RESEARCH ARTICLE

Influence of Ethnicity on Survival of Breast Cancer Patients in Turkey

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Abstract

Background: Kurdish women with breast cancer have more unfavorable prognostic factors than their Turkish and Arab counterparts. However, the effects of these factors on breast cancer survival among these ethnic groups remain unclear. We therefore investigated the impact of ethnicity on survival in breast cancer patients in Turkey. Materials and Methods: Ethnicity, age, stage at diagnosis, tumor characteristics, treatments given (surgery, chemotherapy, radiotherapy and hormone therapy), and survival times were recorded. Kaplan-Meier analysis was used to estimate the overall survival times and survival plots. Log-rank test was used to compare the survival curves.Results: Of the 723 breast cancer patients included in the study, 496 (68.7%) were Turkish, 189 (26.2%) were Kurdish, 37 (5.1%) were Arabic and 1 was Armenian. Kurdish women with breast cancer had larger tumor sizes and higher rates of hormone receptor negative tumors than Turkish and Arab patients. Mean follow-up time was 118.4 [95% Confidence Interval (CI): 95.4-141.3] months, and it was 129.9 (95% CI: 93.7-166.2), 124.2 (95% CI: 108.4-140.1) and 103.1 (95% CI: 85.9-120.4) months for Turkish, Arabic and Kurdish patients, respectively. Conclusions: Kurdish ethnicity is associated with higher rates of hormone receptor negative and triple-negative tumors and with worse survival. Clinical and epidemiological research is warranted to elucidate reasons underlying overall survival, variations in tumor biology, differences in treatment responsiveness, and effects of social factors among ethnic groups in Turkey.

Keywords: Breast cancer - ethnicity - hormone receptor status - survival

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Introduction

Breast cancer (BC) is a significant health problem among women worldwide. In western studies it has been reported that BC survival rates varies among different ethnic groups within the same national populations (Li et al., 2003; Spallek et al., 2012). Despite the overall improvements in BC survival for the last two decades, the difference in survival rates continues between ethnic groups (Wojcik et al., 1998). Several factors such as tumor biology and socioeconomic status (SES) are blamed for the survival disparity among ethnic groups.

Breast cancer (BC) survival may differ in different regions depending on breast health awareness, and diagnostic and therapeutic backgrounds in Turkey (Ozmen, 2008). Western studies implicated that ethnicity is a predictor of survival in BC (McKenzie and Jeffreys, 2009).

The impact of ethnicity on survival for BC has not yet been studied in 3 major ethnic groups (Turkish, Kurdish, and Arabic) living in Turkey. In the studies of Turkey and Western countries, the population of Turkey was all called as ''Turkish'', that is, the ethnicities of the women included in these studies were not specified or taken into consideration.

Using Gaziantep University Oncology Hospital-based cohort of BC patients from Turkey, we investigated the impact of ethnicity on survival for BC, and the possible mechanisms in order to explain the survival disparities.

Materials and Methods

723 women BC patients whose first diagnosis times were ranged from 1986 to 2011 referred to the Oncology Hospital included in the study. The study was approved by Institutional review board of School of Medicine and written informed consent was obtained from all patients. Patients' ethnicity, age and stage at diagnosis, menopausal status, pathologic diagnosis, tumor size, histological grade, hormone receptor [(HR); estrogen receptor (ER), progesterone receptor (PR)] status, human epidermal growth factor receptor 2 (HER2) status, past treatments (surgery, chemotherapy, radiotherapy and hormone therapy), and survival times were recorded.

Staging was performed based on the American Joint Commission on Cancer 2010 staging system. Tumor grade

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was defined based on Bloom-Richardson criteria as I, II, III, and other/unknown (Harris et al., 2007). ER and PR status was recorded on the basis of immunohistochemistry (IHC) [positive (when >5% of tumor cells stained positive during IHC testing), negative or unknown]. HER2 status was recorded on the basis of IHC score (negative: 0 and 1+, positive: 3+). Specimens scored 2+ were further evaluated by fluorescence in situ hybridization (FISH) technique (copies≤2: negative, copies>2: positive).

Statistical analysis: Frequency of distribution was calculated for tumor characteristics, age and stage at diagnosis, menopausal status, and treatment history (surgery, chemotherapy, radiotherapy and hormone therapy) in ethnic groups. Chi-square test was used for comparison of the distributions of tumor characteristics and treatment types among ethnic groups. Kaplan-Meier analysis was used to estimate the overall survival and log-rank test was used to compare the survival curves. Analyses were performed by using Statistical Package for the Social Sciences (SPSS, version 18) software.

Results

Of the patients included 496 (68.7%) were Turkish, 189 (26.2%) were Kurdish, 37 (5.1%) were Arabic and 1 was Armenian. The only Armenian woman was not included in the statistical analysis. Median age for all groups was 47 (20-84). 650 patients had invasive ductal (90%), 32 had lobular (4.4%) and 40 had other carcinoma (5.5%). No significant difference was found in terms of histopathology among ethnic groups. However, invasive lobular carcinoma was not encountered in Arabic women. Median tumor size was 3.7 (0.5-7.2) cm for all groups. Tumor size in Kurdish women was larger than in Turkish patients (p=0.006). Kurdish BC patients were generally diagnosed at later stages (p=0.06); p value did not reach a significant level however there was a trend towards significance (Table 1). ER-positive tumor rates were 75%, 59.8% and 75.7% for Turkish, Kurdish and Arabic women, respectively (Table 1). ER and PR-positive tumor rates between Turkish and Arabic women were similar but they were lower in Kurdish patients (p<0.001). HER2-positive tumor rates were similar among three ethnic groups (p>0.2). Triple-negative subtype (ER-/PR-/HER2-) rates were similar in Kurdish and Arabic women. Triple-negative subtype rates were lowest in Turkish patients (p=0.026) (Table 1). Compared to Turkish and Arabic women with BC, Kurdish women were significantly less likely to receive hormonal therapy due to more HR-negative tumors (p=0.001). However there were no significant treatment differences (surgery, chemotherapy and radiation therapy) among ethnic groups (Table 2).

Mean follow-up time was 118.4 (95% Confidence Interval (CI): 95.4-141.3) months for all groups; 129.9 (95% CI: 93.7-166.2), 124.2 (95% CI: 108.4-140.1) and 103.1 (95% CI: 85.9-120.4) months for Turkish, Arabic and Kurdish women with BC, respectively (Table 2). Compared to Turkish and Arabic women with BC, mean follow-up time was shorter in Kurdish patients (p=0.039). At the time of statistical analysis, 394 (79.4%) Turkish, 134 (70.9%) Kurdish and 33 (89.1%) Arabic women with

Table 1. Distributions of Tumor Characteristics among Ethnic Groups

Variable	% (n)				p-value
	All patients 100 (722)	Turkish 68.7 (496)	Kurdish 26.2 (189)	Arabic 5.1 (37)	
Histopathology					0.5
Ductal carcinoma	90.1 (650)	89.4 (443)	90.5 (171)	97.2 (36)	
Lobular carcinoma	4.4 (32)	5 (25)	3.7 (7)	-	
Other	9.5 (40)	5.6 (28)	5.8 (11)	2.8 (1)	
Tumor size (cm)					0.006
<2.0	9.8 (71)	10.4 (52)	7.4 (14)	13.5 (5)	
2.0 to <5.0	54.3 (392)	57.5 (285)	46 (87)	50.1 (20)	
≥5.0	35.2 (254)	31.3 (155)	46 (87)	32.4 (12)	
Unknown	0.7 (5)	0.8 (4)	0.6 (1)	-	
Stage					0.06
I	3.7 (27)	4.4 (22)	2.1 (4)	2.7 (1)	
II	42.5 (307)	45.7 (227)	36 (68)	32.4 (12)	
III	46.2 (334)	43.2 (214)	51.9 (98)	59.5 (22)	
IV	7.6 (54)	6.7 (33)	10 (19)	5.4 (2)	
Grade					0.09
1	5.6 (40)	7.1 (35)	2.7 (5)	-	
2	43.7 (315)	43.4 (215)	43.4 (82)	48.6 (18)	
3	44.1 (319)	42.9 (213)	47.6 (90)	43.2 (16)	
Unknown	6.6 (48)	6.6 (33)	6.3 (12)	8.2 (3)	
ER status					0.001
ER+	71.1 (513)	75 (372)	59.8 (113)	75.7 (28)	
ER-	27.8 (201)	24.2 (120)	38.1 (72)	24.3 (9)	
Unknown	1.1 (8)	0.8 (4)	2.1 (4)	-	
PR status					0.001
PR+	71.3 (515)	75.2 (373)	60.8 (115)	73 (27)	
PR-	27.2 (196)	23.4 (116)	37.1 (70)	27 (10)	
Unknown	1.5 (11)	1.4 (7)	2.1 (4)	-	
HER2 status					0.2
HER2+	29.6 (214)	27.8 (138)	33.9 (64)	32.5 (12)	
HER2-	69.4 (501)	71.4 (354)	64.6 (122)	67.5 (25)	
Unknown	1 (7)	0.8 (4)	1.5 (2)	-	
ER/PR status					
ER+/PR+	60.9 (440)	65.1 (323)	48.2 (91)	70.3 (26)	<0.001
ER+/PR-	10.2 (74)	10.1 (50)	11.6 (22)	5.4 (2)	0.4
ER-/PR+	10.5 (76)	10.3 (51)	12.6 (24)	2.7 (1)	0.1
ER-/PR-	17.3 (124)	13.7 (68)	25.5 (48)	21.6 (8)	0.001
Unknown	1.1 (8)	0.8 (4)	2.1 (4)	-	
Triple subtypes					
ER+/PR+/HER2+	28.5 (107)	15.1 (75)	12.2 (23)	24.3 (9)	0.1
ER+/PR+/HER2-	45.6 (329)	49.4 (245)	35.4 (67)	45.9 (17)	0.006
ER-/PR-/HER2+	8.2 (59)	6.6 (33)	12.2 (23)	8.1 (3)	0.05
ER-/PR-/HER2-	9.4 (68)	7.5 (37)	13.7 (26)	13.5 (5)	0.026

Table 2. Distributions of Age, Menopausal Status, Treatment Profile and Survival among Ethnic Groups

Variable	% (n)				p-value
	All patients 100 (722)	Turkish 68.7 (496)	Kurdish 26.2 (189)	Arabic 5.1 (37)	
Age					0.4
20-39	24.5 (177)	23.8 (118)	24.4 (46)	35.2 (13)	
40-49	31.4 (226)	30.7 (152)	34.3 (65)	24.4 (9)	
50-64	31.4 (227)	32(159)	29.2 (55)	35.2 (13)	
>65	12.7 (42)	13.5 (67)	12.1 (23)	5.2 (2)	
Menopausal status					0.9
Premenopausal	59.4 (429)	59.5 (295)	58.7 (111)	65.7 (23)	
Postmenopausal	40.6 (293)	40.5 (201)	41.7 (78)	34.3 (14)	
Treatment received					
Surgery	91.4 (660)	92.7 (460)	87.8 (166)	91.8 (34)	0.2
Chemotherapy	81.5 (589)	82.8 (411)	78.3 (148)	81 (30)	0.3
Radiotherapy	66.2 (478)	66.5 (330)	65 (123)	67.5 (25)	0.7
Hormonotherapy	63.4 (458)	67.5 (335)	51.8 (98)	67.5 (25)	0.001
Survival, months					0.03*
Mean (SD)	118.4 (11.7)	129.9 (18.5)	103.1 (8.8)	124.2 (8.1)	
Median	107	101	90	137	

*p for long rank test: among ethnic groups; SD: Standard Deviation

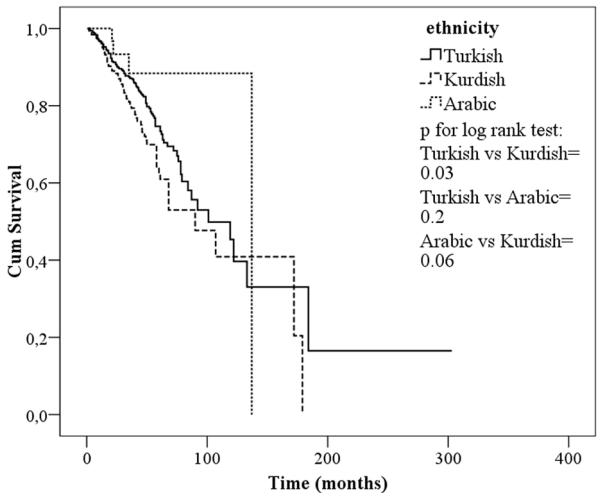

Figure 1. Cumnlative Overall Survival for 722 Women with Breast Cancer

BC were alive. Survival probability for five and ten years was 74.8% and 45.4% for Turkish patients and 60.9% and 40.8% for Kurdish patients (p=0.03, Figure 1).

Discussion

Impact of the ethnicity on survival rates was reported in previous studies among BC patients (Greend and Pai 2008; Bhoo-Pathy et al., 2012; Spallek et al., 2012; Abdullah et al., 2013). This is the first study from Turkey investigating the influence of ethnicity on survival in women BC population. In the present study, we found Kurdish women with BC had worse survival rates than Turkish and Arabic women, although all had health insurance and equal access to care.

Breast cancer (BC) survival disparities among ethnic groups are complex. Survival disparities among ethnic groups… several factors such as… cultural values… and response to treatment (Ma et al., 2010)." was corrected as "Survival disparities among ethnic groups have been explained by several factors such as tumor biology (Li et al., 2002; Rosenberg et al., 2005), SES, cultural values (Reynolds et al., 2000; Newman et al., 2002; Gordon, 2003; Soler-Vila et al., 2003), lifestyle (McKenzie and Jeffreys, 2009), and response to treatment (Ma et al., 2010).

Tumor biology may be influenced by ethnicity, because of the higher frequency of poor prognostic factors such as high grade, HER2 over-expression, HR-negative and triple-negative status in certain ethnic groups (Amend et al., 2006; Telli et al., 2011). Amend et al. (2006) reported that Europan-American women with BC are more likely to be diagnosed with high-grade, ER-negative, PR-negative and triple-negative tumors compared to African-American women. A study from South East Asia showed that Malay and Indian women with BC were more likely to present with unfavorable tumor characteristics (ER-negative, PR-negative or less differentiate tumors) than Chinese women (Bhoo-Pathy et al., 2012).

Our previous study (Kuzhan et al., 2013) and the present study demonstrated that ER and PR status were different among Turkish, Arabic and Kurdish women with BC, however, tumor grade and HER2 status were similar. ER-negative tumor type was higher in Kurdish patients than in Turkish and Arabic women. In addition, Kurdish and Arabic patients had higher rates of ER-/PR-negative and triple-negative tumors than Turkish women. According to our study study results overall survival rates were better in Turkish and Arabic patients than Kurdish patients. Worst survival of Kurdish patients might be explained by more HR-negative and triple-negative tumor rates seen in this ethnicity.

Socioeconomic status (SES) and cultural values are reported to have a relationship with survival disparities seen among ethnic groups. Ethnicity has often been thought to represent SES (i.e. education status, household income, and insurance, etc.) in western literatures (Brawley, 2002). In western populations, BC patients with low SES were correlated with younger age, larger tumor, more advanced stage, higher tumor grade and higher proportion of HR-negative tumors (Li et al., 2002; Rosenberg et al., 2005; Andaya et al., 2012). Patients with low SES were also associated with fewer mammographic screening, unequal access to treatment and poorer treatment adherence (Bradley et al., 2002; Schootman et al., 2003; Hersman et al., 2005). Finally, in western studies, low SES is reported to be associated with more aggressive tumor characteristics and a worse clinical outcome. Unfortunately in Turkey there is no study data whether ethnicity and SES is correlated. However, Adli et al. (2010) reported that in contrast to western studies, there was no significant difference among ethnic groups in Turkey with respect to time to diagnosis, mammographic screening, and access to health care. In addition, our prevous study showed that tumor grade, age and stage at diagnosis were similar among ethnic groups (Kuzhan et al., 2012). However, the present study revealed that Kurdish women with BC were associated with larger tumor sizes compared to Turkish and Arabic women and more advanced stage than Turkish women.

Lifestyle factors, i.e. diet and age at first childbirth, are increasingly being recognized as important prognostic factors of BC (Kroman et al., 1998; McKenzie and Jeffreys, 2009). Due to differences in religious and cultural practices, lifestyle profiles may differ between the ethnic groups in the same population. For example, Chinese women have fewer children, breast feed for shorter period and have their first child later compared to the Malay and Indian. The incidence of BC was highest among Chinese but they normally present at early stages with lesser tumor and consequently, their survival is the higher compared to other ethnic groups in Malaysia (Yip et al., 2006; Yusuf et al., 2013). Muslim ethnic groups migrated from Turkey are at a younger age at their first childbirth and less likely to have alcohol consumption compared to local-born non-Muslims. These factors may explain the differences in incidence and mortality between immigrants from Turkey and local-borns (Zeeb and Razum, 2003; Spallek et al., 2012).

Treatment response to hormone therapy and chemotherapy may be affected by genetic differences. Differences in activity of CYP450 group of enzymes which metabolize antihormonal drugs and higher

frequencies of polymorphisms within certain genes affecting the metabolism of doxorubicin have been reported before (Lal et al., 2007; Fan et al., 2008; Ma et al., 2010). Hence, differences in the effectiveness of some anticancer drugs among certain ethnic groups may partly explain the survival disparities.

We had detailed information about tumor characteristics, prognostic and predictive determinants, and treatment records, however we did not have clear evidence about the causes of deaths whether they related to BC or not. In addition we did not have adequate data for social factors and response to treatment ratios.

In conclusion, Kurdish women with BC in this study are worse survival than Turkish and Arabic women, despite equal access to health care and similar treatment patterns. The underlying reasons for the survival disparity are unclear and additional epidemiological and genetic studies are required.

References

Abdullah NA, Wan Mahiyuddin WR, Muhammad NA et al (2013) Survival rate of breast cancer patients in Malaysia: a population-based study. *Asian Pac J Cancer Prev*, **14**, 4591-4.

Adli M, Kuzhan A, Alkis H, Dirier A (2010). Assessment of the relationship between clinical and socioeconomic/cultural characteristics of the breast cancer patients. In: 'Abstract Book of 9th National meeting of radiation oncology', (Ed) Akyol F. Miki Publications, Ankara pp.179.

Amend K, Hicks D, Ambrosone CB (2006). Breast cancer in African-American women: differences in tumor biology from Europan-American women. *Cancer Res*, **66**, 8327-30.

Andaya AA, Enewold L, Horner MJ et al (2012). Socioeconomic disparities and breast cancer hormone receptor status. *Cancer Causes Control*, **23**, 951-8.

Bhoo-Pathy N, Hartman M, Yip CH et al (2012). Ethnic differences in survival after breast cancer in South East Asia. *PLoS One*, **7**, 30995.

Bradley CJ, Given CW, Roberts C (2002). Race, socioeconomic status, and breast cancer treatment and survival. *J Natl Cancer Inst*, **94**, 490-6.

Brawley OW (2002). Disaggregating the effects or race and poverty on breast cancer outcomes. *J Natl Cancer Inst*, **94**, 471-3.

Fan L, Goh BC, Wong CI et al (2008). Genotype of human carbonyl reductase CBR3 corralates with doxorubicin disposition and toxicity. *Pharmacogenet Genomics*, **18**, 623-31.

Gordon NH (2003). Socioeconomic factors and breast cancer in black and white Americans. *Cancer Metastasis Rev*, **22**, 55-65.

Greend MA, Pai M (2008). Social determinants of Black-White disparities in breast cancer mortality: a review. *Cancer Epidemiol Biomarkers Prev*, **17**, 2913-23.

Harris L, Fritsche H, Mennel R et al (2007). American society of clinical oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol*, **25**, 5287-312.

Hersman D, McBride R, Jacobson JS et al (2005). Racial disparities in treatment and survival among women with early-stage breast cancer. *J Clin Oncol*, **23**, 6639-46.

Kuzhan A, Adli M, Alkis HE, Caglayan D (2013). Hormone receptor status and HER2 status in patients with breast cancer by races in southeastern Turkey. *J BUON*, **18**, 619-22.

Kroman N, Wohlfahrt J, Andersen KW et al (1998). Parity, age at first childbirth and the prognosis of primary breast cancer. *Br J Cancer*, **78**, 1529-33.

Lal S, Wong ZW, Jada SR et al (2007). Novel SLC22A16 polymorphisms and influence on doxorubicin pharmacokinetics in Asian breast cancer patients. *Pharmacogenomics*, **8**, 567-75.

Li CI, Malone KE, Daling JR (2002). Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. *Cancer Epidemiol Biomarkers Prev*, **11**, 601-7.

Li CI, Malone KE, Daling JR (2003). Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Arch Intern Med*, **163**, 49-56.

Ma BBY, Hui EP, Mok TSK (2010). Population based differences in treatment outcome following anticancer drug therapies. *Lancet Oncol*, **11**, 75-84.

McKenzie F, Jeffreys M (2009). Do lifestyle or social factors explain ethnic/racial inequalities in breast cancer survival? *Epidemiol Rev*, **31**, 52-66.

Newman LA, Mason J, Cote D et al (2002). African American ethnicity, socioeconomic status, and breast cancer survival: a meta-analysis of 14 studies involving over 10,000 African-American and 40,000 White American patients with carcinoma of the breast. *Cancer*, **94**, 2844-54.

Ozmen V (2008). Breast cancer in the world and Turkey. *J Breast Health*, **4**, 7-12.

Reynolds P, Hurley S, Torres M et al (2000). Use of coping strategies and breast cancer survival: result from the black/white cancer survival study. *Am J Epidemiol*, **152**, 940-9.

Rosenberg J, Chia YL, Plevritis S (2005). The effect of age, race, tumor size, tumor grade, and disease stage on invasive ductal breast cancer survival in the SEER database. *Cancer Res Treat*, **89**, 47-54.

Schootman M, Jeffe DB, Reschke AH, Aft RL (2003). Disparities related to socioeconomic status and access to medical care remain in the United States among women who never had a mammogram. *Cancer Causes Control*, **14**, 419-25.

Soler-Vila H, Kasl SV, Jones BA (2003). Prognostic significance of pyhsicosocial factors in African and white breast cancer patients. *Cancer*, **98**, 1299-308.

Spallek J, Arnold M, Razum O et al (2012). Cancer mortality pattern among Turkish immigrants in four Europan countries and in Turkey. *Eur J Epidemiol*, **27**, 915-21.

Telli ML, Chang ET, Kurian AW et al (2011). Asian ethnicity and breast cancer subtypes: a study from the california cancer registry. *Breast Cancer Res Treat*, **127**, 471-8.

Wojcik BE, Spinks MK, Optenberg SA (1998). Breast carcinoma survival analysis for African American and white women in an equal-access health care system. *Cancer*, **82**, 1310-8.

Yip CH, Taib N, Mohamed I (2006). Epidemiology of breast cancer in Malaysia. *Asian Pac J Cancer Prev*, **7**, 369.

Yusuf A, Ab Hadi IS, Mahamood Z et al (2013). Understanding the breast cancer experience: a qualitative study of Malaysian women. *Asian Pac J Cancer Prev*, **14**, 3689-98.

Zeeb H, Razum O (2003). Krebshaufigkeit bei turkischen Staatsburgern in Deutschland. *Forum DKG*, **2**, 42-5.