

RESEARCH ARTICLE

Breast Cancer in Bedouin-Arab Patients in Southern Israel: Epidemiologic and Biologic Features in Comparison with Jewish Patients

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Abstract

Background: Breast cancer (BC) is the most frequent cancer type, and the leading cause of death from cancer among women in Israel. The Bedouin-Arab (BA) population in southern Israel is characterized by a high rate of consanguinity, common hereditary disorders, and transition from a semi-nomadic, traditional society to a more sedentary and urbanized society. In this hospital-based study, the demographic and the clinicopathological characteristics of BC in BA were compared with Jewish patients. **Materials and Methods:** 85 BA patients treated at the Soroka Medical Center, Beer Sheba, during the years 2004-2012, were studied and compared with 180 consecutive Jewish patients treated during the year 2007. Clinicopathological features compared included age, menopausal state, number of births, a history of BC in first-degree relatives, tumor size (T), extent of lymph-node involvement (N), distant metastases (M), stage, grade, estrogen and progesterone receptor (ER/PR), and Her2 status. Types of treatment, relapse rate and site, as well as outcome were also studied. Cox's regression models were applied for studying disease-free, and overall survival. **Results:** Compared with Jewish patients, BA patients were younger (average age 49 ± 12 yrs vs 59 ± 13 , $p < 0.001$), had a lower rate of BC in first-degree relatives ($p < 0.001$), and a larger number of births (6 ± 4.2 vs 2.5 ± 1.9 , $p < 0.001$). BA patients had larger tumors ($p = 0.02$), more extensive lymph-node involvement ($p = 0.002$), and more advanced stage ($p = 0.003$). Grade, ER, PR, and Her2 status were similar in the two ethnic groups. Relapse type was most commonly systemic in BA patients ($p = 0.05$), and loco-regional in Jewish patients ($p = 0.02$). Median survival was 63, and 35 months for Jewish and BA patients, respectively (log-rank test, $p = 0.02$). In Cox multivariate analysis, stage and PR status (HR-0.14, $p < 0.0001$; HR-3.11, $p = 0.046$), but not ethnicity, influenced overall survival. **Conclusions:** BC presents a decade earlier, and with more advanced disease in BA compared with Jewish patients. Biologic parameters including grade, ER, PR, and Her2 status were similar in both groups. Although prognosis was worse in BA than in Jewish patients, it was affected only by stage and PR status, but not by ethnicity.

Keywords: Breast cancer - Bedouin arab - prognosis - stage - age.

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Introduction

Breast cancer (BC) is the most frequent cancer type and the leading cause of death among women in Israel (Baron-Apel, Israel Center for Disease Control). Time-trends in the incidence of BC have been different in Jewish and Israeli-Arab populations. Following a steady rise over a few decades, the incidence of BC in Jews decreased by 3% from 1996 through 2007. In contrast, the incidence of BC in Israeli-Arabs continued to increase by 98% over the same time-period. Age-adjusted incidence rates in Jews and Israeli-Arabs in 2010 reached levels of 91, and of 53 cases per 100,000 per year, respectively (Israel Cancer Registry, Jerusalem).

Bedouin-Arabs (BA), who are part of the Israeli-Arab population of Israel, reside in the Negev, a desert and

a semidesert region of southern Israel. BA account for almost 20% of the one-million population of the Negev (Israel Central Bureau of Statistics), and almost all Israeli-Arabs living in the Negev are BA. The genetics of BA of the Negev resembles that of the population of the Arabian Peninsula (Nebet et al., 2001) supporting the view that the BA population of the Negev originated in the Arabian Peninsula (Bailey et al., 1980). Numerous hereditary disorders, a few of which are peculiar to the BA population of the Negev have been described (Kenan et al., 2002; Zlotogora et al., 2013), and are related to a high rate of consanguinity in this population (Kenan et al., 2002).

In recent decades, the BA population of the Negev has undergone transition from a semi-nomadic, traditional society to a more sedentary and urbanized society. This changeover has been associated with altered lifestyle and

nutrition including abandonment of traditional foods for “modern foods” (Fraser et al., 2001), and use of unfortified white-flour bread instead of whole wheat bread as the main dietary staple (Abu-Saad et al., 2009). Compared with Jewish women, BA women have a higher rate of obesity and age-adjusted body mass index (Fraser et al., 2008), and a higher saturated fatty acid composition in human milk (Silberstein et al., 2013). Since genetics, hormones, and environment may all interact to cause BC, the high prevalence of consanguinity, combined with a rapid changeover in lifestyle and nutrition, make the BA population of the Negev highly attractive for studying BC.

Materials and Methods

Study population

Following approval by the Institutional Review Board, we searched our registry and computerized database to identify newly-diagnosed BC patients who were referred

to the oncology clinic at the Soroka University Medical Center (SUMC), Beer Sheva. Patients with histological diagnosis of BC other than invasive ductal carcinoma, or a previous history of another primary tumor were excluded from the study. Only patients for whom complete clinical and pathologic data were available were included in the study. The group of BA patients consisted of all BA patients referred to the oncology clinic from January 1st 2004 to December 31st 2012. This group of patients included 85 patients who comprised 3.5% of the total BC patients referred to SMC during the study period. The control group consisted of 180 consecutive Jewish patients referred to the oncology clinic during one year, from January 1st 2007 to December 31st 2007. Patients' medical records were retrospectively reviewed and demographic and clinical data were recorded. Baseline data included age, parity, menstruation status, place of birth (for Jewish patients), a history of breast cancer in first-degree relatives, tumor size (T), lymph-node involvement (N),

Table 1. Demographic and Clinicopathological Characteristics of BC Patients: (1) BA patients, (2) Jewish patients.

Demographics and clinicopathological characteristics		Study population			p value*
		Bedouin-Arab N=85 n (%)	Jewish N=180 n (%)	All N=265 n (%)	
Ethnic origin (for Jewish patients only)	Ashkenazi		103 (57)		
	Sephardic		63 (35)		
	Israel-born		15 (8)		
Age at diagnosis (years)	Mean±SD**	49±12	59±13	56±14	<0.0001
	Median	49	58	54	
	Range	22-84	31-90	22-90	
First-degree family history of breast cancer	Yes	4 (4)	36 (20)	40 (15)	0.009
	No	55 (65)	139 (77)	194 (73)	
	Unknown	26 (31)	5 (3)	31 (12)	
Number of births	Mean±SD**	6±4.2	2.5±1.9	3.6±3.2	<0.0001
	Median	6	2	3	
	Range	0-19	0-13	0-19	
Menstruation status	Premenopausal	36 (46)	44 (26)	80 (32)	<0.0001
	Perimenopausal	19 (24)	17 (10)	36 (14)	
	Postmenopausal	28 (30)	111(65)	135(54)	
Tumor size (T)	T1	25 (29)	84 (47)	109(42)	0.023
	T2	26 (31)	57 (32)	83 (32)	
	T3	26 (31)	31 (17)	57 (22)	
	T4	5 (6)	7 (4)	12 (5)	
Nodal status (N)	N0	32 (40)	92 (52)	124 (48)	0.005
	1-3 lymph-nodes	27 (33)	66 (37)	93 (36)	
	Ø 4 lymph-nodes	22 (27)	20 (11)	42 (16)	
Metastasis	Yes	7 (9)	13 (7)	20 (8)	0.69
	No	74 (91)	167 (93)	241 (92)	
Stage	1	16 (28)	60 (23)	76 (29)	0.003
	2	29 (34)	74 (41)	100 (39)	
	3	33 (39)	34 (19)	67 (25)	
	4	7 (8)	12 (7)	19 (7)	
Grade	Well-differentiated (G1)	12 (14)	38 (21)	50 (19)	0.54
	Moderately-differentiated (G2)	22 (26)	48 (27)	70 (26)	
	Poorly-differentiated (G3)	22 (26)	41 (23)	63 (24)	
	Unknown	29 (34)	53 (29)	82 (31)	
ER status	Positive	65 (77)	142 (79)	207 (78)	0.38
	Negative	20 (24)	38 (21)	58 (22)	
PR status	Positive	44 (52)	103 (57)	147 (56)	0.4
	Negative	41 (48)	77 (43)	118 (45)	
Her2 status	Positive	16 (19)	49 (27)	65 (25)	0.15
	Negative	69 (81)	128 (73)	197 (74)	
Hormone receptor pattern	Yes	64 (75)	145 (81)	209 (79)	0.56
	No	21 (25)	35 (19)	56 (21)	
Triple negative” pattern	Yes	23 (13)	11 (13)	34 (13)	1
	No	157 (87)	74 (87)	231 (87)	
Her2 positive” pattern	Her2 positive, all	16	49	65	0.06
	Her2 positive, ER-positive	6 (38)	35 (71)	41(63)	
	Her2 positive, ER-negative	10 (62)	14(29)	24(37)	

and presence or absence of distant metastases (M), stage according to 2002 AJCC classification system (Singletary et al., 2002), grade according to Scarff-Bloom-Richardson system (Elston et al., 1991), expression of estrogen and progesterone receptors, and Her2 status. Whenever pathologic data was available in addition to clinical data, the pathologic data was determinant for stage. Treatment data consisted of type of surgery for BC, type of adjuvant treatment (chemotherapy, hormonal, or radiotherapy). Outcome measures included most recent status, and site of relapse.

Statistical analysis

Demographic and clinical parameters were presented by descriptive statistics. The χ^2 and the Mann-Whitney U tests were used as appropriate. All statistical tests were two-sided, and statistical significance was defined at a level p less than 0.05. Overall and disease free survival (OS and DFS) was defined as the time from diagnosis to time of death from any cause, and time of documented local or distant recurrence of tumor, respectively. Cox proportional hazard models were used to compare DFS and OS between groups. The following variables were converted into dichotomic parameters: Age (>50 years vs <50 years), ethnicity (Jewish vs Bedouin-Arab), tumor (3-4 vs 1-2), node (-ve vs \pm ve), stage (1-2 vs 3-4), grade (1-2 vs 3), ER (-ve vs \pm ve), PR (-ve vs \pm ve), and Her2 status (\pm ve vs -ve). Statistically-significant parameters in the univariate analyses were included in the multivariate Cox's analyses, and Kaplan-Meier estimates were calculated. Statistical analyses were conducted using SPSS version 20 for windows (SPSS inc., Chicago, IL USA).

Results

Table 1 summarizes the frequencies of baseline characteristics of all BC patients by ethnicity. A total of 265 patients were included in the study. Out of these, 85 patients were BA while 180 patients belonging to the control group were Jewish. Most Jewish patients (103 patients, 57%) were of the Ashkenazi extraction, and only 15 patients (8%) were Israeli-born. The average age of BA patients was 49 years (range 22 to 84 years), while the average age of Jewish patients was 59 years (range 31 to 90 years, $p < 0.0001$). First degree family history of BC was more common in the Jewish than the BA group ($p < 0.0001$). The average number of births in the BA group was 6 (range 0 to 19), and 2.5 (range 0 to 13) in the Jewish group ($p < 0.0001$). A higher proportion of BA patients were pre- or perimenopausal than Jewish patients ($p < 0.0001$). BA patients had larger tumors than Jewish patients ($p = 0.024$), had more extensive lymph-node involvement ($p = 0.002$), a higher frequency of metastatic disease ($p = 0.013$), and more advanced stage ($p = 0.003$). No difference was observed in regard to grade, estrogen or progesterone receptor, or Her2 status between the two groups. Table 2 shows types of treatment and outcome results in BA compared with Jewish patients. More BA patients received neo-adjuvant chemotherapy compared with Jewish patients ($p < 0.0001$). A higher proportion of BA patients tended to undergo mastectomy than Jewish

patients ($p = 0.082$), while a higher proportion of Jewish than BA patients showed a trend for receiving adjuvant chemotherapy ($p = 0.078$). There was no difference between the two groups in regard to receiving hormonal treatment. Systemic relapse was more common in the BA than the Jewish group ($p = 0.020$), while the Jewish group showed a trend towards having locoregional

Table 2. Treatments and Outcome of BC Patients: (1) BA patients, (2) Jewish patients

Treatments and outcome	Study population			p value*
	All N=265 n (%)	Jewish N=180 n (%)	Bedouin-Arab N=85 n (%)	
Type of breast surgery				
Biopsy only	13 (15)	20 (11)	33 (13)	0.082
Lumpectomy	46 (54)	123 (68)	169 (64)	
Mastectomy	25 (29)	37 (21)	62 (23)	
Axillary lymph-node dissection	1 (1)	0 (0)	1 (0.4)	
Neoadjuvant chemotherapy				
Yes	36/74 (49)	40/167 (24)	76 (32)	<0.000
No	38/74 (51)	127/167 (77)	165 (68)	
Adjuvant chemotherapy				
Yes	29/72 (40)	76/167 (46)	105 (44)	0.078
No	43/72 (60)	91/167 (54)	134 (56)	
Adjuvant hormonal treatment				
Yes	66/73 (89)	135/167 (81)	201 (83)	0.059
No	7/73 (9)	32/167 (19)	39 (16)	
Relapse				
Yes	17 (20)	30 (17)	47 (18)	0.088
No	58 (68)	133 (74)	191 (72)	
Unknown	8 (9)	17 (9)	25 (9)	
For relapsed patients, site of relapse:				
a. Locoregional				
Yes	1/17 (6)	11/30 (37)	12/47 (26)	0.02
No	16/17 (94)	19/30 (63)	35/47 (74)	
b. Contralateral breast				
Yes	1/17 (6)	4/30 (13)	5/47 (11)	0.426
No	16/17 (94)	26/30 (87)	42/47 (89)	
c. Systemic				
Yes	16/17 (94)	21/30 (70)	37/47 (79)	0.052
No	1/17 (6)	9/30 (30)	10/47 (21)	
Recent status				
Dead	19 (22)	34 (19)	53 (20)	0.308
Alive	66/85 (78)	146 (81)	212 (80)	

Table 3. Cox's Univariate Analysis of Factors Predicting Overall Survival in BC Patients

Parameter	HR*	95%CI**	p value
Stage	2.68	2.00-3.58	<0.0001
Age	1.06	1.04-1.09	<0.0001
Jewish vs Bedouin-Arab	0.33	0.17-0.64	<0.001

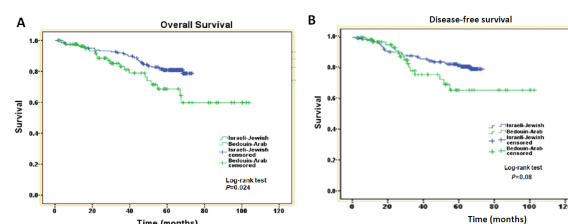


Figure 1. Kaplan-Meier Survival Curves Showing Survival of BA Patients Compared with Jewish Patients: (A) Overall Survival, (2) Disease-free Survival

relapse compared with the BA group ($p=0.052$). In Cox's univariate analysis, the following parameters affected OS: stage (HR-0.19, $p=0.02$), and PR status (HR-3.15, $p=0.05$), but not ethnicity. Results of Cox's univariate analysis are shown in Table 3. Also in Cox multivariate analysis, stage and PR status (HR-0.14, $p<0.0001$; HR-3.11, $p=0.046$), but not ethnicity influenced overall survival. In Cox's univariate analysis, none of these parameters affected PFS. Kaplan-Meier, overall and progression-free survival curves are shown in Figure 1.

Discussion

We have studied the characteristics of BC in BA and Jewish patients, two different ethnic groups residing in the same geographical region of southern Israel. The average age at presentation of BA patients was 49 years, a decade earlier than Jewish patients. A similar difference in the average age of BC patients between Israeli-Arab women and Jewish patients has previously been reported in patients residing in the Jerusalem area (Nissan et al., 2004), and in northern Israel (Zidan et al., 2012). Several studies reported a similar pattern of earlier diagnosis of BC in Arab countries (Chouchane et al., 2013; Slaou et al., 2014). A younger age of BC patients has also been reported from many developing countries (Amaya-Ruiz et al., 2014; Keramintia et al., 2014). A comparable difference in age-distribution of BC in women has been observed in minority populations in other countries (Hemminki et al., 2011).

Younger onset, around the age of 50 years, of BC in populations with low BC prevalence compared with late-onset of BC in high-risk populations may be explained by several ways: *i*) under-representation of BC in the elderly population due to under-diagnosis or incomplete registration, *ii*) a difference in BC biology, and *iii*) a high proportion of younger people in populations with low BC prevalence. Since all citizens of Israel, including BAs receive government mandated health services funded by an income-related health tax, under-diagnosis in the elderly BA patients seems unlikely. In addition, since SMC is the only medical center providing both primary and tertiary services to cancer patients in southern Israel, incomplete registration of BA patients is also highly improbable. The finding of a younger mean age at diagnosis in BA (which is also the case with respect to the total Israeli-Arab population) may be a result of a different age-pyramid in Israeli-Arabs in general and BA in particular, over-representing younger age groups and under-representing older age groups. Thus, younger age at diagnosis may merely reflect a larger proportion for the younger age groups and a much smaller proportion for the older age groups in the total population, and consequently also among the patients. Similar findings in regard to BC and age distribution were previously described in the total Arab population in Israel (Keynan-Boker et al., 2013). Tumor characteristics in regard to grade, estrogen and progesterone receptors, and Her2 in our study were similar in both ethnic groups, making a difference in BC biology a less plausible explanation.

In contrast to Jewish patients, BA patients were

diagnosed with larger tumors, more extensive lymph-node involvement, and more advanced stage. Also the rate of systemic relapse was much higher in BA than in Jewish patients. Survival analysis has shown worse outcome of BA patients with significantly shorter OS compared with Jewish patients. This finding of more advanced tumor presentation of BC in BA patients concurs with two previous reports on Palestinian patients residing in the Jerusalem area, and in Arab patients residing in northern Israel (Zidan et al., 2012). A late stage at presentation and locally-advanced BC has typically been reported in studies from Arab countries (Ortashi, 2013), and has been ascribed in these studies to failure to seek medical attention for early but palpable BC (Donnelly et al., 2013). Cultural reluctance to participate in screening mammography programs in the Arab population has been mentioned as a major impediment for early diagnosis of BC in these countries (Bener et al., 2010). The policy of the national BC screening program in Israel is to recommend bi-annual mammography to women at average risk at age 50-74 years, and annual mammography to women at increased familial risk from age 40. The program estimates that 72% of Israeli women have undergone the study within the past two years. Screening rates among Arab women (including BA women) have steadily increased, and at present are nearly identical to that of Jewish women. The relatively young age of BC presentation in BA women, combined with the late stage at presentation and locally-advanced BC in this population suggest that the national recommendations for BC screening starting at the age of 50 years are less effective in detecting early BC in BA women of younger age.

As previously mentioned, the pattern of BC biologic parameters, including estrogen and progesterone receptor status, Her2 expression, and grade in our study was similar in BA and Jewish patients. The finding of common biologic parameters in BC in BA and in Jewish patients is in contrast to a report on Israeli-Arab patients residing in northern Israel that described a higher proportion of high-grade, triple-negative or Her2-positive tumors in Israeli-Arab compared with Jewish patients (Zidan et al., 2012). As in our study, the proportion of hormone receptor-positive BC in Palestinian patients residing in the district of Jerusalem was similar to that observed in Jewish patients (Nissan et al., 2004). A high proportion of BC showing aggressive patterns including high-grade, triple-negative or Her2-positive tumors was reported in BC patients from Saudi Arabia. Saudi women had almost 14-fold lower risk of developing low-grade BC than did Swiss patients, suggesting a high-grade pathway in BC development in Saudi women (Al-Kuraya et al., 2005). The difference in tumor biology between BA patients in southern Israel and patients from Saudi Arabia emphasizes the importance of different acquired factors in the development of BC between these two populations.

Despite a high prevalence of consanguinity in the BA population, BA patients in our study had a lower rate of BC in first-degree relatives compared with Jewish patients. Although under-reporting of a family history of BC in BA women must be considered, it is more likely that consanguinity has no effect or could have a mild

protective effect on BC risk in BA women. This finding concurs with a report describing a lower risk of BC in Arab women whose parents were consanguineous compared with those whose parents were non-consanguineous (Kenan et al., 2002).

The number of births in BA patients in our study was 2.5 fold larger than in Jewish patients. Reproductive factors have long been associated with increased risk of developing BC. The relative lower prevalence of BC in the Israeli-Arab compared with the Jewish population in the past could be related to a higher birth rate in Israeli-Arabs. Because of the relatively small number of BA patients included in our study, we could not study the time-trend in the incidence of BC in BA patients during the study period. Lifestyle and nutrition have changed in the BA population of the Negev in recent years. In addition to a declining birth rate, BAs' diet has become rich in carbohydrates (Fraser et al., 2001; 2008), and the rate of obesity in BA women has increased (Abu-Saad et al., 2009). As a result of all these factors, it is anticipated that the prevalence of BC in BA women will rise, following a similar pattern to that observed in the Jewish population.

Survival analysis has shown worse outcome of BA patients with significantly shorter OS compared with Jewish patients. Also the rate of systemic relapse was much higher in BA than in Jewish patients. However, survival rates in the two populations were similar after adjusting for stage and age, suggesting a common biology of BC in the two populations. Survival analysis was based on different follow-up periods for the two populations: a relatively widely-distributed follow-up period according to the year of diagnosis for BA patients, and a six-year follow-up period for Jewish patients. Despite a relatively short follow-up period for some BA patients diagnosed in recent years, it is unlikely this limitation could significantly affect survival analysis in our study.

In summary, we compared BC in two distinct populations living in southern Israel. BC was diagnosed in BA women a decade earlier than in the Jewish population. Biologic parameters were however similar in both populations, a finding that differs from that described in both Israeli-Arab patients residing in northern Israel, and patients from Saudi Arabia. Because of life-style changes in BA in recent years, the prevalence of BC in BA women is expected to rise, following a similar pattern to that observed in the Jewish population.

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