RESEARCH ARTICLE

Risk Factors for Stage IV Breast Cancer at the Time of Presentation in Turkey

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Abstract

Background: Breast cancer (BC) is the one of the most common cancers in women. It is also a leading cause of death. Unfortunately, some patients initially present with distant metastases and are diagnosed with stage IV disease that is nearly always, by then, incurable. This retrospective analysis investigated the risk factors for stage IV BC that may underlie such late presentation. Materials and Methods: In all, 916 patients with BC who visited the medical oncology polyclinic of eight different centres in Turkeybetween December 2011 and January 2013 were analysed. Results: A total of 115 patients (12.6%) presented with stage IV disease. In univariate analysis; to comparing these with patients at other stages, no statistical difference was found for median diagnosis age or age at menarche (p=0.611 and p=0.820), whereas age at menopause and age at first live birth were significant (p=0.018 and p=0.003). No difference was detected in terms of accompanying diseases, use of oral contraceptives and hormone replacement therapy, smoking, alcohol consumption and the rate of family history of BC between the patients (p=0.655, p=0.389, p=0.762, p=0.813, p=0.229, p=0.737). However, screening methods were employed less often, the rate of illiteracy was higher, and the rate of other cancers was higher in patients with stage IV BC (p=0.022, p=0.022, p=0.018). No statistical difference was observed between the patients in terms of tumour histopathology, and status of oestrogen receptor, progesterone receptor, or human epidermal growth factor-2 receptor (p=0.389, p=0.326, p=0.949, p=0.326). Grade 3 tumours were more frequent in patients with stage IV disease (p<0.001). On multivariate analysis, risk factors for stage IV breast cancer at the time of presentation were found to be age at first live birth and educational level (p=0.003 and p=0.047). Conclusions: Efforts should be made to perform mammography scans, in particular, at regular intervals through national training programs for all women, particularly those with family histories of breast and other types of cancer, and to establish early diagnosis of BC long before it proceeds to stage IV. Additionally, women's education had better be upgraded. In order to make women aware of BC, national education-programmes must be organised.

Keywords: Stage IV breast cancer - risk factors - mammography - education - Turkey

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Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and is a leading cause of cancer death among women worldwide, accounting for 23% of cancer diagnoses (1.38 million women) and 14% of cancer deaths (458,000 women) per year (Jemal et al., 2011 ; Redig and McAllister, 2013).There are many risk factors associated with the development of BC. They may involve age, gender, race, benign breast diseases, family history of BC, life style, diet-related factors, smoking, long-term exposure to high-dose endogenous or exogenous estrogens, environmental factors, and exposure to ionizing radiation (Worsham et al., 2007; Cheng et al., 2008; Iwasaki and Tsugane, 2011; Johnson et al., 2011; Xue et al., 2011; Zhang et al., 2011; Kruk and Czerniak, 2013;

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Mirkin et al., 2013; Reynolds, 2013; Wang et al., 2013; Walsh and Schneider, 2013).

The spread of the primary tumour beyond the chest wall and regional lymph nodes is defined as metastasis (Marino et al., 2013). Despite improvements in diagnostic methods, approximately 10% of patients present with stage IV disease (Ruiterkamp et al., 2012). The disease at this stage is typically considered incurable (Largillier et al., 2008; Lobbezoo et al., 2013). Thus, the stage at the time of diagnosis is very important in terms of mortality.

In this retrospective analysis, we investigated whether there were any differences in terms of risk factors between patients with stage IV disease and those who presented with other stages of the disease.

Materials and Methods

In total, 916 patients diagnosed with BC who presented to the medical oncology polyclinics of Abant İzzet Baysal University, Faculty of Medicine, Van Training and Research Hospital, Ankara Oncology Training and Research Hospital, Ali Osman Sönmez Oncology Hospital, Balikesir State Hospital, Akdeniz University, Faculty of Medicine, Yildirim Beyazit University Faculty of Medicine and Sakarya Training and Research Hospital between December 2011 and January 2013 were analysed retrospectively. Data regarding the patients including age at diagnosis, age at menarche, menopausal status, age at menopause if applicable, age at first live birth, accompanying disease(s), use of oral contraceptives (OC) and hormone replacement (HR) therapy, history of smoking and alcohol consumption, educational status, whether screening was performed regarding BC prior to the diagnosis, family history of BC or other types of cancer, tumour histopathology, tumour receptor properties, and the grade and stage of the disease were recorded.

Statistical analyses were performed using the SPSS software (ver. 20.0 for Windows; IBM Corp., Armonk, NY). The variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov–Smirnov/ Shapiro–Wilk tests) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standart deviations for normally distributed variables. Since age of diagnosis, age at menarche, age at menopause and age at first live birth values were normally distributed; the Student's test was used to compared these parameters between the metastatic and nonmetastatic groups.

Descriptive analyses of the variables with a non-normal distribution were performed using the Mann–Whitney U test. The groups of age, accompanying diseases, the use of OC and HR therapy, smoking and alcohol consumption, educational status, whether screening was performed prior to diagnosis, family history of BC or other types of cancer, and tumour properties were analysed using cross-tables with respect to whether the patient was within the metastatic stage or not. P values<0.05 were considered to indicate statistical significance

For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Hosmer–Lemeshow goodness of fit statistics was used to assess model fit. A 5% type–I error level was used to infer statistical significance.

Results

With respect to disease stage, 115 (12.6%), 461 (50.3%), 225 (24.6%), and 115 (12.6%) patients were at stages I, II, III, and IV, respectively. No statistical difference was observed between stage IV and other stages in terms of the age at diagnosis or age at menarche (p=0.611 and 0.820, respectively).

The mean age at menopause was 49.6±4 years in stage IV, and 48.2±4.4 years in other stages (p=0.018). The mean age at first live birth was 18.7±7.8 years in stage IV, and 20.8±6.5 years in the other stages (p=0.003; Table 1).

Table 1. Comparison of Demographic Characteristics of the Patients

	Metastasis Mean±SD	No Metastasis Mean±SD	p value
Age at diagnosis	51.3±13.6	50.7±11.4	0.611
Age at menarche	12.9±1.6	13±1.5	0.820
Age at menopause	49.6±4.0	48.2±4.4	0.018*
Age at first live birth	18.7±7.8	20.8±6.5	0.003*

*SD:Standard Deviation

Table 2. Comparison of Risk Factors of Patient

	Metastasis n (%)	No Metastasis n (%)	p value
Accompanying diseases			0.655
Yes	43 (37.4)	322 (40.2)	
No	72 (62.6)	479 (59.8)	
Use of OC			0.389
Yes	14 (12.2)	122 (15.2)	
No	101 (87.8)	679 (84.8)	
HR Therapy			0.762
Yes	11 (9.6)	84 (10.5)	
No	104 (90.4)	717 (89.5)	
Smoking			0.813
Yes	15 (13)	111 (13.9)	
No	100 (87)	690 (86.1)	
Alcohol consumption			0.229
Yes	0 (0)	10 (1.29)	
No	115 (100)	791 (98.8)	
Level of Education			0.022*
Illiterate	29 (25.2)	85 (10.6)	
Literate	13 (11.3)	63 (7.9)	
Primary school	53 (46.1)	425 (53.1)	
Senior high school	14 (12.2)	67 (8.4)	
University	3 (2.6)	21 (2.6)	
Unknown	3 (2.6)	146 (17.5)	
Screening			0.022*
Yes	4 (3.5)	81 (10.1)	
No	111 (96.5)	720 (89.9)	
Family History of BC			0.737
No	99 (86.1)	694 (86.6)	
First-degree relative	6 (5.2)	74 (9.2)	
Second-degree relative	10 (8.7)	33 (4.1)	
Other types of cancer			0.018*
Yes	38 (33.1)	188 (23.5)	
No	77 (66.9)	613 (76.5)	

*OC:oral contraceptive , HR:hormone replacement, BC:Breast cancer

In all, 12 (10.4%) patients from the stage IV group and 47 (5.9%) patients from the other groups were nulliparous. Note the higher percentage of nulliparous patients with stage IV disease (p<0.001).

No statistically significant difference was observed between patients who presented with stage IV disease and those without metastasis in terms of accompanying diseases, the use of OC and HR therapy, and history of smoking or alcohol consumption (p=0.655, 0.389, 0.762, 0.813, and 0.229, respectively).

With respect to level of education, more illiterates and literates who did not receive any formal education had stage IV disease than other groups (p=0.022). Screening methods were used more frequently in patients without metastasis than in those with metastasis (p=0.022). However, only 85 (9.2%) patients out of the entire patient population were subjected to any pre diagnosis screening.

A family history of BC and other types of cancer was found to be more common in patients with stage IV disease versus those not presenting with metastasis (p=0.737 and 0.018, respectively; Table 2).

No statistically significant difference was found between patients who had stage IV BC and those who were at other stages at the time of admission in terms of tumour pathology, oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER-2) receptor (p=0.389, 0.326, 0.949, and 0.326, respectively). The rate of grade 3 tumours was higher in patients with stage IV disease (p <0.001; Table 3).

In the multivariate analysis, the statistical difference was not found between the age at diagnosis, age of menopause; screening,family history of BC and grades of tumor, as a risk factor in the metastatic BC (p=0.362, p=0.281, p=0.327, p=0.624, p=0.772, p=0.423). However, the statistically difference was found between age at first live birth and education 0.937(95% CI: 0.898-0.978), p=0.003 and 2.010 (95% CI: 1.010-3.999), p=0.047, respectively; Table 4).

Table 3. Comparison of the Tumour Properties of Patients

		Metastasis n (%)	No Metastasis n (%)	p value
Tumour pathology	IDC	100 (87)	672 (83.9)	0.389
	ILC	11 (9.6)	90 (11.2)	
	Other	4 (3.5)	39 (4.9)	
ER	Negative	34 (29.6)	250 (31.2)	0.326
	Positive	81 (70.4)	551 (68.8)	
PR	Negative	42 (36.5)	295 (36.8)	0.949
	Positive	73 (63.5)	506 (63.5)	
HER2	Negative	70 (60.9)	525 (65.5)	0.326
	Positive	45 (39.1)	276 (34.5)	
Grade	1	3 (2.6)	75 (9.4)	<0.001*
	2	41 (35.7)	367 (45.8)	
	3	43 (37.4)	217 (27.1)	
	Unknown	28 (24.3)	142 (17.7)	

*IDC: Invaziv ductal carcinoma, ILC: Invaziv lobuler carcinoma, ER: oestrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor

Table 4. In Multivariate Analysis, Risk Factors for Metastatic Breast Carcinoma

Risk Factors	OR(95%CI)	p values
Age at diagnosis	1.017 (0.980-1.056)	0.362
Age at menopause	1.044 (0.965-1.131)	0.281
Age at first live birth	0.937 (0.898-0.978)	0.003*
Screening	1.738 (0.576-5.248)	0.327
Education	2.010 (1.010-3.999)	0.047*
Other types of cancer	0.851 (0.445-1.628)	0.626
Tumor grade(1)	0.583 (0.067-5.036)	0.624
Tumor grade(2)	0.892 (0.408-1.949)	0.775
Tumor grade(3)	1.382 (0.626-3.051)	0.423

OR:Odds Ratio CI:Confidence Interval

Discussion

The incidence of BC increases with age. In one study, 34.3% of patients with BC were ≥ 65 years (Kilciksiz et al., 2012). Advanced age was determined to be important among the reasons for admission with stage IV BC. In a study that investigated reasons for admission at advanced stages, particularly in patients with BC, advanced age was determined to be an important factor (Chang et al., 2003; Burgess et al., 2006; Ermiah et al., 2012; Macià et al., 2013; Ghazali et al., 2013). Another study reported that patients with metastasis at the time of diagnosis were older than those who became metastatic during follow-up (median age: 61 years) and that 77.3% of them were in the post-menopausal period (Jimeno et al., 2004).The most important reason for delay was determined to be fear of being diagnosed with cancer and the complications that may develop during cancer treatment in older women (Burgess et al., 2006). No difference was detected between patients at stage IV and the other patients with respect to the age of diagnosis in our analysis.

Factors including early age at menarche and late age at menopause, nulliparity, advanced age at the time of first pregnancy, limited number of births, and long-term exposure to endogenous estrogens are considered to increase the risk for BC (Daniilidis et al., 2010). In a study performed in Norway, early age at menarche, late age at menopause, advanced age at the time of first pregnancy, and reproductive events were found to have life-long effects on the risk of BC (Horne et al., 2013). In the present study, age at menopause was also higher in patients with stage IV disease. The rate of nulliparous women was higher in these patients.

Exogenous oestrogen use is also considered to increase the risk of BC. In a previous study, the use of OC was found to increase the risk of BC whereas reduced use of OC resulted in a decreased risk of BC (Chlebowski et al., 2009).

Similarly, HT therapy has been found to result in an increased incidence of BC (De et al., 2010; Neutel and Morrison, 2010; Hayes et al., 2013). However, in the present study, no difference was established in terms of the use of OC or HR therapy.

The relationship between smoking and BC is controversial. Although certain studies have reported that smoking increases the risk of BC, a number of studies did not find a relationship between active or passive smoking and BC (Xue et al., 2011; Johnson et al., 2012; Reynolds, 2013). Several studies have shown that alcohol consumption results in an increased risk of BC, in particular hormone receptor-positive BC (Ma et al., 2006; Novelli et al., 2008; Neutel and Morrison, 2010;

Hayes et al., 2013). In the present study, neither smoking nor alcohol consumption was associated with risk for BC.

The incidence of BC was lower in literate women than in illiterates or those who were literate but lacked a formal education. This could be related to economic levels and accessibility to health services (Kruk, 2007). Previous studies conducted on BC patients also showed that illiteracy was among the reasons for admission with advanced-stage disease (Talpur et al., 2011; Ermiah et al., 2012; Mohiuddin et al., 2012).

Screening is important to identify BC at an early stage. Advanced age and low levels of education are among the reasons for not undergoing mammography (MMG) screening (Wells and Roetzheim, 2007; Reyes-Ortiz and Markides, 2010). MMG screening studies were conducted in Australia to reduce mortality from BC (Roder et al., 2008; Morrell et al., 2012). In another study, mortality due to BC was reduced by 26% in patients who were invited to a screening program for BC (Njor et al., 2012). In other related studies, MMG screening resulted in less DB-related mortality (van Schoor et al., 2011; Puliti and Zappa, 2012) and reduced BC by 15% compared to self- and clinical breast examinations in patients aged 39-69 years (Nelson et al., 2009). Awareness of breast health, being educated, and BC screening may be of great importance in reducing the incidence of late-stage BC (Gullatte et al., 2006; Banning, 2011).

Screening mammography may be effective for women with a first-degree family history of breast cancer, irrespective of level of familial risk (Walker et al., 2013).

Family history is one of the most important risk factors for BC, with 15-20% of patients with BC reporting it in other family members. In cases with one patient diagnosed with BC among first-degree relatives of the patient, the risk is increased by 1.8 times. In cases with two affected individuals among first-degree relatives, the risk is increased by 2.9 times (Schairer et al., 2013).

We found the same pattern in the present study. In addition, although the presence of a family history of cancer might be expected to increase awareness, the exact opposite was observed. It is possible that fear of social exclusion due to the diagnosis of cancer and possible complications due to therapies may be reasons for ignoring certain symptoms and seeking medical advice only at an advanced stage.

Consequently, it can be concluded that women, particularly those with a family history of cancer, should be provided MMG screening at certain intervals via national training/screening programs, and that this is of great significance for diagnosing BC at an early stage, at which it may be curable, before it proceeds to a metastatic phase.

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