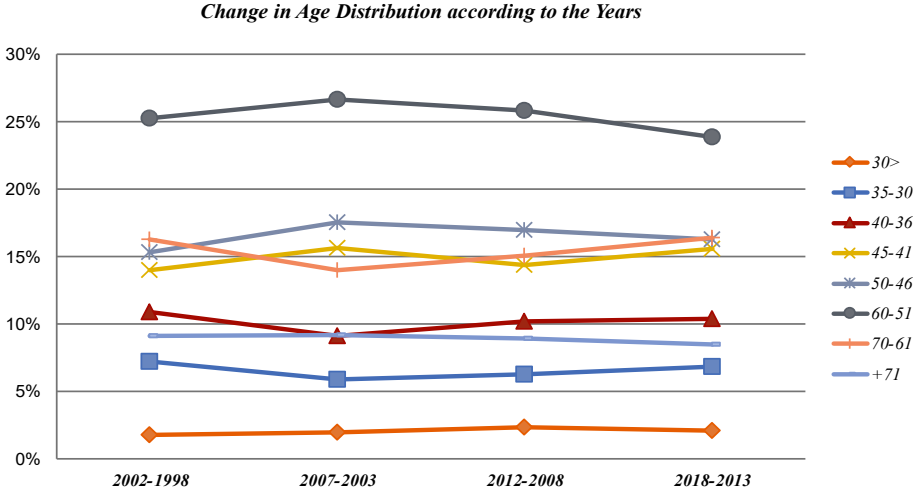

Figure 1. Illustrates the Distributions of Age Groups and Their Trends Over Time

Table 1. Clinicopathological Factors associated with Breast Cancer Diagnosed at Age ≤40 versus at Age >40

Variables	Overall (%) (N=23594)	Age ≤40 Years (%) (n=4535;19.2%)	Age >40 Years (%) (n=19059;80.8%)	P-value
Presentation				<0.001
Symptomatic	19,502 (91.4)	3,978 (96.7)	15,524 (90.2)	
Asymptomatic or screening	1,824 (8.6)	137 (3.3)	1687 (9.8)	
Age at first menarche				0.67
<12	557 (4.5)	113 (4.7)	444 (4.5)	
≥12	11,719 (95.5)	2,292 (95.3)	9,427 (95.5)	
First gestational age				<0.001
<30	2,389 (23.9)	496 (28.7)	1,893 (29.6)	
≥30	7,625 (76.1)	1,231 (71.3)	6,394 (70.4)	
Lactation				0.585
Yes	7,779 (96.4)	1,398 (96.6)	6,381 (96.3)	
No	293 (3.6)	49 (3.4)	244 (3.7)	
Duration of lactation				<0.001
≤24 months	5,242 (64.9)	1,040 (71.9)	4,202 (63.4)	
>24 months	2,830 (35.1)	407 (28.1)	2,423 (36.6)	
Family history of cancer				0.818
Negative	8,705 (63.7)	1,716 (64.4)	6,989 (63.6)	
Breast cancer	2,392 (17.5)	454 (17)	1,938 (17.6)	
Ovarian cancer	156 (1.2)	32 (1.2)	124 (1.1)	
Other cancers	2,410 (17.6)	462 (17.4)	1,948 (17.7)	
Breast cancer histology				0.246
DCIS	836 (5.8)	151 (5.3)	685 (5.9)	
Invasive cancer	13,596 (94.2)	2,679 (94.7)	10,917 (94.1)	
Clinical TNM stage				<0.001
Stage I-II	13,381 (88.9)	2,519 (85.8)	10,862 (89.6)	
Stage III-IV	1,679 (11.1)	417 (14.2)	1,262 (10.4)	
Clinical N stage				<0.001
Node-positive	6,022 (37.5)	1,321 (42.4)	4,701 (36.3)	
Node-negative	10,057 (62.5)	1,794 (57.6)	8,263 (63.7)	
Clinical stage				<0.001
Stage I-II	12,588 (83.3)	2,366 (80.6)	10,222 (84.0)	
Stage III-IV	2,525 (16.7)	571 (19.4)	1,954 (16.0)	
Pathologic T category				<0.001
T1	5,163 (45.8)	907 (41.2)	4,256 (47.0)	
T2	5,176 (46.0)	1,055 (47.9)	4,121 (45.5)	
T3-4	923 (8.2)	240 (10.9)	683 (7.5)	
Pathologic N category				<0.001
N0	6,611 (53.3)	1,183 (48.6)	5,428 (54.5)	
N1	3,367 (27.2)	708 (29.1)	2,659 (26.7)	
N2-3	2,416 (19.5)	541 (22.2)	1,875 (18.8)	
Pathologic TNM stage				<0.001
Stage I	3,391 (29.3)	563 (24.7)	2,828 (30.5)	
Stage II	5,358 (46.4)	1,088 (47.7)	4,270 (46.0)	
Stage III-IV	2,809 (24.3)	630 (27.6)	2,179 (23.5)	
Breast surgery				0.026
BCS	10,554 (60.8)	1,969 (59.1)	8,585 (61.2)	
Mastectomy	6,813 (39.2)	1,364 (40.9)	5,449 (38.8)	

Missing values were excluded from the analysis. DCIS, ductal carcinoma in situ; BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 1. Continued

Variables	Overall (%) (N=23594)	Age ≤40 Years (%) (n=4535;19.2%)	Age >40 Years (%) (n=19059;80.8%)	P-value
Axillary surgery				<0.001
SLNB	4,421 (34.1)	750 (29.4)	3,671 (35.2)	
SLNB+ALND	2,155 (16.6)	460 (18.0)	1,695 (16.3)	
ALND	6,399 (49.3)	1,343 (52.6)	5,056 (48.5)	

Missing values were excluded from the analysis. DCIS, ductal carcinoma in situ; BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

higher *Ki67* scores. The associations between age and Ki-67 values are shown in Table 5 comparing our study with other studies.

Discussion

In 2018, 2.1 million new cases of breast cancer were detected globally. In recent years, there has been

Table 2. Comparison of Tumor Subtypes by Immunohistochemistry of Patients Diagnosed with Breast Cancer at Age ≤40 Years versus >40 Years (n=9066)

	Overall	≤40 age	>40 age	P-value
Histological type				<0.001
Invasive ductal carcinoma	9,951 (73.2)	2,023 (75.5)	7928 (72.6)	
Invasive lobular carcinoma	925 (6.8)	109 (4.1)	816 (7.5)	
Mixed type	1,156 (8.5)	232 (8.7)	924 (8.5)	
Other types	1,564 (11.5)	315 (11.8)	1,249 (11.4)	
Histological grade				<0.001
I-II	6,295 (55.9)	1,013 (46.2)	5,282 (58.2)	
III	4,967 (44.1)	1,178 (53.8)	3,789 (41.8)	
Focality				<0.001
Unifocal	9,049 (84.3)	1,703 (80.7)	7,346 (85.2)	
Multifocal/ Multicentric	1,685 (15.7)	407 (19.3)	1,278 (14.8)	
Estrogen receptor				<0.001
Positive	8,928 (74.7)	1,581 (69.0)	7,347 (76.0)	
Negative	3,024 (25.3)	709 (31.0)	2,315 (24.0)	
Progesterone receptor				0.009
Positive	7,525 (64.8)	1,367 (62.4)	6,158 (65.4)	
Negative	4,088 (35.2)	824 (37.6)	3,265 (34.6)	
HER2				<0.001
Positive	2,537 (27.8)	549 (31.9)	1,988 (26.8)	
Negative	6,597 (72.2)	1,173 (68.1)	5,424 (73.2)	
Hormonal receptor				<0.001
HR Positive	9,373 (79.3)	1,692 (75.7)	7,681 (80.1)	
HR Negative	2,447 (20.7)	544 (24.3)	1,903 (19.9)	
Tumor Subtypes (N=9066)				<0.001
HR(+)*HER2*(-)	5,495 (60.6)	912 (53.4)	4,583 (62.3)	
HR(+)*HER2*(+)	1,709 (18.9)	393 (23)	1,316 (17.9)	
HR(-)*HER2*(+)	787 (8.7)	147 (8.6)	640 (8.7)	
HR(-)*HER2*(-)	1,075 (11.9)	255 (14.9)	820 (11.1)	
Tumor Subtypes* (N=4057)				<0.001
Luminal A	1,253 (30.9)	173 (22.5)	1,080 (32.8)	
Luminal B / *HER2*(-)	1,462 (36.0)	269 (35.0)	1,193 (36.3)	
Luminal B / *HER2*(+)	543 (13.4)	139 (18.1)	404 (12.3)	
Non-luminal B / *HER2*(+)	366 (9.0)	73 (9.5)	293 (8.9)	
Triple negative	433 (10.7)	115 (15.0)	318 (9.7)	

*categorized according to *Ki-67* scores; missing values were excluded from the analysis; HR= hormone receptor.

Table 3. Multivariate Logistic Regression Analyses for Pathological Parameters Associated with Breast Cancer Diagnosed at Age 40 or Younger Compared to Older Age Group.

Factors	Odds Ratio	95% CI	p-value
Tumor Type (IDC vs other)	1.229	1.059-1.428	0.007
Foci (multifocal/multicentric vs unifocal)	1.469	1.255-1.720	<0.001
Estrogen Receptor (negative vs positive)	1.538	1.263-1.872	<0.001
Progesteron receptor (negative vs positive)	1.453	1.206-1.751	<0.001
Histologic Grade (III vs I-II)	1.633	1.428-1.867	<0,001
pT Category (T3-4 vs T1-2)	1.325	1.059-1.659	0.014
pN Category (N+ vs N0)	1.163	1.025-1.321	0.019

IDC, invasive ductal carcinoma

Table 4. Clinicopathologic Factors Associated with *Ki-67* Scores in the Turkish Registry (n=4057)

Variables	Category	Total (n%)	*Ki-67* mean/median score (% ±SD)	p
Age (year)	All	4057	29.66±24.47/20(1-95)	
Age	≤40 years	769 (19.0)	37.21±26.92	<0.001
	>40 years	3,288 (81.0)	27.90±23.51	
Clinical T category	I-II	3,822 (94.2)	29.50 ±24.30	0.100
	III-IV	235 (5.8)	32.21 ±26.95	
Clinical N category	N positive	940 (23.2)	32.32±25.01	<0.001
	N negative	3,117 (76.8)	28.86 ±24.25	
Clinical stage	Stage I-II	3,772 (93.0)	29.42 ±24.26	0.033
	Stage III-IV	285 (7.0)	32.93 ±26.89	
Pathologic T category	I-II	3,777 (93.1)	29.45±24.46	0.044
	III-IV	280 (6.9)	32.50±24.39	
Pathologic N category	N positive	1,913 (47.2)	30.95±23.57	0.002
	N negative	2,144 (52.8)	28.52±25.19	
Pathologic stage	Stage I-II	3,235 (79.7)	29.05±24.56	0.002
	Stage III-IV	822 (20.3)	32.06±23.97	
Breast surgery (n=4006)	BCS	3,349 (83.6)	29.39±24.50	0.105
	Mastectomy	657 (16.4)	31.09±24.25	
Histological type	IDC	3,016 (74.3)	31.88±24.45	<0.001
	ILC	292 (7.2)	14.60±14.55	
	Mixt	358 (8.8)	23.48±20.59	
	Other	391 (9.6)	29.44±28.51	
Histological grade(n=3797)	I-II	2,147 (56.5)	17.26±15.24	<0.001
	III	1,650 (43.5)	45.78±24.28	
Focality(n=4032)	Unifocal	3,318 (82.3)	29.99±24.73	0.030
	Multifocal/Multicentric	714 (17.7)	27.89±23.07	
Estrogen receptor	Positive	3,295 (81.2)	24.04±20.45	<0.001
	Negative	762 (18.8)	53.96±25.54	
Progesterone receptor	Positive	2,882 (71.0)	23.39±20.02	<0.001
	Negative	1,175 (29.0)	45.06±27.40	
HER2	Positive	909 (22.4)	38.37±21.53	<0.001
	Negative	3,148 (77.6)	27.15±24.69	
Hormonal receptor	HR Positive	3,340 (82.3)	24.32±20.63	<0.001
	HR Negative	717 (17.7)	54.54±25.57	
Ki-67 score	Low(≤15%)	1,634 (40.3)	8.16±4.02	<0.001
	Intermediate (16-30%)	1,008 (24.8)	23.64±4.58	
	High(>30)	1,415 (34.9)	58.78±16.59	

Table 4. Continued

Variables	Category	Total (n%)	*Ki-67* mean/median score (% ±SD)	p
Ki-67 score	<20%	2285 (56.3)	8.89±4.61	<0.001
	≥20%	1772 (43.7)	45.77±21.26	
Ki-67 score	<35%	2666 (65.7)	14.23±8.77	<0.001
	≥35%	1391 (34.3)	59.23±16.37	
Molecular subtypes	Luminal A	1253 (30.9)	9.07±6.37	<0.001
	Luminal B/*HER2*(-)	1462 (36.0)	32.26±20.54	
	Luminal B/*HER2*(+)	543 (13.4)	40.38±19.70	
	Non luminal B/*HER2*(+)	366 (9.0)	35.39±23.73	
	Triple negative	433 (10.7)	62.19±25.07	

SD, standard deviation; p, probability p-value; (*), statistically significant difference with $p < 0.05$. Missing values were excluded from the analysis. BCS, breast conserving surgery.

Table 5. Comparison of the Association between *Ki-67* and Age in the Present Study with Other Reports

Author Name-		Age (year)			
	Ki-67 score	<35	35-39	40-59	50-69
		%	%	%	%
Fredholm(2016)	<20%	18.8	26.9	40.1	51.2
	≥20%	81.2	73.1	59.9	48.8
		<35	>35		
Cancello (2013)	<20%	22.5	41.5		
	≥20%	75.9	58.3		
		<40	>40		
Bouferraa (2022)	<10%	19.4	26.3		
	10-20%	33.9	15.8		
	>20%	46.8	57.9		
		<35	45-90		
Martínez (2019)	<14%	7.7	17.8		
	15-30%	17.8	31.6		
	>30%	15.8	15.8		
	Missing	58.5	34.6		
Present study		<40	>40		
	<20%	32.1	46.4		
	≥20%	67.9	53.6		

a significant increase in premenopausal breast cancer patients, particularly in low- and middle-income countries. Notably, up to 55.2% of all breast cancer cases in countries with a low Human Development Index (HDI) occur in premenopausal women [14]. Young breast cancers are particularly significant due to their distinct tumour biology, different clinical outcomes compared to postmenopausal women, and age-specific challenges. Breast cancer comprises approximately 14% of cancers occurring in younger individuals. Furthermore, early-onset cases account for 7-10% of all breast cancer diagnoses [15, 16]. Breast cancer is the most prevalent cancer in women aged 30 to 39, underscoring its status as a serious health concern for young women. A cross-sectional study utilizing three breast cancer risk assessment methods – Gail, Tyrer-Cuzick, and BRCAPRO – reported that women aged 35 to 39 have a mean risk of ±0.8% for developing breast cancer [17]. The incidence of early-onset breast cancer is not uniform across different regions worldwide.

In the United Kingdom, 9% of breast cancer diagnoses occur in women under the age of 45, while in the United States, this rate is 11% [18]. The 2018 ESO-ESMO conference reported that 4% of new breast cancer cases in the United States in 2017 involved women under 40 years old [19]. In contrast, a study examining breast cancer prevalence in Brazil found that 20.6% of patients were under 45, and 4.4% were under 35 [20]. In the United States, breast cancer incidence varies among 16 different racial and ethnic groups. One study indicated that the risk of being diagnosed with invasive breast cancer before age 50 was 72% higher among women of various ethnicities compared to non-hispanic white women [21]. Globally, early-onset breast cancer rates have steadily increased over the past two decades [5, 19]. Notably, the median

age of breast cancer patients in developing countries is approximately 10 years younger than in developed countries [22]. Morrow et al.'s study of breast cancer patients under 45 reported a median age of 39.5 years [23]. Similarly, a United Kingdom-based study involving 2,956 patients diagnosed under 40 found an average age at diagnosis of 36 years [4]. In Croatia, the median age in patients under 40 was reported as 37 years, consistent with the present study's findings [24].

Orlandini et al. reported a significantly higher median tumor size in patients under the age of 40. In their study, the median tumour size at diagnosis for this group was 25.0 mm, compared to 20.9 mm in the standard group [20]. In the POSH study, the median tumour diameter at diagnosis was 22 mm [4]. Gajdos et al found that the probability of patients younger than 36 presenting with a palpable mass could be as high as 87%, with a median tumor size of 2.0 cm [25]. Another study revealed that 15.1% of patients under 35 and 14.2% of those under 40 presented with tumors measuring between 1 mm and 10 mm. However, in patients over 40, this proportion increased to 18.2%. Notably, tumours 5 cm and larger were over 8% in all groups under 40 but dropped to below 4% for those over 40 [26].

A separate study reported that young patients were most frequently diagnosed with T2 tumours (45.7%). In contrast, the diagnosis rate at the nonpalpable stage was 35.7% in older patients but decreased to 7.3% in patients under 40 [27]. In our study, the most common pathologic T stage in patients under 40 was T2. Among our patients under 40, 41.2% were diagnosed with T1, compared to 47% for those over 40. At diagnosis, the T3-T4 rate was 10.9% for patients under 40 and 7.5% for those over 40. Additionally, 95.7% of tumours in patients under 40 and 95.1% in those over 40 were invasive. Our in situ carcinoma rates were 5.3% in patients under 40 and 5.9% in those over age 40. It is noted that in the United States, 25% of in situ breast cancers are diagnosed in women under age 50 [28].

Many studies concur that axillary involvement in breast cancer is more advanced in patients diagnosed at an early age compared to those diagnosed later in life [3, 20, 25, 27, 29]. Maliko et al. found that axillary lymph node negativity was present in 83.6% of patients over 40, but this rate dropped to 67.5% in patients under 40. Additionally, the study reported that the frequency of N3 stage axillary involvement was 4.5% in patients under 40, compared to just 1.5% in those over 40 [27]. Another study indicated that axillary negativity was only 20% in patients under 40 at diagnosis, whereas it was 88% in the 40–55 age range and 95% in those above 55 [7]. Yet another study, which reported relatively higher axillary involvement, noted that lymph node positivity was 55.6% in patients under 40, while this rate significantly decreased to 42.5% in patients over 40 [30]. In our study, axillary lymph node involvement was absent in 48.6% of patients under 40, while it was not observed in 54.5% of those over 40.

Numerous authors concur that young patients are often diagnosed at an advanced stage [3, 20, 25, 27, 31]. Stage III disease was found to occur most frequently in individuals under the age of 40, accounting for 30.4% of cases, whereas Stage I patients were predominantly in the over- age 40 group, representing 38.4% [30]. Saghir et al. reported that a large proportion (42.2%) of patients under 40 were diagnosed at Stage II, with a significant portion (23.2%) at Stage III. In our study, the frequency of Stage III-IV diagnoses among patients under 40 was 19.4%, which significantly decreased to 16% among those over 40 [32].

In early-onset breast cancer, as in all age groups, invasive ductal carcinoma is the most prevalent tumour type [32, 33]. One study reported that 85% of patients under the age of 40 had ductal carcinomas, whereas lobular cancers were present in only 5% [34]. Similarly, a study from Netherlands found that the incidence of invasive lobular cancer in younger patients (3.1%) was significantly lower than in older patients (12.3%) [27]. Additionally, approximately 12% of women under 40 with breast cancer had BRCA-1 or BRCA-2 germline pathogenic variants [29]. Although genetic predisposition is frequently considered when breast cancer is diagnosed at a young age, most cases in studies of breast cancer in individuals under 40 are generally sporadic [4]. It has also been reported that ER and PR negativity are more prevalent in young breast cancer patients, both with and without BRCA germline variations, compared to those over age 40 [35].

Several studies have indicated an inverse correlation between ER status and age [7, 35, 36]. Anders et al. reported that quantitative ER mRNA expression was lower in young breast cancer patients [36]. Within our series, ER positivity was observed in 69% of patients under the age of 40 and 76% of those over age 40. PR positivity was found to be 62.4% in the under-40 group and 65.4% in the over-40 group. Although PR status showed no significant difference between age groups, ER positivity was notably lower in those under 40. Another study reported that the prevalence of luminal A subtype increased from 49% in patients aged 15–39 to 71.6% in those over 50 [35].

Breast cancers in younger women are more likely to be triple-negative (TNBC) [3], with these cancers accounting for 26% of TNBC cases [37]. Many studies have documented the high incidence of both TNBC and *HER2*-positive breast cancer in young patients. However, most breast malignancies in young patients are hormone receptor-positive tumors [3, 29]. In our study, the luminal A subtype was identified at a frequency of 22.5% in patients under 40 and 32.8% in those over 40. TNBC occurred in 14.9% of patients under 40, compared to 11.1% in the older group. Additionally, *HER2*-positive breast cancer was significantly more frequent in our patients under 40 (31.6% compared to 26.6% in the older group).

Many authors have reported that the expression of Ki-67, a marker of tumour proliferation, is significantly higher in young patients compared to older patients [24, 26, 30, 33, 38, 39]. Eric et al. reported a mean Ki-67 value of 25 (range: 11–48) for patients under 40, while patients over 60 had an average value of 10.4 (range: 5–25) [24]. In a study comparing patients with triple-negative breast cancer at similar stages, researchers found significantly

higher Ki-67 levels in the younger group, with an average of 80% (range: 1–100), compared to 70% (range: 20–95) in the older group [33]. In our study, the mean Ki-67 expression for patients under 40 was 37.2% (± 26.9), significantly higher than for patients over 40, where the mean was 27.9% (± 23.5). When examining Ki-67 expression values of 20% and above, the average for patients over 40 was 44.3% (± 20.6), while for younger patients, it was notably higher at 50.5% (± 22.5). This pattern persisted in groups with 60% or more Ki-67 expression. A detailed analysis of the relationship between Ki-67 values and clinicopathologic findings is presented in Table 4. Table 5 offers a comprehensive comparison of our findings with those of other studies concerning Ki-67 and age.

One study reported that only 16.5% of patients under the age of 40 had histopathologic grade I breast cancer, compared to 39.3% in patients over 60 years old. Additionally, the same study found that the frequency of grade III breast cancer was significantly higher in the younger patient group than in those aged 60 and older [24]. Another study indicated that 53.4% of patients under 40 were classified as grade III [32]. Tzikas et al. observed an exceptionally high rate of grade III in patients under 40, reporting a Grade III rate of 91.4% in their study [33]. In our study, we detected a high histological grade with frequencies of 53.8% in individuals under 40 and 41.8% in those over 40. These results suggest that high histological grade was statistically more common in individuals under 40.

Some studies have found a significantly higher rate of multicentric tumours in younger patients, particularly in comparison to those over 60 [24]. Bitencourt et al. reported detecting multifocality in 13.0% and multicentricity in 12.0% of their young patient cohort [40]. In our study, the frequency of multifocality/multicentricity was 19.3% in individuals under 40, whereas this condition was observed at a frequency of 14.8% in those over 40.

Selecting an appropriate surgical method is crucial for young patients. Surgical options should be presented while considering the mass's size, the axilla's condition, and the patient's concerns about body-image integrity and cosmetic outcomes [41]. Bouferraa et al. reported that, although mastectomy is most common in patients under 40, breast conserving surgery (BCS) is more frequently performed in those over 40 [30]. Consistent with previous findings, young age remains a significant prognostic factor for locoregional recurrence in women undergoing breast-conserving surgery [34]. Voogd et al. found that the risk of local recurrence after breast-conserving surgery is notably higher in patients under 35 compared to those over 65 [42]. However, local recurrence rates do not differ significatly between younger and older patients who undergo mastectomy [43].

Cosmetic outcomes and the preservation of body-image integrity in young patients cannot be overlooked. Although immediate breast reconstruction with mastectomy procedures are highly effective in maintaining aesthetics, Rosenberg et al. reported that in the first years after surgery, young patients who underwent bilateral mastectomy were more concerned about their appearance than those treated with BCS or unilateral mastectomy [41]. It is therefore essential to explain potential complications thoroughly and allow adequate time for decision-making when proposing such surgical approaches.

In a study covering 2016–2020, ALND was performed in 8.7% of young patients who had primary surgery, but in 32.6% of those recieved surgery after neoadjuvant chemotherapy [27]. Consistent with these findings, our study demonstrated higher mastectomy rates in patients younger than 40 years compared with those older than 40, and a similar pattern for axillary dissection: ALND was performed in 70.6% of patients under 40.

In conclusion, our findings indicate that breast cancer in patients under 40 years of age is characterized by higher rates of hormone receptor negativity and elevated Ki-67 levels. It is frequently associated with triple-negativity subtypes, as well as multifocal or multicentric disease. Due to these underlying histopathologic features and the presentation of more advanced stages in younger patients, this group experiences higher rates of mastectomy and axillary dissection. Consequently, breast cancer in younger patients may carry a more dismal prognosis that should be taken into account when planning treatment strategies. This highlights the importance of considering more extensive local and systemic therapies in this population.

Author Contribution Statement

Concept and design: N Cabıoğlu, V Özmen, M Müslümanoğlu, A İğci. Analyses of data: N Cabıoğlu. Acquisition, or interpretation of data: All authors. Drafting of the manuscript: N Cabıoğlu, Z Türkyılmaz. Critical revision of the manuscript for important intellectual content: N Cabıoğlu, Z Türkyılmaz, E Özkurt, A İğci, M Müslümanoğlu, M Kapkaç, L Yeniay, I Taşdelen, E Aksaz, A Haydaroğlu, V Çelik, E Gazioğlu, S Gökgöz, K Şenol, B Önal, S Özbaş, E Ok, A Akcan, N Z Cantürk, S Koçak, B Güllüoğlu, S Demirer, A Koyuncu, M Tükenmez, S Girgin, T Çolak, E Karadeniz, MN Akcay, M Oltulu, A Kebudi, S Emiroğlu, C Uras, V Özmen.

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Availability of data

The datasets of the present study are available from the corresponding author upon reasonable request.

Study registration

The present study has been registered as the "MF18-04 Turkish National Breast Cancer Registry Study" in the Turkish Federation of Breast Diseases Societies (TFBDS).

Name the ethical committee that approved the research

The Istanbul Faculty of Medicine Ethics Committee at Istanbul University.

Conflict of Interest

None.

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