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The Role of Age in Breast Cancer Subtypes: A Comparative Study in Young and Older Women

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ABSTRACT

Molecular pathological classification shows that triple-negative and human epidermal growth factor receptor 2 (HER-2**)** positive breast cancer subtypes are associated with a worse prognosis compared to luminal disease; therefore, the main aim was to evaluate the effect of age on the identification of molecular subtypes and whether the disparity in outcomes between patients aged ≤ 35 years and those aged > 35 years is due to the diversity of molecular subtypes. Women who are diagnosed with breast cancer at a young age (≤ 35 years) have significantly shorter overall survival durations. Trial participants included 216 patients ≤ 35 years and 212 patients > 35 years who were randomly selected from all breast cancer patients who visited the Department of Oncology, Ege University. Using immunohistochemistry, the molecular subtyping was based on the Ki-67 proliferation index, cerb-B2, progesterone receptors (ER, PR), and estrogen. Cerb-B2 (-), Ki-67 ≤ 15, ER (+), and PR (+) were considered indicators of luminal illness. Luminal B patients had ER/PR (+), cerb-B2 (-)/(+), and Ki-67 ≥ 15. The triple-negative disease was considered if all three receptors were negative, whereas HER-2-positive disease was defined by the presence of cerb-B2 and the absence of hormone receptors. 19% of the younger group were triple negative, and 52% of the younger group were Luminal B. The majority of the group > 35 years old was Luminal B (39%) as it is comparable to the very young population; however, Luminal A (31%) with good prognostic aspects came next. The two age groups did not differ statistically in molecular subtypes; however, the triple-negative subtype and Ki-67 ≥ 15%, which are associated with a worse prognosis, were numerically greater in the group aged ≤ 35 years. The prognosis of young women with breast cancer is worse. However, the molecular subtypes of the two different age groups did not differ significantly in our study. The limited size of the study cohort may account for this, but it may also indicate that age is a separate predictive factor from other clinicopathologic characteristics. However, given that the largest category in the very young population had Luminal B and triple negatives, this diversion may account for the poorer prognosis of the disease in this group.

Keywords: Breast cancer, Molecular subtype, Prognostic factor, Young and older women

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Introduction

Breast cancer becomes more common as people age. The vast majority of cases are identified beyond the age of 50. Throughout her life, a woman has a 12.8% chance of having breast cancer [1]. Breast cancer is caused by a complex combination of variables, including age, gender, genetics, food, and hormone abnormalities. The main risk factors for breast cancer are age and gender. Breast cancer develops 100 times more frequently in women

than in males [2]. Many people are at risk of developing breast cancer as they become older. Breast cancer develops at a rate of 0.04% in women aged 30-39 years, with the risk increasing by 10% or more each year [3]. Breast cancer in first-degree relatives and greater breast density are variables linked to a twofold higher risk of breast cancer in women between the ages of 40 and 49 years (BIRADS 4) [4]. Breast cancer has morphological, genomic, and clinical heterogeneity. Both molecular markers, including the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER-2), as well as factors like tumor size, age, histological grade, and nodal involvement, were unable to account for this variability. Over the past decade, the advent of technologies like gene expression arrays has shed light on the molecular categorization of breast cancer. The pathogenesis, outcomes, and responsiveness to therapy of the illness are influenced by the patient's genetic makeup and cellular microenvironment. As a result, each patient's breast cancer therapy has to be unique. At the molecular level, breast cancer is unique in several ways. These tumor-related variables help to tailor treatment to each patient's unique needs and offer information on prognosis. Triple-negative and human epidermal growth factor receptor 2 (HER-2) positive breast cancer subgroups are associated with a worse prognosis than luminal disease, based on molecular pathological categorization. Women who receive a breast cancer diagnosis before the age of 35 have significantly worse 5-year disease-free survival and overall survival times [5]. Based on this rationale, the main goal is to assess how age affects the identification of molecular subgroups and if the differences in outcomes between patients aged ≥ 35 years and those aged > 35 years are due to the variety of molecular subgroups.

Materials and Methods

The study was planned as a single-center, retrospective, descriptive study. A total of 216 patients ≤ 35 years and randomly selected 212 patients of all breast cancer patients > 35 years, presented to the Ege University Faculty of Medicine (EUFM) Department of Oncology diagnosed with breast cancer were enrolled in the study. Demographic data, clinicopathological characteristics, and treatment modalities were reviewed and recorded for each patient. Estrogen and progesterone expression were assessed by examining pathology reports of patients. Values of 1% and above are considered "positive," while < 1% are negative for the percentage of ER and PR expressions [6]. HER-2 expression was evaluated by examining pathology reports of patients. HER-2 expression as assessed in immunohistochemistry (IHC) staining intensity of 0, 1+, 2+, and 3+; 0 and 1+ values are accepted "negative," and 3+ values are accepted "positive." Patients considered as IHC 2+ were categorized according to the FISH test results. FISH-positive patients were classified as "positive," FISH FISH-negative ones as "negative." If the FISH test was not performed IHC 2+ patients were classified as "indeterminate." [6]. Ki-67 expression was assessed by examining pathology reports of patients. Ki-67 determination technique cannot be standardized because of the addition of a variable factor in the evaluation of this marker (To distinguish luminal B from luminal A tumor cut-off point was 13.25%) [7]. St Gallen International Expert Consensus adopted unanimously in 2013 that the Ki-67 cut-off value of 14% is not an appropriate threshold value to define the luminal B subtype. The cut-off value for the majority ranges from 15-25%. As a result, a clear consensus has not been achieved on the evaluation of Ki-67 protein. Therefore, as the cut-off value of Ki-67 in this study, we agreed to 15%. Ki-67 ≤ 15% tumors were assessed as luminal A. p53 expression was assessed by examining pathology reports of patients. Values of 1% and above are considered "positive," while < 1% is negative for the percentage of p53 expressions.

Molecular subtyping was based on estrogen, progesterone receptors (ER, PR), cerb-B2, and Ki-67 proliferation index assessed by IHC. Luminal A disease was defined as ER(+), PR(+), cerb-B2(−), Ki-67≤ %15. Patients with ER/PR(+), cerb-B2(−)/(+), Ki-67 ≥ %15 were classified as Luminal B. When all three receptors were negative, it was accepted as a triple negative disease and HER-2-positive disease was characterized by a lack of hormone receptors and the presence of cerb-B2.

In the evaluation of the findings obtained in this study SPSS (Statistical Package for Social Sciences) 18 program (SPSS Inc., Chicago, Ill., USA) was used. Data were analyzed using descriptive statistical methods (mean, standard deviation) as well as the Chi-square test, Fisher's exact Chi-square test and Student's *t*-test were used for the comparison of qualitative data. Results were evaluated at a 95% confidence interval and $P < 0.05$ was considered statistically significant.

Approval was obtained from the Medical Research Ethics Committee of EUFM Research Ethics Committee with the number 12-6.1/7 dated July 12, 2012.

Results and Discussion

We looked back at the pathology reports of 216 women with breast cancer who were 35 years of age or younger and who came to the EUFM Department of Oncology. 276 patients over the age of 36 were chosen at random from the records of 4116 female breast cancer patients to compare. The study included 212 patients whose files had enough information and pathology results. Family history, histologic type, tumor size, tumor location, positive lymph nodes, ER, PR, HER-2 expression, Ki-67, p53 status, molecular subtypes, and metastatic circumstances at diagnosis were comparisons between these two groups.

Patient characteristics are listed in **Table 1**.

In **Figure 1**, two groups are compared based on subtype analysis. Molecular subtypes did not differ statistically significantly between the two age groups. Nonetheless, the group of people aged ≤ 35 years had a statistically larger triple-negative subtype and Ki-67 ≥ 15%, which are linked to a worse prognosis.

Table 1. Patient characteristics

	≤ 35 years (n (%))	**> 35 years(n (%))**	**P-value**
Age (n = 428), median (IQR)	33 (21-39)	50 (43-59)	< 0.001
T (n = 397)			
T1	49 (25.1%)	62 (30.7%)	0.096
T2	117 (60%)	123 (60.9%)	
T3-4	29 (14.9%)	17 (8.4%)	
N (n = 369)			
N0	63 (32.6%)	58 (33%)	0.949
N1-3	130 (67.4%)	118 (67%)	
M (n = 428)			
M0	196 (90.7%)	181 (85.4%)	0.087
M1	20 (9.3%)	31 (14.6%)	
Histology (n = 428)			
Invasive ductal	147 (68.1%)	141 (66.5%)	0.100
Invasive lobular	10 (4.6%)	18 (8.5%)	
Ductal and lobular	19 (8.8%)	12 (5.7%)	
Inflammatory	18 (8.3%)	10 (4.7%)	
Other	22 (10.2%)	31 (14.6%)	
Family history (n = 350)			
Yes	27 (15.5%)	31 (17.6%)	0.598
No	147 (84.5%)	145 (82.4%)	
ER (n = 428)			
Positive	136 (63%)	144 (67.9%)	0.281
Negative	80 (37%)	68 (32.1%)	
PR (n = 428)			
Positive	129 (59.7%)	124 (58.5%)	0.796
Negative	87 (40.3%)	88 (41.5%)	
HER2 (n = 422)			
Positive	128 (59.8%)	123 (59.1%)	0.887
Negative	86 (40.2%)	85 (40.9%)	
p53 (n = 428%)			
Positive	87 (40.3%)	94 (44.3%)	0.395
Negative	129 (59.7%)	118 (55.7%)	
Ki-67 (n = 304)			
Median (IQR)	20 (10-40%)	20 (10-30%)	0.168

≤ 14	43 (26.5%)	48 (33.8%)	0.209
> 14	119 (73.5%)	94 (66.2%)	
Subtype (n = 320)			
Luminal A	29 (17.5%)	48 (31.2%)	0.024
Luminal B	87 (52.4%)	60 (39.0%)	
HER2 enriched	18 (10.8%)	18 (11.7%)	
Triple-negative	32 (19.3%)	28 (18.2%)	

ER: Estrogen receptor, IQR: Interquartile range, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

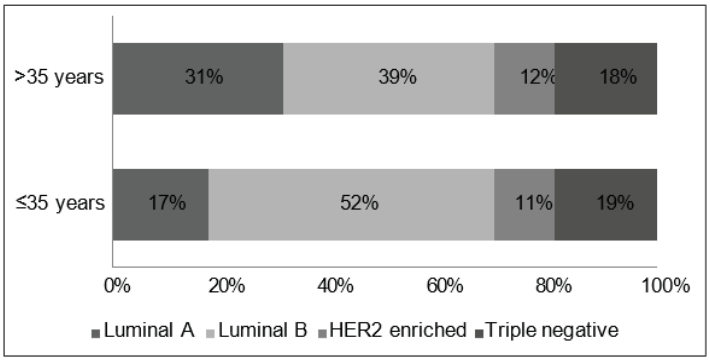

Figure 1. Comparison of molecular subtypes according to different age groups.

14% of cancer-related fatalities are caused by breast cancer, which accounts for 23% of all cancer occurrences. As one age, the risk of breast cancer rises. Age, tumor size, histological type, positive axillary lymph node, tumor grade, hormone receptor, and HER-2 status are important prognostic variables for breast cancer. Breast cancer in young, premenopausal women progresses more aggressively than in older, postmenopausal women [8]. According to several studies, young people are diagnosed with advanced illnesses [9]. In addition, young patients had high hormone receptor expression and low histological grade and lymph node involvement rates [10]. Based on their prognostic relevance, histopathological subgroups of breast cancer may be categorized into three groups [11]. The prognosis is excellent for mucinous, tubular, and papillary carcinomas; it is bad for invasive ductal and atypical medullary carcinomas, and it is intermediate for medullary and invasive lobular carcinomas. Invasive ductal carcinoma is the most prevalent of these histologic subtypes. Additionally, the most common histological type in our analysis was invasive ductal carcinoma.

When invasive breast cancer is present, lymph node involvement plays a significant role in the disease's stage and offers valuable prognostic data. High-grade tumors that include nodes are prone to develop early in life, as early as age 36. The age distribution of low-grade cancers and tumors without nodal involvement is late-onset [12]. Nevertheless, our investigation did not find significant variations between the two groups in terms of the number of lymph nodes involved.

The biology of breast cancer has been better understood because of several research studies over the last ten years that describe gene expressions. To better classify these tumors, gene expression profiling studies have been carried out to comprehend the genetic heterogeneity of breast cancer. These studies, when combined with clinical data, are providing guidance. Furthermore, gene expressions can help identify new molecular targets for drug development and have therapeutic value in predicting prognosis and responsiveness to treatment. In addition to determining the genetic expression patterns of breast cancer cells, DNA microarray technology is utilized to create an intrinsic gene set for breast cancer that distinguishes molecular subtypes with varying prognoses and responses to therapy [13]. Despite having a higher predictive power than the currently employed method, gene expression microarrays used for molecular subtyping appear to be far from being applied in routine clinical settings due to their lack of validity and standardization, as well as their higher cost. IHC marker-based diagnostic techniques are still employed in clinical practice despite significant advancements in biological understanding.

The two groups in our study did not significantly vary in terms of ER, PR, or HER-2 positive. According to Colleoni *et al*. [14], patients under the age of 35 had a higher incidence of ER, PR-negative tumors than individuals above that age. These patients also had greater levels of Ki-67 expression. There was no discernible difference in HER-2 expression. Furthermore, younger individuals in this research had a greater frequency of grade 3 tumors

[14]. However, there were no age group differences in our study. Only Ki-67 > 15% was higher in the 35 and younger age group. In breast cancer, hormone receptor positivity is a separate predictor of outcome. A better prognosis and a response to hormone treatment are indicated by ER and PR positive. It has been shown that 45-69% of patients with invasive tumors have PR-positive disease, whereas 37-80% of patients have ER-positive illness. The percentage of ER-positive cells is linked to tumor responsiveness to hormone therapy and differentiation. Tumors that are both ER and PR positive have the best response rate to therapy [15]. The prognosis for tumors with elevated ER is comparatively favorable [16].

Amplification and overexpression of HER-2-neu have been shown in 25–30% of individuals with breast cancer. In several investigations, HER-2-neu amplification/overexpression was found to negatively impact disease-free survival and survival durations, especially in individuals with positive lymph nodes [17]. The study by Fourati *et al*. [18] found that 966 patients with breast cancer had 4 subtypes based on molecular categorization, with 51% having luminal A, 13% having luminal B, 13% having HER-2+, and 22% having triple negative. 18 In our analysis, a total of 216 patients had 87 (52%) luminal B, 32 (19%) triple-negative, 29 (17%) luminal A, and 18 (11%) HER-2+. In contrast to popular belief, Luminal B was greater in both age groups. One way to understand this is as a clinicopathologic reflection of the possible genetic and regional variations. Our results, which come from the Europe-Central Mediterranean area, may differ from Western statistics because the majority of the data about breast cancer molecular subtypes comes from Western sources.

Luminal B and triple-negative tumors were more common in those aged 35 and younger among the molecular subtypes. The poor progression of breast cancer in those aged 35 and under may be explained by the intermediate and poor prognostic characteristics of these two subtypes. According to Carey *et al*. [19], premenopausal African-American women with breast cancer were more likely to have the triple-negative subtype of the disease than the luminal A subtype. In contrast to luminal A, Sorlie *et al*. [13] found that the HER-2+ and basal-like subtypes were linked to the lowest survival periods.

The strongest predictor of recurrence and death in early-stage breast cancer, according to Kronqvist *et al*. [20], was the level of Ki-67 immunopositivity in tumor cells of 10% or higher. According to the same study, patients who had ER-positive of less than 20% and p53 positivity of more than 30% were linked to a worse prognosis [20]. At the time of diagnosis, metastases are present in 5% to 15% of invasive breast cancers [21]. 9.3% of individuals in our research who were diagnosed before the age of 35 had metastases. These findings align with data from the literature. For those aged 36 years and up, the ratio was 14.6%. The two groups differed significantly from one another statistically.

According to Ihemelandu *et al*. [22], patients under 35 had a lower average survival time than those 36 and older [22]. Despite being prevalent in the 36–50 years age range, the Luminal A subtype does not have a lengthy survival period. Despite having a greater incidence of basal cell-like, the age group of 51–65 years had the longest mean survival time when compared to the age groups of 36–50 years and 66–80 years. As a result, cancers that develop in younger and older age groups may differ.

The prognosis for young women with breast cancer is worse. The prognosis of breast cancer is known to be strongly correlated with new molecular categorization. However, no statistically significant variation in molecular subtypes between the two different age groups was found in our investigation. The limited size of the research cohort may account for this, but it may also suggest that age is a separate predictive factor from the other clinicopathologic characteristics. However, given that the biggest subgroup in the very young population had Luminal B and triple negatives, this diversion may account for the disease's worse prognosis.

Conclusion

The poor prognosis of younger individuals indicates that the tumor biology of their breast cancer subtypes differs. The unique prognostic characteristics in this group must thus be demonstrated to plan the appropriate treatment method. More research on the topic is needed, including bigger case series and genotypic analysis.

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