RESEARCH ARTICLE

Clinicopathologic Features and Molecular Subtypes of Breast Cancer in Young Women (Age ≤35)

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Abstract

Introduction: Breast cancer in young women is a relatively rare disease; however it tends to be more aggressive and is the leading cause of cancer death in this population. The aim of this study is to investigate the clinical and biological features of breast cancer arising in young Turkish breast cancer patients. Materials and Methods: Patients with breast cancer aged 35 or less (≤35 years) were selected for the study. In total 211 cases were included. Pathologic features; histologic subtypes, grade, lymphovascular invasion, axillary involvement, and stage were recorded for each. Results: The most common subtype was luminal B (36.5%), followed by luminal A (30.8%), triple negative (23.2%) and HER2+(9.5%) subtypes. Twelve percent of the patients had stage 4, 32.7% had stage 3, 46.4% had stage 2, and 6.2% had stage 1 disease at the time of diagnosis. Mean tumour diameter was 3.87 cm (range 0.3-13 cm). The axillary lymph nodes were positive in 74.4% of the patients, while lympho-vascular invasion was seen in 56.4%. Some 9.5% of patients had grade 1, 51.2% had grade 2, and 31.8% had grade 3 tumors. Conclusions: Young women with breast cancer in Turkey are more likely to present with luminal B subtype. Tumors in young women are more likely to present with advanced disease, to be high grade and and to have more lymphovascular invasion. Further research should focus on whether we need new treatment strategies for young patients with breast carcinoma.

Keywords: Young patients - breast cancer - molecular characteristics - clinicopathological features - Turkey

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Introduction

Breast cancer is the most frequent cancer among women and it is the second leading cause of cancer death around the world (Ferlay et al., 2010; DeSantis et al., 2011). Breast cancer in women under 40 years is not a common condition. However, prevalence of breast cancer in pre- menopausal women has been increasing in several countries over the last years (Cardoso et al., 2012; Keramatinia et al., 2014). Around 6.6% of all breast cancer cases are diagnosed in women less than age 40, 2.4%of women less than 35, and 0.65% in women less than 30 (Anders et al., 2009; Fredholm et al., 2009). 2.8% of breast lesions under the age of 25 years were malignant (Khursid et al., 2013).

Breast cancer tends to be more aggressive in young women. Young breast cancer patients present with more advanced stage. A study from Mount Sinai medical Center, New-York had demonstrated that patients younger than 36 years have larger tumors, more nodal involvement, and are more likely to be diagnosed with stage II or III cancer than the patients above 36 years (Gajdos et al., 2000). As mammography is not recommended in women less than 40 years they usually present with a palpable mass and it is concluded that delays in diagnosis may contribute to later stage (Friedman et al., 2006; Ruddy et al., 2014). Tumors in young women are more likely to be high grade, and to have high proliferation index and lymphovascular invasion (Thapa et al., 2013).

Many studies have confirmed the increased proportion of hormone receptor (HR) negativity and human epidermal growth factor receptor 2 (HER2) over expression in young women with breast cancer (Bleyer et al., 2008; Keegan et al., 2012). Young women were most likely to be diagnosed with HR+/HER2- subtype of breast cancer, followed by triple negative, HR+/HER2+ and HR-/HER2+ subtypes. However compared with older women young women had higher proportions of HR+/HER2+, triple negative and HR-/ HER2+ breast cancer (Keegan et al., 2012).

Despite discrepancies in adverse prognostic features, younger age has been shown to be an independent predictor of adverse outcome. A retrospective evaluation

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of more than 1,200 women diagnosed with early-stage breast cancer evaluated the relationship between age, typical prognostic factors, treatment, and patient outcome. Interestingly, age younger than 35 proved to be a powerful independent prognostic factor in multivariate analyses, including all potential patient, treatment, and pathology variables, and this was true for time to recurrence, time to distant failure, and overall mortality (Nixon et al., 1994). A second retrospective study evaluating more than 200,000 women in the SEER database, who were diagnosed with breast cancer between the years of 1988-2003, revealed that those under the age of 40 were 39% more likely to die when compared to those age 40 or older . Moreover, the highest mortality disparity between younger (<40 years) and older women (≥40 years) was present in early stage, rather than later stage disease (Gnerlich et al., 2009).

The aim of this study is to investigate the clinical and biological features of breast cancer arising in young Turkish breast cancer patients.

Materials and Methods

Patients with breast cancer aged 35 or less (≤35 years) were selected for the study. In total 211 patients were included. Pathologic features; histologic subtypes, grade, lymphovascular invasion, axillary involvement, stage was recorded. Tumour staging was performed according to the 7th edition of American Joint Committee Cancer TNM staging for breast carcinoma. Four subtypes were defined: 1) Luminal A; oestrogen receptor (ER) + and/or progesterone receptor (PR) +, HER2 -, grade 1 or grade 2 tumours, 2) Luminal B; ER + and/or PR + and HER2 + tumours or ER+ and /or PR+ and HER2- grade 3 tumours, 3) HER2+; ER -, PR- and HER2 + tumours, 4) Triple negative; ER-, PR-,HER2- tumours. HER2 status was evaluated with immunochemistry and +3 was defined as positive, those with +2 were further evaluated by FISH. Statistical analysis was performed using the SPSS 16.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA).

Results

211 young patients with breast cancer were included. All were women. Median age was 32 (23-35). Twelve percent of the patients had stage 4, 32.7% of patients had stage 3, 48.3% of patients had stage 2, 6.6 % of patients had stage 1 disease at the time of diagnosis. Twenty six patients had metastatic disease and the most common site of metastasis was bone (62% of metastatic patients). Fifteen percent of the patients were treated with neoadjuvant chemotherapy. The majority of patients underwent surgical treatment with curative intent. The most common surgery was mastectomy with axillary lymph node dissection (76.8%). Breast conserving surgery was performed in only 33 patients (15.6%). Three of the patients had bilateral breast carcinoma at the time of diagnosis. Seven of the patients diagnosed with breast cancer in the contra lateral breast during follow up.

The most common histologic subtype was invasive ductal carcinoma (80.1%). Lobular carcinoma, medullary carcinoma, mixed types and other types were 4.7%, 4.3%, 4.7% and 3.3% respectively. Mean tumour diameter was 3.87 cm (range 0.3-13 cm). The axillary lymph nodes were positive in 74.4% of the patients. Mean positive lymph nodes were 6.66 (0-42). Lympho- vascular invasion was seen in 56.4% of the patients. 9.5% of patients had grade 1, 51.2% had grade 2, 31.8% had grade 3 tumors. ER was positive in 56.4% and PR was positive in 39.8% of the patients. CerbB2 was +3 in 21.3% of the patients, and +2 in 9.5% of the patients. From 20 patients who had cerbB2 +2 by immunochemistry 14 had cerbB2 positive disease by FISH. The most common subtype was luminal B (36.5%) followed by Luminal A (30.8%), triple negative (23.2%) and HER2+ (9.5%) subtypes.

Table 1. Clinical and Biological Features of Young Patients (≤35 years) with Breast Cancer (n=211)

Stage	I	15	(6.2%)
	II	102	(48.3%)
	III	69	(32.7%)
	IV	26	(12.3%)
Histology	ductal carcinoma	169	(80.1%)
	lobular	10	(4.7%)
	medullary	9	(4.3%)
	mixed	10	(4.7%)
	others	7	(3.3%)
T	T1	31	(14.7%)
	T2	107	(50.7%)
	T3	56	(26.5%)
	T4	13	(6.2%)
N	Node negative	54	(25.6%)
	Node positive	157	(74.4%)
Metastasis	M0	180	(85.3%)
	M1	26	(12.3%)
Tm grade	Grade 1	20	(9.5%)
	Grade 2	108	(51.2%)
	Grade 3	67	(31.8%)
	Unknown	16	(7.6%)
ER	Negative	92	(43.6%)
	Positive	119	(56.4%)
PR	Negative	127	(60.2%)
	Positive	84	(39.8%)
cerbB2 (IHC and/or FISH)	Negative	157	(74.4%)
	Positive	54	(25.6%)
Molecular subtypes	Luminal A	65	(30.8%)
	Luminal B	77	(36.5%)
	Triple negative	49	(23.2%)
	HER2+	20	(9.5%)
Surgery	None	13	(6.2%)
	BCS	33	(15.6%)
	MRM	162	(76.8%)
Neoadjuvant chemotherapy	Yes	32	(15.2%)
	No	179	(84.8%)

Discussion

Breast cancer is a relatively rare disease in young women, only 2.4% of all breast cancers in women less than 35 years old (Anders et al., 2009; Fredholm et al., 2009). In this study we analyzed the molecular subtypes and clinicopathological characteristics in young women (≤35 years) with breast carcinoma. Luminal B was the most common subtype in this population, followed by Luminal A, triple negative and HER2 + subtypes. Our study is in parallel with the results of the Colliens et al.

They revealed a lover proportion of Luminal A disease and a higher proportion of Luminal B disease in young breast cancer patients compared to numbers from population based studies (Collins et al., 2012). Wei reported that the Luminal B and triple negative were the most common subtypes in patients younger than 35 years, while in the Luminal B and triple negative subtypes patients <35 years had a higher risk of death (Wei et al., 2013). Other studies reported that Luminal A was the most common subtype in the young breast cancer patients (Lin et al., 2009; Tang et al., 2011). There were more triple negative and less Luminal A tumors in the young group compared with the elderly (Tang et al., 2011). A number of studies have showed that differences in biologic subtypes may vary by race as a function of age. In the Carolina Breast Cancer Study 39 of premenopausal African-American women had basal like breast cancers, while 36% had Luminal A cancers. These rates were reported in comparison to the the 16% of non-African American premenopausal women who had basal like cancers, and 54% who had Luminal A subtype (Carey et al., 2006).

Thapa et al. reported that in young breast cancer patients (≤40 years) larger tumor size, positive lymph nodes, lymphatic and vascular invasion, grade 2-3 tumors were more common (Thapa et al., 2013). In our study the axillary lymph nodes were positive in 74.4% of the patients. A retrospective study from Denmark of 10,356 women diagnosed before 50 years reported that patients ≤35 years were at higher risk of being node positive (51% *vs* 46%, p=0.02) compared with the patients between 35-50 years (Kroman et al., 2000). A study from Mount Sinai Hospital showed that patients younger than 36 years had larger tumors, more nodal involvement and more likely to be diagnosed with stage 2 or 3 cancers (Gajdos et al., 2000). In our study 81% of the patients were diagnosed with stage 2-3 tumors. This can be due to the lack of screening programmes in this age group. A recent evaluation within the National Comprehensive Cancer Network Breast Cancer Outcomes Database Project revealed that women diagnosed with breast cancer at the age of ≤40 years suggested that the symptomatic presentation instead of a mammographic abnormality were more common in young women and associated with diagnostic delays (Partridge et al., 2010). Moreover clinical and radiological examinations in younger women have a limited accuracy, which might lead to a delay in the diagnosis (Di Nubila et al., 2006).

Johnson had reported that the incidence of breast cancer with distant involvement at the time of diagnosis for women aged 25-39 years is increasing (Johnson et al., 2013). In our study 12% of the patients had metastatic disease at the time of diagnosis. This is higher than it is reported in the POSH study (2.5%) where women aged ≤40 years were recruited (Copson et al., 2014).Our finding is similar with another study from Turkey; Uyetürk et al. reported that 12.6% of breast cancer patients were presented with stage IV disease. There was no difference between stage IV and other stages in terms of age at diagnosis (Uyeturk et al., 2013).

The most common surgery was mastectomy with axillary lymph node dissection (76.8%). Breast conserving surgery was performed in only 33 patients (15.6%). Young age is an important and independent risk factor for local recurrence after breast cancer surgery (Miles et al., 2012). Age younger than 35 years is not only a risk factor for local recurrence, it is also proved to be an independent prognostic factor for time to recurrence, time to distant failure, and overall mortality for patients with breast cancer (Nixon et al., 1994). No survival differences are seen in retrospective series comparing BCT and mastectomy (Litiere et al., 2012). Young age is not a contra indication for breast conservation, but the risks should be discussed with the patient.

Three of the patients had bilateral breast carcinoma at the time of diagnosis. Seven of the patients were diagnosed with breast cancer in the contra lateral breast during follow up. Diagnosis of breast cancer in very young patients raises the suspicion of BRCA mutation. In patients with BRCA mutation contra lateral breast cancer risk is 40% at 10 years (Metcalfe et al., 2004). However BRCA testing is not available in most of the hospitals and young women with breast carcinoma are not routinely tested for BRCA mutations in Turkey.

Young women with breast cancer in Turkey are more likely to present with Luminal B subtype. Tumors in young women are more likely to present with advanced disease, to be high grade and and to have more lymphovascular invasion. Further research should investigate whether we need new treatment strategies in young patients with breast carcinoma.

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References

Anders CK, Johnson R, Litton J, Phillips M, Bleyer A (2009). Breast cancer before age 40 years. *Semin Oncol*, **36**, 237-49.

Bleyer A, Barr R, Hayes-Lattin B, et al (2008); Biology and Clinical Trials Subgroups of the US National Cancer Institute Progress Review Group in Adolescent and Young Adult Oncology. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer*, **8**, 288-98.

Cardoso F, Loibl S, Pagani O, et al (2012); European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer*, **48**, 3355-77.

Carey LA, Perou CM, Livasy CA, et al (2006). Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*, **295**, 2492-502.

Collins LC, Marotti JD, Gelber S, et al (2012). Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. *Breast Cancer Res Treat*, **131**, 1061-6.

Copson E, Maishman T, Gerty S, et al (2014). POSH study steering group, Eccles D. Ethnicity and outcome of young breast cancer patients in the United Kingdom: the POSH study. *Br J Cancer*, **110**, 230-41.

DeSantis C, Siegel R, Bandi P, Jemal A (2011). Breast cancer statistics, 2011. *CA Cancer J Clin*, **61**, 409-18.

Di Nubila B, Cassano E, Urban LA, et al (2006). Radiological features and pathological-biological correlations in 348

women with breast cancer under 35 years old. *Breast*, **15**, 744-53.
Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.
Fredholm H, Eaker S, Frisell J, et al (2009). Breast cancer in young women: poor survival despite intensive treatment. *PLoS One*, **11**, 7695.
Friedman LC, Kalidas M, Elledge R, et al (2006). Medical and psychosocial predictors of delay in seeking medical consultation for breast symptoms in women in a public sector setting. *J Behav Med*, **29**, 327-34.
Gajdos C, Tartter PI, Bleiweiss IJ, Bodian C, Brower ST (2000). Stage 0 to stage III breast cancer in young women. *J Am Coll Surg*, **190**, 523-9.
Gnerlich JL, Deshpande AD, Jeffe DB, et al (2009). Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg*, **208**, 341-7.
Johnson RH, Chien FL, Bleyer A (2013). Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. *JAMA*, **309**, 800-5.
Keegan TH, DeRouen MC, Press DJ, Kurian AW, Clarke CA (2012). Occurrence of breast cancer subtypes in adolescent and young adult women. *Breast Cancer Res*, **14**, 55
Keramatinia A, Mousavi-Jarrahi SH, Hiteh M, Mosavi-Jarrahi A (2014). Trends in incidence of breast cancer among women under 40 in Asia. *Asian Pac J Cancer Prev*, **15**, 1387-90.
Khurshid A, Faridi N, Arif AM, Naqvi H, Tahir M (2013). Breast lesions in adolescents and young women in Pakistan-a 5 year study of significance of early recognition. *Asian Pac J Cancer Prev*, **14**, 3465-7.
Kroman N, Jensen MB, Wohlfahrt J, et al (2000). Factors influencing the effect of age on prognosis in breast cancer: population based study. *BMJ*, **320**, 474-8.
Lin CH, Liau JY, Lu YS, et al (2009). Molecular subtypes of breast cancer emerging in young women in Taiwan: evidence for more than just westernization as a reason for the disease in Asia. *Cancer Epidemiol Biomarkers Prev*, **18**, 1807-14.
Litiere S, Werutsky G, Fentiman IS, et al (2012). Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol*, **13**, 412-9.
Metcalfe K, Lynch HT, Ghadirian P, et al (2004). Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol*, **22**, 2328-35.
Miles RC, Gullerud RE, Lohse CM, et al (2012). Local recurrence after breast-conserving surgery: multivariable analysis of risk factors and the impact of young age. *Ann Surg Oncol*, **19**, 1153-9.
Nixon AJ, Neuberg D, Hayes DF, et al (1994). Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol*, **12**, 888-94.
Partridge AH, Hughes ME, Ottesen RA, et al (2012). The effect of age on delay in diagnosis and stage of breast cancer. *Oncologist*, **17**, 775-82.
Ruddy KJ, Gelber S, Tamimi RM, et al (2014). Breast cancer presentation and diagnostic delays in young women. *Cancer*, **120**, 20-5.
Tang J, Wu CC, Xie ZM, Luo RZ, Yang MT (2011). Comparison of Clinical Features and Treatment Outcome of Breast Cancers in Young and Elderly Chinese Patients. *Breast Care (Basel)*, **6**, 435-440.
Thapa B, Singh Y, Sayami P, et al (2013). Breast cancer in young women from a low risk population in Nepal. *Asian Pac J Cancer Prev*, **14**, 5095-9.
Uyeturk U, Tatli AM, Gucuk S, et al (2013). Risk factors for stage IV breast cancer at the time of presentation in Turkey. *Asian Pac J Cancer Prev*, **14**, 7445-9.
Wei XQ, Li X, Xin XJ, Tong ZS, Zhang S (2013). Clinical features and survival analysis of very young (age<35) breast cancer patients. *Asian Pac J Cancer Prev*, **14**, 5949-52.