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ORIGINAL ARTICLE

Risk factors and histopathological features of breast cancer among women with different menopausal status and age at diagnosis

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Summary

Purpose: *Although there are studies that investigate different risk factors and clinicopathological features of breast cancer in women at different age groups and menopausal status, there is a need for studies with larger study populations due to controversial findings. We conducted this study to identify demographic parameters in breast cancer patients and histopathological features of the tumors for different age groups and compare them to demonstrate significant differences, if any.*

Methods: *3325 women diagnosed with breast cancer in Hacettepe University Oncology Hospital Outpatient Clinic between January 1994 and March 2014 were included in this study.*

Results: *Postmenopausal women who were older than 65 were found to have higher number of children, higher rates of oral contraceptive use, greater age at menarche, and have higher rates of first full-time pregnancy before the age of 30. On the other hand, higher rates of grade 3 tumors, advanced lymph node stage, lymphovascular invasion, and triple negative breast cancers were more frequently seen in premenopausal women below the age of 35. Since earlier age at the time of diagnosis is associated with bad prognosis, early diagnosis of breast cancer gains importance in younger women.*

Conclusion: *Implementing targeted screening programs of breast cancer for younger women may become a need in the future. Meanwhile, well-education on risks of breast cancer and regular self-examination for early diagnosis need to be emphasized for the prevention of breast cancer and related diseases in young ages.*

Key words: *breast cancer, clinicopathological, risk factors, survival*

Introduction

Breast carcinoma is the most common cancer in women worldwide [1] and it is responsible for approximately 40000 deaths each year in the United States [1].

Age at menarche, age at first full-term pregnancy, use of oral contraceptives, lactation, body-mass index (BMI), family history, use of hormone replacement therapy (HRT) and parity have been shown to impact breast cancer risk [2,3].

Metastasis is the most common cause of breast cancer deaths [4]. Despite the advances, 20-30% of patients with early breast cancer will experience relapse presenting with distant metastatic disease [5]. Indeed, 6-10% of patients show metastatic disease at initial diagnosis of breast cancer [6]. Risk of recurrence is primarily affected by stage at initial presentation and the biological features of the tumor. Tumor size, nodal involvement, grade, lymphovascular invasion, and estrogen receptor (ER) and human epidermal growth

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factor receptor 2 (HER2) status are all independent risk factors for relapse [7,8].

While the stage at diagnosis is currently the most important prognostic variable [7,8], it has been noted that there is a significant difference in survival among the molecular subtypes of breast cancer [9-11].

Studies carried out thus far have shown that risk factors as well as histopathological features of breast malignancies may vary among different age groups [12,13]. A detailed review of the literature demonstrates that the important cut-off values for age groups are 35 and 65 years. Moreover, menopausal status is also an important factor influencing clinicopathological characteristics of patients with breast cancer [14-17].

Prognostic factors are used for the estimation of how aggressive the tumor may evolve and also for the decision of treatment approach.

We conducted this study to find out if breast cancer shows different clinicopathological features in patients with different menopausal status and age. The main objective of this study therefore was to identify demographic parameters of the patients and histopathological features of the tumors for each group (premenopausal <35 years, premenopausal ≥ 35 years, postmenopausal <65 years and postmenopausal ≥ 65 years) and compare them to demonstrate significant differences, if any.

Methods

All patients involved in this study provided an informed consent form. Approval from Hacettepe University Ethics Committee was obtained prior to starting this study.

This retrospective cohort study included 3325 women diagnosed with breast cancer between January 1994 and March 2014 who have been followed by the Department of Medical Oncology at Hacettepe University, Institute of Oncology. There were 97 patients with missing data of exact date of diagnosis and date of birth who were excluded from the study. Finally, a total of 3228 patients with breast cancer were eligible for statistical analysis. Detailed information on the use of contraceptives, use of HRT, age at first full-term pregnancy, total duration of lactation in months, age at menarche, menopausal status, family history of breast or ovarian cancer, and number of biological children were collected for group comparisons. In statistical analysis risk factors were grouped and coded as follows: use of contraceptives (yes/no), use of HRT (yes/no), age at first full-term pregnancy (<30 years, ≥ 30 years, nulliparous), breast feeding (yes/no), age at menarche (<12 years, ≥12 years) [18], menopausal status (premenopausal/postmenopausal), and number of biological children (0,1, ≥ 2 children).

Staging of tumor size and lymph node status were done according to guidelines of American Joint Committee on Cancer [19]. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2) and grouped into 4 different categories: normal body weight (BMI: 18.5-24.9 kg/m^2); overweight (BMI: 25-29.9 kg/m^2) ; obese (BMI: 30.0- 34.9 kg/m^2) and morbid obese (BMI: ≥35 kg/m^2) according to World Health Organization criteria [20].

Data on ER and PR status, HER2 expression, lymphatic invasion, vascular invasion, perineural invasion and extracapsular extension (ECE) were obtained from medical record review. ER and PR status were assessed by immunohistochemistry (IHC). Positive result was assumed in case of nuclear staining in more than 5% of tumor cells. Immunohistochemical methods were used for determination of HER-2 expression. Complete membrane staining in more than 10% of tumor cells was accepted as positive (a score of 3+), whereas scores of 0 and 1 were accepted as negative. In case of a score of 2, fluorescence in situ hybridization (FISH) was performed.

Tumor subtypes were classified as luminal A (ER positive and/or PR positive/HER-2 negative), luminal B (ER positive and/or PR positive/HER-2 positive), HER2 overexpressing (ER negative/PR negative/HER2 positive) and triple negative (ER negative/PR negative/HER-2 negative) [21].

Given that age and menopausal status may interact in affecting patients' prognosis, patients were divided into four groups according to their menopausal status and age at the time of diagnosis: premenopausal <35 years (group 1), premenopausal ≥ 35 years (group 2), postmenopausal <65 years (group 3), and postmenopausal ≥ 65 years (group 4).

Distributions of number and percentages were analyzed across the four main subgroups of the main independent variable (premenopausal <35 years, premenopausal ≥ 35 years, postmenopausal <65 years and postmenopausal ≥ 65 years). The main dependent variables were the clinicopathological features (molecular subtype, lymphovascular invasion, lymph node status, tumor size, tumor grade).

Statistics

The differences between groups with regard to risk factors and tumor histopathological features were examined using chi-square test for categorical variables, while one way ANOVA and Student's t tests were used for continuous variables. The computer software program SPSS 22.0 was used for the analysis (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The missing values for the relevant cross tables were excluded from the statistical analysis. A two-sided p value <0.05 was considered as statistically significant.

Results

A total of 3228 patients were included and analyzed in this study. The mean patient age was 54.9 ±11.88 years. Patient demographic data are shown in Table 1 and the distribution of clinicopathological parameters with p values are given in Table 2.

Patients were divided into four groups depending primarily on their menopausal status and their age. Premenopausal women who were younger than 35 were placed in group 1 which consisted of 380 cases. There were 1322 premenopausal women who were equal or older than years 35 and these constituted group 2. Group 3 included 1034 patients who were postmenopausal as well as younger than 65 years of age. The latter group 4 had 273 patients who were also postmenopausal and were equal or older than 65 years of age. While patients who had premature menopause were placed in group 3, women with late menopause were included in group 2.

Table 1. Patient demographic characteristics

Characteristics	*N*	*%*	
Age, years (N=3228)			
18-24			
25-29	213	0.7	
30-39	281	8.7	
40-49	797	24.7	
50-54	581	18	
55-59	479	14.8	
60-64	404	12.5	
>65	662	20.5	
Mean	*Min*	*Max*	*SD*
54.9	*22*	*95*	*11.88*
Age at the time of diagnosis, years (N=3228)			
<35	327	10.1	
35-64	2568	79.6	
>64	333	10.3	
Mean	*Min*	*Max*	*SD*
49.16	*13*	*92*	*11.809*
Age at menarche, years (N=3009)			
<12	859	28,5	
≥12	2150	71.5	
Mean	*Min*	*Max*	*SD*
13.26	*8*	*24*	*1.38*
Age at first full-term pregnancy, years (N=3150)			
Nulliparous	441	14	
<30	2401	76.2	
≥30	308	9.8	
Mean	*Min*	*Max*	*SD*
23.32	*13*	*55*	*4.963*
Menopausal status (N=3228)			
Premenopause	1773	54.9	
Postmenapause	1455	45.1	
BMI (N=2933)			
Normal	1034	35.3	
Overweight	1063	36.2	
Obese	604	20.6	
Morbid obese	232	7.9	
Mean	*Min*	*Max*	*SD*
27.424	*18.56*	*55.56*	*5.06091*
Use of oral contraceptives (N=3167)			
Yes	754	23.8	
No	2413	76.2	

SD: standards deviation

Of the patients, 28.5% had menarche before the age of 12 and 71.5% had after the age of 12. Patients in group 1 more commonly had menarche before the age of 12 (32.9%) compared to group 4 (22.7%). Likewise, patients in group 4 more commonly had their menarche after the age of 12 (77.3%) compared to group 1 (67.1%) (p=0.003).

While 88.6% of the patients had their first full term pregnancy before the age of 30, 11.4% had it after. First full-term pregnancy rate before the age of 30 was 10.5% in group 1, 14.9% in group 2, 8.9% in group 3 and 5.9% in group 4. The difference among these groups with regard to age of first full-term pregnancy was statistically significant (p<0.001).

According to BMI classification 35.3% of the patients had normal body weight, 36.2% were overweight, 20.6% were obese and 7.9% were morbidly obese. Group 1 and group 2 had significantly lower rates of obesity (10.3 and 11.9%, respectively), compared to group 3 and group 4 (24.9 and 25.3%, respectively). Similarly, group 3 and 4 had more morbid obese patients compared to group 1 and 2 (p<0.001).

The rate of oral contraceptive use in group 1 was 25.8%, in group 2 was 28.7%, in group 3 was 22.4% and in group 4 was 5.8%. When compared to other groups, group 4 had significantly lower rates of oral contraceptive use (p<0.001).

A total of 59.3% patients had luminal A, 16.4 had luminal B, 10.3% had HER-2 overexpressing and 14% had triple negative breast cancer. While significantly more patients in group 4 had luminal A breast cancer compared to other groups (p=0.006), luminal B and HER2 overexpressing type did not show any difference among 4 groups (p=0.45). On the other hand, triple negative breast cancer was most commonly seen in group 1 compared to other groups (p=0.001).

The rate of grade 3 tumors was significantly higher among patients in group 1 (57.8%) compared to others (p<0.001). While the frequency of grade 2 tumors did not differ among group 2 (45.6%), group 3 (47.3%) and group 4 (47.7%)

Table 2. Clinicopathological features of breast cancer patients

Features		*Premenopausal*				*Postmenopausal*						
		<35 years		*≥35 years*		*<65 years*		*≥65 years*		*Total*		
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*p value*
Age at menarche	<12 years	125	32.9	404	30.6	268	25.9	62	22.7	859	28.5	
	≥12 years	255	67.1	918	69.4	766	74.1	211	77.3	2150	71.5	0.003
Age at first full-term pregnancy	<30 years	255	89.5	995	85.1	886	91.1	269	94.1	2405	88.6	
	≥30 Years	30	10.5	174	14.9	87	8.9	17	5.9	308	11.4	<0.001
BMI	Normal	214	59.6	498	39.4	259	25.4	63	21.9	1034	35.3	
	Overweight	101	28.1	450	35.6	391	38.3	121	42	1063	36.2	
	Obese	37	10.3	240	19	254	24.9	73	25.3	604	20.6	
	Morbid obese	7	1.9	77	6.1	117	11.5	31	10.8	232	7.9	<0.001
Oral contraceptive use	No	287	74.2	969	71.3	850	77.6	307	94.2	2413	76.2	
	Yes	100	25.8	390	28.7	245	22.4	19	5.8	754	23.8	<0.001
Molecular subtype	Luminal A	177	51.5	722	59.6	574	59.2	200	67.6	1673	59.3	
	Luminal B	73	21.2	208	17.2	148	15.3	34	11.5	463	16.4	
	HER-2 overexpressing	36	10.5	124	10.2	107	11	23	7.8	290	10.3	
	Triple negative	58	16.9	158	13	140	14.4	39	13.2	395	14	0.006
Grade	Grade 1	20	6.1	160	13	126	12.9	48	17.3	354	12.6	
	Grade 2	119	36.2	559	45.6	462	47.3	132	47.7	1272	45.3	
	Grade 3	190	57.8	508	41.4	388	39.8	97	35	1183	42.1	<0.001
Tumor size	No primary tumor	18	4.6	46	3.3	44	3.9	16	4.8	124	3.8	
	T1	84	21.6	439	31.8	385	34.4	109	32.8	1017	31.6	
	T2	183	47	643	46.5	525	46.9	154	46.4	1505	46.7	
	T3	91	23.4	205	14.8	129	11.5	30	9	455	14.1	
	T4	13	3.3	49	3.5	37	3.3	23	6.9	122	3.8	<0.001
Lymph node status	N0	135	36.1	632	48.4	496	47.4	149	49.2	1412	46.6	
	N1	116	31	359	27.5	295	28.2	76	25.1	846	27.9	
	N2	75	20.1	181	13.9	124	11.8	42	13.9	422	13.9	
	N3	48	12.8	134	10.3	132	12.6	36	11.9	350	11.6	0.001
Extracapsular extension	No	308	81.3	1134	83.3	911	82.7	262	80.1	2615	82.5	
	Yes	71	18.7	228	16.7	190	17.3	65	19.9	554	17.5	0.518
Perineural invasion	No	358	94.2	1305	95.9	1038	94.4	303	92.9	3004	94.9	
	Yes	22	5.8	56	4.1	62	5.6	23	7.1	163	5.1	0.099
Lymphatic invasion	No	254	66.8	1022	75.1	864	78.3	244	74.6	2384	75.2	
	Yes	126	33.2	339	24.9	239	21.7	83	25.4	787	24.8	0.001
Vascular invasion	No	263	69.2	1024	75	863	78.2	252	77.1	2402	75.6	
	Yes	117	30.8	342	25	240	21.8	75	22.9	774	24.4	0.004

(p=0.56), it was significantly lower in group 1 (36.2%) (p<0.001).

When all groups were analyzed, a primary tumor could not be assessed in 3.8% of the patients (TX), while 46.7% had stage T2 breast cancer. All groups had similar rates of stage T4 breast cancer (p=0.72). However, of all groups, group 1 had significantly more patients with stage T3 cancer (23.4%) and fewer patients with stage T1 disease (21.6%) (p<0.001).

Of all groups, 46.6% of the patients did not have a lymph node involvement (N0). Similar to T staging, the rate of N0 breast cancer was significantly lower (36.1%) and N2 breast cancer was significantly higher (20.1%) among patients in group 1 compared to other groups (p=0.001).

When all groups were compared with each other, no significant difference was found regarding ECE (p=0.518) and perineural invasion (p=0.099). On the other hand patients in group 1 had significantly higher rates of lymphatic (33.2%) and vascular invasion (30.8%) compared to other groups (p=0.001 and p=0.004, respectively), while other groups did not show any difference (p=0.127 and p=0.156, respectively).

Discussion

This is a retrospective cohort study based on the database consisting of 3228 women with breast cancer who were diagnosed in Hacettepe University Oncology Hospital between January 1994 and March 2014.

Higher menarche age is shown to be correlated with lower risk of breast cancer in the literature. The earlier encounter and prolonged exposure to estrogen increases the risk for breast cancer. The risk is greater in postmenopausal than in premenopausal women. Breast development is maximum between the ages of 10 and 20. This time period is characterized by increased sensitivity of breast tissue to carcinogens. The earlier menarche will cause earlier breast development hence earlier exposure to estrogen. Therefore older age at menarche will decrease the risk for breast cancer in premenopausal women [22,23]. In this study the rate of women who had menarche after the age of 12 was found to be higher than in women who had menarche after the age of 12. Among the women who had menarche after the age of 12, it can be seen that the postmenopausal ≥65 group had higher rates. Premenopausal <35 women had the highest rate to have menarche before the age of 12. However, these results were not consistent with the literature [22,23]. Having many years passed since the menarche and the study being retrospective prevents elimination of recall bias and information bias.

Erica et al. found that the age at the time of diagnosis was not related with the age at first full-term pregnancy being higher than 30 (<40 and >40) in women with breast cancer [24]. In this study the higher age of diagnosis was found to be related to decreased rate of late first full-term pregnancy (p<0.001). Since the years of women's education have prolonged and the women became more involved in workplace in the recent years, the age at first full-term pregnancy may have become higher in the younger group. The higher age at first full-term pregnancy is related with increased exposure to estrogen. This may have caused earlier breast cancer development which explains the higher rates of late first full-term pregnancy in younger group.

In this study the rate of oral contraceptive use was higher in the premenopausal ≥35 group (28.7%). According to studies carried out thus far, higher BMI in postmenopausal women was found to be associated with higher risk of breast cancer development [1]. This is explained by estrogen release by the adipose tissue in the postmenopausal stage which increases the risk for breast cancer [25]. On the contrary, higher BMI decreases the risk of breast cancer development in premenopausal women [26]. Lower body weight was shown to be a risk factor in premenopausal women [27]. At premenopausal stage, higher BMI causes anovulatory cycles, hence the decreased exposure to estrogen which lowers the risk of breast cancer [28]. In our current study the highest rate of normal BMI was found to be in the premenopausal <35 group. The rate of overweight, obese and morbidly obese patients was highest in the postmenopausal ≥65 group. These results showed that the higher age was correlated with higher BMI.

When the tumor grades are evaluated the rate of grade I tumors was higher in the postmenopausal ≥65 group (17.3%) than the premenopausal <35 group (4.6%). In all groups grade II tumors had the highest rate. The rate of patients with grade III tumor in the premenopausal <35 group was higher than the ≥65 group. Increased age is related with decreased rate of grade III tumors. There are studies in the literature that demonstrated similar results. In a study by Bonnier et al., the patients were separated into three groups: under the age of 35, 35 and older, and postmenopausal under the age of 70. Grade III percentage

was greater in women with breast cancer under the age of 35 than the other two groups [29]. In a study by Sidoni et al., women with breast cancer were separated into two groups as under the age of 40 and over the age of 60. They found grade III tumors to be more frequent in women under the age of 40. Both studies support our findings [30].

When the lymph node involvement was analyzed it was seen that the patients with N0 stage cancer had the highest rate (46.6%) at diagnosis and from the premenopausal <35 group to postmenopausal ≥65 group; this rate increased gradually. In a study by Wildiers et al. the rate of lymph node metastasis in women with breast cancer decreased up to the age of 70 and increased after the age of 70 [31]. Another study by Botteri et al. showed that the rate of lymph node involvement was decreased up to the age of 65 and axillary lymph node involvement was increased after the age of 65 [32]. In our study the rate of lymph node involvement was higher in the younger group which was consistent with relevant studies in the literature. However, the expected rise in lymph node involvement rate was not seen in the postmenopausal ≥65 group.

Although not many studies are published on lymphovascular invasion in women with breast cancer, most of the studies in the literature supported our findings. In one study where women with breast cancer were divided into two groups, as the age of 35 and/or under and over the age of 35, the rate of lymphovascular invasion was higher in women aged 35 and/or under (31%) than in women aged over 35 (20%) (p=0.005) [33]. In a similar study, the rate of lymphovascular invasion was found to be 49.5% in women aged 35 and/or under and 31.8% in women aged over 35 (p<0.01) [34]. In a study conducted in China, women were divided into two groups as aged <40 and aged 40 and/or over. The rate of women with lymphovascular invasion was higher in the group aged under 40 (39.6%) compared to the group aged 40 and/or over (33.2%) (p=0.003) [4]. In our study the rate of women with lymphovascular invasion was shown to be higher in younger breast cancer patients (under the age of 35). This was regarded as a significant finding since lymphovascular invasion indicates bad prognosis [35].

There are very few studies on perineural invasion related with breast cancer prognosis. The two studies we have referred showed that perineural invasion was not related with breast cancer prognosis [36,37]. There was only one study published so far on the relationship between perineural invasion and age. In that study premenopausal and postmenopausal women with breast cancer aged <35 and 35 and/or over, were compared. There were 8.2% of patients with perineural invasion aged <35 and 7.9% of patients were aged 35 and/or over (p=0.99). Premenopausal women were 43.3% and postmenopausal were the 56.7% of the whole group (p=0.963). Neither results were statistically significant [38] . In our current study the rate of perineural invasion was 7.1% in postmenopausal ≥65 group and it was not statistically significant compared to the premenopausal <35 group of which 5.8% had perineural invasion (p=0.099).

The analysis showed that luminal A breast cancer was more frequent in the postmenopausal ≥65 group (67.6%) compared to the premenopausal <35 group (51.5%). HER2 overexpressing breast cancer was most frequently seen in the premenopausal <35 group (10.5%) whereas least frequently noted in postmenopausal ≥65 group (7.8%). Although the difference between the groups regarding HER2 overexpressing and luminal B breast cancer rate was not statistically significant, it may still be clinically of importance and further studies with larger patient groups are required to elucidate this argument. Triple negative breast cancer was more frequently seen in the premenopausal <35 group (16.9%) than the postmenopausal ≥65 group (13.2%). There are published studies that support these findings. In a study by William et al., ER-negative tumors were found to be more frequent and the risk decreased after menopause for ER-negative tumors. Increase in the rate of ER-positive tumor incidence by age was found to be statistically significant. Also the incidence of luminal A breast cancer increased with age whereas triple negative breast cancer was more frequently seen in younger patients [39]. In a study by Masaaki et al., when compared to ER-positive breast cancer, triple negative breast cancer was associated with younger ages at the time of diagnosis [40].

Conclusion

Lymph node metastasis, tumor diameter, molecular subtype and histological grade are the most important prognostic parameters known for breast cancer after distant metastasis. Also steroid hormone receptors (estrogen and progesterone receptors), oncogenes (HER2/neu), tumor suppressor genes (p53), proliferation markers (Ki-67), angiogenesis and proteases are known to affect breast cancer prognosis. In our study presence of lymph node metastasis, lymphovascular inva-

sion, triple negative breast cancer, greater tumor size, grade III tumors, which were regarded as indicators of bad prognosis, were seen more frequently in premenopausal women below the age of 35. Since younger age at diagnosis is associated with bad prognosis, early diagnosis of breast cancer gains in importance in younger women. If this study is supported by further studies, implementing new screening programs of breast cancer for younger women, perhaps targeting a subpopulation who is at higher risk may become a need in the future. Meanwhile, good education on the risks of breast cancer and regular self examination for early diagnosis need to be emphasized for the prevention of breast cancer and related diseases in young ages.

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Conflict of interests

The authors declare no confict of interests.

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