Epidemiology of women diagnosed with breast cancer in Jordan

A 5-year survival analysis and patients' characteristics from 2 public hospitals

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ABSTRACT

الأهداف: قياس معدل النجاة خلال خمس سنوات لدى المصابات بسرطان الثدي في الأردن خلال الفترة من 2011م و 2014م، والبحث عن العوامل المؤثرة في ذلك.

المنهجية: أجريت هذه الدراسة بأثر رجعي وقد شملت الدراسة جميع الأردنيات اللاتي تشخصن بسرطان الثدي في مستشفيين الرئيسيين التابعين للقطاع الصحي العام ما بين 2011م-2014م وانهيت الدراسة في 2018م. وجمع الباحثون المعلومات المتعلقة بالعوامل الديموغرافية والمرضية من سجلات المستشفيين ما بين 2011م و2018م.

النتائج: اشتملت الدراسة على 838 امرأة وبلغ متوسط العمر 51 عام ومدة المتابعة 2.4 عام. لدى غالبية المرضى سرطان الأقنية ونوع إيجابي من مستقبلات هرمون الاستروجين (ER). وبلغ إجمالي النجاة على قيد الحياة خلال 5 سنوات وفق كابلان – ماير 84% و للمرحلة الأولى 98% وللمرحلة الثانية 94% وللمرحلة الثالثة 86% وللمرحلة الرابعة من المرض46%. واتضح أن المرحلة التي يتشخص فيها المرض، وانتشار المرض في العقد اللمفاوية من أهم العوامل التي تؤثر على معدل النجاة.

الخلاصة: معدل إصابة الأردنيات بسرطان الثدي في تزايد، ولكن مع تحسن الكشف عن المرض تتحسن معدلات النجاة، وتزيد احتمالية النجاة إذا تشخص في مراحله الأولى. اتباع استراتيجية شاملة وطنية وتطبيق برامج الفحص المبكر لسرطان الثدي ستساعد في تحسين النتائج الصحية للمرض وتخفيف عبء المرض على الدولة.

Objectives: To evaluate the epidemiology, prognostic factors, and 5-year overall survival (OS) of females with breast cancer (BC) diagnosed between 2011 and 2014 in Jordan.

Methods: A retrospective medical review of females who were diagnosed with BC between 2011 and 2014 at the 2 leading public health providers in Jordan was performed. The endpoint of the study was 2018. Data were extracted from the medical files between 2011 and 2018, including demographic clinical data on the patient level. Survival by age, laterality, grade, stage, and treatments modes were calculated by the Kaplan Meier method.

Results: A total of 877 women were included with median age of 51 years and follow-up duration of 2.4 years. Majority of the patients had ductal carcinoma and estrogen receptor (ER) positive type. The 5-year OS for patients with stage I , II, III, and IV, 94%, 86%, and 46% ($p<0.001$), respectively. The tumor stage and nodal status were the main prognostic variables affecting the overall survival.

Conclusion: The incidence in Jordan is increasing, yet survival rates are improving with increased diagnosis during early stages. Therefore, strategies for implementing universal screening programs are advocated to improve clinical outcomes and to reduce the disease burden.

Keywords: breast neoplasm, survival, epidemiology, prognosis, Jordan

Breast cancer (BC) is the main cancer type (24.2% of cancer cases) in women across the world.[1] Developing countries, such as countries in the Eastern Mediterranean region (EMR), varied in cancer incidence and mortality rate, 2 and similarly BC is the main type of cancer 2 with 95 thousands newly cancer cases were reported from 6 national cancer registries in the EMR between 1998 and 2007.[3] This numbers is potentially underestimated due to lack of documentation and quality of data.[2]

Jordan is a country located in the EMR with upper-middle-income level, with a population of 10.20 million cancer accounting for 12% of all cases of death in 2016 in Jordan.[4,5] Several retrospective studies described the epidemiology and patients' characteristics of BC in Jordan and how they are linked with patients' survival.[6,7] However, these studies were published a decade ago and did not included all patients' characteristics that may affect survival. Nevertheless, these studies outlined increasing in cancer incidence, and highlighted that the cancer patterns are changing rapidly in Jordan. Overall survivals (OS) were shown to improve over the years too. Of note, the tumor stage was often shown as a leading factor to survival outcome.[6-8] However, this was concluded without consideration of cancer staging and estrogen receptor (ER), progesterone receptor (PR), and human epidermal receptor (HER2) status, tumor size, smoking, marital status, menopausal status, type of treatment, age, tumor grade, laterality, degree of ER positivity, lymph node status (tumor, nodal, and metastasis [TNM]) on OS. Thus, comprehensive assessment of factors and drivers is warranted.

Cancer treatment is offered at subsidized costs by public providers in Jordan which is mainly franchised by the government fund and tax payers. The composite of the public sector in Jordan is the Ministry of Health (MOH), the military's Royal Medical Services (RMS), and 2 university hospitals. The MOH is the leading health provider for cancer treatment for civil employees and their dependents, accounting for almost 40% of cancer cases, according to the Jordan Cancer Registry's (JCR) data accessed from the Jordan MOH records. Jordan Cancer Registry is a population-based registry established in 1996 under the domain of MOH. Cancer notification is compulsory since 1996 through a ministerial decree from all possible notification sites in the kingdom including both public and the private. Jordan Cancer Registry monitor cancer incidence in Jordan and trends over time. Referral cases are treated by other providers, including university hospitals (5%) and RMS (15%), where treatment modalities are not available within the MOH.[9,10] Although approximately 30% of cases are treated at King Hussein Cancer Center (KHCC),[8] this represents cases for those that are well off. This study evaluated the epidemiology, 5-year OS, and prognostic factors related to BC in the 2 leading public hospitals in Jordan to underpin the status of cancer care and strategies to improve prognosis and to reduce the disease burden

Methods. Ethical approval was obtained from the medical ethics committee of the MOH, Bashir, and University of Jordan Hospital (UJH), Amman, Jordan before starting data collection and in concordance with Declaration of Helsinki. Patients were not consented since the information was not directly collected from patients. This retrospective medical review included females with Jordanian nationality and diagnosed with BC in 2 central public hospitals in Amman, the capital of Jordan; UJH and Bashir Hospital between 2011 and 2014. Data were obtained from hospital records and the JCR from 2011 to 2018. The JCR has been established since 1996 under the provision of the MOH, and it collects all cancer data from all health care providers in Jordan, including all governmental hospitals, private hospitals, RMS, and university hospitals.[11] The UJH is a leading public hospital in Amman, Jordan where half of the population reside in. In addition to its contribution as major referral hospital for patients living in the remote governances.[12] Bashir Hospital is the biggest governmental hospital in Jordan that treats cancer patients, with separate departments including radiotherapy and chemotherapy.[11] Socio-demographic characteristics, tumor characteristics, and clinical outcomes (overall death) were also obtained from JCR and hospital medical files.

Only female cases with Jordanian nationality diagnosed with BC between 2011 and 2014 were included. Male patients with other nationality such as refugee were excluded. In addition, patients whom their medical files could not be reached or were not diagnosed between 2011-2014 were also excluded.

Following the diagnosis with BC, each patient was followed until the end of study period (April 2018) unless they died or lost contact. Data on the above mentioned variables was collected by a research assistant and filled in a data collection sheet designed in Micsrosoft Excel 2016. Patient information was handled confidentially and anonymously using the patients' national numbers.

Prior related research has been identified from the PubMed database using the medical subject heading (MESH) terms and free text related to breast cancer ("breast neoplasms/drug therapy, economics, mortality, radiotherapy, surgery, therapy" [MESH] OR

"carcinoma, ductal, breast/drug therapy, economics, mortality, radiotherapy, surgery, therapy"[MESH] OR ([early or primary or operable or early stage or stage I or stage II adj (breast adj (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumor) AND MESH and free text related to epidemiology ("disease-free survival/ or survival analysis/ or survival/ or survival rate/"[MESH] OR (surviv* or mortalit* or epidemiology)). In addition to a free text of Jordan and Middle East was used".

Statistical analysis. The analysis was performed using STATA/SE, version 15. The demographic, tumor characteristics, and treatments offered to patients were summarized. The change in OS probabilities with time (such as, 1- and 5-year OS), in addition to survival probabilities adjusted by age, ER status, nodal status, stage, and treatment, were performed by the Kaplan Meier (KM) method. The associations between these factors and OS were tested by log rank test. [13,14]

The OS rate adjusted by prognostic factors was performed by Cox proportional hazard regression with a stepwise backward elimination approach.[13,15] Initially, all the previously discussed prognostic factors discussed previously were considered in the model,[6,16-21] and then excluded one at a time based on the least significant variables until all the remaining variables were significant. The results of Cox's regression are presented as a hazard ratio (HR) for each covariate with 95% confidence interval (95% CI), and a *p*-value <0.05 indicating a statistically significant association.

Since the Cox model assumes a constant HR over time,[15,22] this was checked using the Schoenfeld-residuals test, with $p<0.05$ indicating violation of the proportional hazard assumption, and, thus, a time-varying interaction expression was added to imply the non-proportionality of the HR. For the variables with proven time-varying effect, the estimated variable effect on the mortality rate at a particular time point was obtained using the following formula: (hazard ratio) HR = HR (main effect) * HR (time varying effect)(t),

Where HR (main effect) is the HR for the main variable effect, HR (time varying effect) is the time varying HR for the variable, and t is the particular time point.

Results. The distribution of BC cases by demographic and clinical characteristics is presented in Table 1 and Table 2. A total of 877 patients were included in the analysis. Approximately half of the cohort were diagnosed within the age group of 40-59 years. The median age was 51 years (interquartile range [IQR]: 43-60). The majority of the patients were married and non-smokers.

The left and right sides of the breast were equally affected (Table 2). Approximately 87% of the patients were diagnosed with ductal carcinoma. Approximately, 45% of patients showed moderate differentiation, whilst 0.5% showed well-differentiation. The majority of the tumors had a positive ER and PR receptor type and 49% have negative HER2 status. Half of the patients has luminal A subtype. More than half of the tumors did not spread to the axillary lymph nodes. The tumor size was <5 cm in 63.8% of the cases; 15.1% had stage I, 28.8% had stage II, 36% had stage III, and 14.1% had stage IV. According to the treatment received, approximately 33.1% received surgical therapy combined with 2 adjuvant therapy (endocrine

Table 1 - The percentages of breast cancer cases stratified by tumor characteristics.

Demographic' characteristics	n	(%)
Age (years)		
<30	18	(2.1)
30–39	113	(12.9)
40–49	275	(31.4)
50–59	241	(27.5)
60–69	166	(19.0)
>70	63	(7.2)
Menopausal status		
Premenopausal	433	(49.4)
Postmenopausal	444	(50.6)
Marital status		
Single	56	(6.4)
Widowed	31	(3.5)
Married	761	(86.8)
Divorced	14	(1.6)
Unknown	15	(3.5)
Smoking status		
Non smoker	630	(71.8)
Smoker	21	(2.4)
Past smoker	53	(6.0)
Unknown	19.73	(19.7)
Comorbidities		
0	592	(67.5)
1	140	(16.0)
2	98	(11.2)
3	34	(3.9)
4	13	(1.5)
Treatment		
Surgery	83	(9.5)
Surgery plus systemic adjuvant	217	(24.7)
Surgery plus radiotherapy	202	(23.0)
Surgery plus 2 adjuvant	290	(33.0)
Surgery plus 3 adjuvant	19	(2.2)
Non-surgical treatment	66	(7.53)
Vital status		
Alive	777	(88.6)
Dead	100	(11.4)

Values are presented as number and percentages (%).

Table 2 - The percentages of breast cancer cases stratified by tumor characteristics.

Tumor characteristics	n	(%)
ER status		
Negative	163	(18.6)
Positive	576	(65.7)
Unknown	138	(15.7)
PR status		
Negative	249	(28.4)
Positive	423	(49.0)
Unknown	198	(22.6)
Molecular subtype Luminal A	428	(48.8)
Luminal B	108	(12.3)
Triple negative	101	(11.5)
HER2 positive	69	(7.9)
Unknown	171	(19.5)
Grade based on NCB		
1 (well-differentiation)	28	(3.2)
2 (moderately differentiation)	393	(44.8)
3 (poorly differentiation)	248	(28.3)
4 (undifferentiation)	4	(0.5)
Unknown	204	(23.3)
TNM staging		
0 (in situ)	10	(1.1)
I	132	(15.1)
II	253	(28.9)
III	316	(36.0)
IV	124	(14.1)
Unknown	42	(4.8)
Clinical tumor size		
<5	560	(63.9)
5.1-10	198	(22.6)
10.1-15	29	(3.3)
15.1--25	3	(0.3)
Unknown	87	(9.9)
Lymph node status (NCB)		
Positive	229	(26.1)
Negative	540	(61.6)
Unknown	108	(12.3)
Histological type		
Ductal	762	(86.9)
Lobular	37	(4.2)
Mixed lobular and ductal	5	(0.6)
Medullary	6	(0.7)
Carcinoma NOS	12	(1.4)
Adenocarcinoma	4	(0.5)
Other types	51	(5.8)
Site of breast		
Bilateral	3	(0.3)
Left	422	(48.2)
Right	422	(48.2)
Unknown	29	(3.3)

ER: estrogen receptor, HER2: human epidermal receptor, NCB: needle core biopsy, NOS: not otherwise specified, PR: progesterone receptor, TNM: tumor, nodal, metastasis. Well differentiation cancer refers to cancer cell that look like normal cell whereas moderate differentiation somehow look like normal cell. The more the similarity of cancer cell appearance to the healthy one, the lower the tumor grade is. Tumors with low grade are associated with less aggressive prognosis

treatment, chemotherapy, or radiotherapy) (Table 2). The median follow-up duration ranged between one and 5 years (median of 2.4 years). Of the patients, 88.6% were known to be alive during the follow-up duration (Table 2).

The 1- and 5-year OS are illustrated in Figure 1A. Using the KM method, the percentages of women surviving 1, 2, 3, 4, and 5 years after being diagnosed with BC were 94%, 87%, 85%, 84%, and 84%, respectively. Overall survival by age, ER status, nodal status, type of treatment, and tumor stage are illustrated in Figure 1B-1F. The 5-year OS was the highest for the 40-49 years age group, whereas the lowest 5-year OS were in the >70 years age group (p=0.015). The 5-year OS for patients with ER-positive was higher than patients with ER-negative status (p<0.001). Patients with negative nodal status was associated with lower 5-year OS as compared to positive nodal status (p=0.001).

Based on tumor stage, the 5-year OS for patients with stage III and IV were lower than patients with stage I and II (p<0.001). Patients who received surgery combined with 2 adjuvant therapies showed higher OS compared to those who received surgery with one adjuvant therapy (p<0.001).

The result of the Cox regression is presented in Table 3. Tumor and demographic characteristics were considered potential prognostic confounders in the model. However, only age, ER, tumor size, tumor stage, and lymph node status were found to be significant contributors for the OS and, thus, were kept in the model. In addition, the proportional hazard assumption was violated for lymph node status, implying that its effect on the OS varied over time (Table 3). Tumor, nodal, metastasis staging (p<0.001) and ER status (p<0.001) strongly affected the survival. Patients with stage I had a significantly better OS when compared with other stages (p≤0.001). Patients with positive ER (p<0.001) had significantly better OS compared with the patients with negative ER status.

In addition, there was a significant increase in the overall death by 40% with each one cm increase in the tumor size. Patients with negative lymph node status had a better OS compared with positive lymph node status (p=0.068). However, the higher risk of overall death associated with positive lymph node status as compared to negative one decreased by 76% (time-varying HR: 0.24; 95% CI: 0.08, 0.76) for each year of follow-up time.

Patients within the age group of 40-49 years had better OS compared with other age groups, whereas patients aged <30 or over 70 years were significantly associated with the lowest OS (p=0.003).
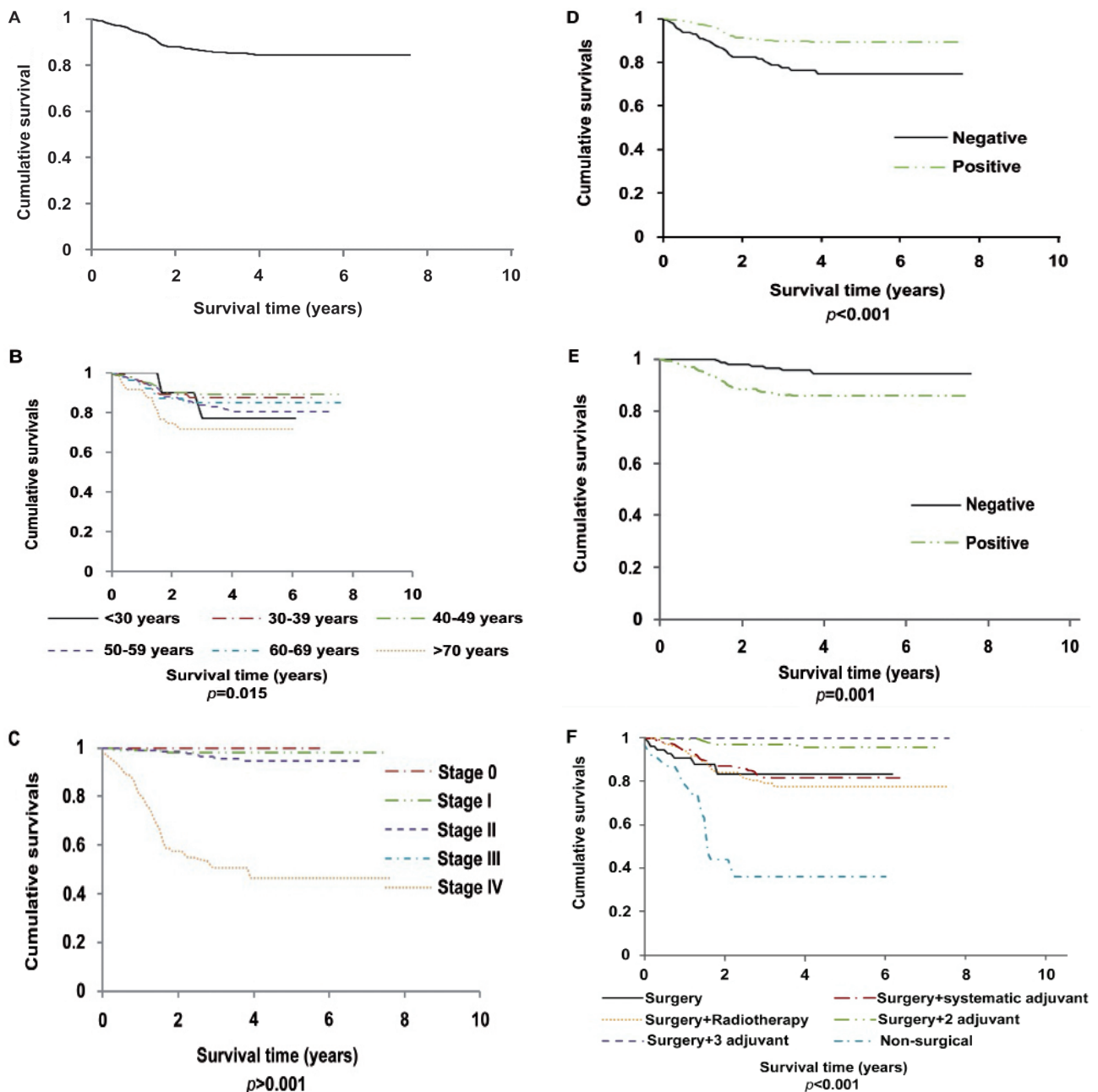
Figure 1 - Overall survival rate stratified by demographic or tumor characteristics. **A)** Overall survival rate; **B)** Survival rate by age group; **C)** Survival rate by tumor stage; **D)** Survival rate by ER status; **E)** Survival rate by lymph node status; and **F)** Survival rate by type of treatment.

Discussion. This study outline the distribution and survival of BC patients treated between 2011 and 2014 at 2 leading central public health providers in Amman, the capital of Jordan. The 5-year OS regardless of tumor and clinical characteristics, were 84% compared with 64%, and 59.6% in the previous years. This highlights improvement in prognosis and survival.[6,7] Improvement has also been witnessed in other countries. This highlights

the promising advancement in cancer treatment and the increased awareness of screening programs on national levels. The 5-year OS in Iran was 0.8%, in Morocco 0.9%, and in Saudi Arabia was 82.6%.[23,24] Whereas the pooled 5-year OS in other studies conducted in 22 countries in the EMR was 0.7% (95% CI: 0.7, 0.7).[23] The variances in OS may highlight disparities and

Table 3 - Covariates associated with overall mortality in the time-dependent Cox model.

Covariates	Hazard ratio (95%CI)	*P*-value
Main coefficients		
TNM Staging		<0.001
1	(reference)	
0	NA (NA)	1
2	3.53 (0.4, 31.48)	0.2
3	17.45 (1.72, 177.36)	0.016
4	73.63 (7.07, 766.46)	<0.001
Nodal type		0.068
Negative	(reference)	
Positive	8.93 (0.65, 122.62)	0.01
ER receptor type		
Negative	(reference)	
Positive	0.31 (0.18, 0.54)	<0.001
Tumour size	1.4 (1.14, 1.71)	0.002
Age (years)		0.003
>70	(reference)	
<30	1.24 (0.26, 6.03)	0.787
30-39	0.13 (0.04, 0.44)	0.001
40-49	0.22 (0.09, 0.55)	0.001
50-59	0.4 (0.17, 0.94)	0.035
60-69	0.29 (0.11, 0.79)	0.015
Time-varying coefficients		
Nodal status		
Negative	(reference)	
Positive	0.24 (0.08, 0.76)	0.015

ER: estrogen receptor, NA: not applicable,
TNM: tumor, nodal, metastasis

inequity in cancer care across the area. This outlines the need for international screening programs to bridge inequity in cancer care across countries.[25,26]

It is of note that the survival rate of developing countries fall far behind developed countries. The 5-year OS in Canada was 88%, the United States was 91%, European countries were 73.5-89.1%, and Australia (2012-2016) was 91%.[23,28-31] Variation in survival rates amongst countries reflects the variation in the introduction of national detection programs and the early BC screening. Particularly, the detection of BC in early stages is associated with less aggressive treatment and better OS in addition to different life spans for the registry data available. This is in agreement with reports from Jordan over the years, where it has been shown that survival rates are improving.

Tumor stage and ER type were the most influential prognostic factors related to OS. Approximately 45% of patients were in the early stage, which was in line with the EMR countries, whereas in a study conducted in the US approximately 65% were in the early stage.[28] Early detection of BC due to regular mammogram follow-ups in developed countries, in addition to lack of awareness

and cultural beliefs in the EMR, such as Jordan, could explain these differences in BC epidemiology amongst various countries.[25,32]

In this study, the 5-year OS for patients in stage I was 98% and in stage IV was 46%, whereas the 5-year OS ranged from 82.7% to 96% for stage I and from 5.8% to 34.6% for stage IV were reported in previous studies conducted in Jordan. Such results should be underlined in national and public campaigns to spread awareness across community of necessity to seek help or diagnosis in early stages.[6,7]

Age was a significant predictor of OS.[6,7] Consistent with some countries in the EMR, The lowest OS were in the group that was <30 years and the group that was >70 year.[32] Meanwhile, the highest OS in the age group of 40-49 years contributed to the greater access to detection programs and the public campaigns targeted at this age group.

Moreover, the lymph node status and ER receptor appeared to be prognostic factors in previous studies. This could be explained due to the aggressive nature of the disease in cases with positive lymph node and negative ER status. Patients with positive ER status respond more to hormonal therapy; therefore, targeted treatment selections based on ER status are crucial to ensure an effective response for BC.[33,34]

Study limitations. First it is a retrospective study, where incomplete recording of demographic data presented considerable challenges at the time of data analysis. However, unrecorded data were possible were verified from the JCR records. The retrospective nature of the study cohort merits discussion of the effect of censoring. Potentially, information on time to outcome event were not available for all study participants (such as, censoring issue). However, this was accounted for by using time-dependent survival analysis.

All cancer cases diagnosed and treated in Jordan have been registered in the JCR since 1996, where the demographic characteristics and survival outcomes are reported.[11] However, the registry does not collect treatment patterns and all prognostic factors. Bodies responsible for data collection and registry on the JCR should be enforced to enhance comprehensibility and accuracy. Yet, we believe that collecting data and matching information where possible with the hospital records enables a robust analysis and conclusions that are required to measure the survival rate of BC. Therefore, the data in this study was based on 2 leading public hospitals (hospital-based registry)—the UJH and Bashir Hospital—which represent almost one third of the BC cases in Jordan (unpublished data from the

cancer registry for 2011–2014). However, access to RMS and KHCC was not granted.

An 82.6% of the Jordanian citizens are living in the central area with small proportions residing in the north and south area.[8] Therefore, people in the south and central are treated in Amman, while people in remote and rural areas have access to transportation to travel to the central area and get treatment in public hospitals. People residing in the north are treated in the King Abdallah Hospital, Amman Jordan which represents approximately 5% of the BC cases. However, they are transferred to Bashir Hospital for radiotherapy. Therefore, this hospital-based study represents the majority of average patients living in the central and south of Jordan.

Implication to health policy and practice. Improvement in BC survival was noticed over decades due to early detection of BC and improvement in treatments offered. This highlight potential strategy of shifting diagnosis of BC to its early stage with the expansion of early detection program. Efforts should be maximized to ensure the screening campaign reach out to remote governorates, refugee camps, and unprivileged communities near the boarders. Walk-in clinics and ambulatory screening units are advocated.

Since the tumor stage has been shown to be an important predictor of survival, early screening of BC is warranted to detect cancer in its early stage. Age was also found to influence survival rate.[6,7] This must have great implications to the message sent to the public, where married aged women are seen as at a greater risk for worse prognosis. It is vital to highlight that time of diagnosis is crucial for better prognosis and observing any change. Therefore, public messages that highlight the need to seek help, regardless of age, are of vital importance.

Although the introduction of Jordan BC screening program in 2007 to raise the awareness on screening of BC in its early phases,[35] still young female are reluctant to get screening due to social and cultural believes, which could hinder BC detection and thus delaying the diagnosis to later stage.[36,37] Therefore, educating young female and women at school, Universities, and social media and break up the cultural barrier that could hinder reaching out for screening. Thus, future research should target screening program especially for high risk women (over 40 years old) and increase the public awareness on BC.

Moreover, complete recording of cancer patients' care and treatment pathways in hospitals, clinics and laboratories (histopathology reports) are vital for survival studies. Universal screening rather than opportunistic screening, particularly in communities where the culture might make females reluctant to seek early screening, could present an effective strategy to maximize survival and clinical outcomes.

In conclusion, Jordan witnessed an improvement in BC survival over the last decade. Tumor stage, ER status and age were significant prognostic factors. The prognosis of BC get worse with late stage and younger age highlighting that the implementation of early detection screening programs could help shift the diagnosis to early stages and could prolong survival.

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