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Original article

Breast cancer in women aging 35 years old and younger: The Egyptian National Cancer Institute (NCI) experience

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ABSTRACT

Objective: The aim is to identify the epidemiological and clinicopathological features associated with young breast cancer (BC) patients and to discuss factors affecting tumor recurrence and DFS.
Patients & methods: A retrospective analysis was conducted based on medical records from young females patients aged ≤35 years with pathologically confirmed primary breast cancer treated during 2008–2010 at NCI. Cases with non invasive cancer and non carcinoma histology are excluded.
Results: Of the 5408 cases diagnosed with breast cancer, 554 were young. Four hundred & fifty eight patients representing 9.2% were within our inclusion criteria. Almost half of the patients (45.9%) presented with stage III. Axillary nodes involvement was in 63.9%, 83.3% were grade 2. More than one quarter of tumors was hormone receptors negative (28.8%) & Her2 was over-expressed in 30%. Mastectomy was offered in 72% while conservative breast surgery in 26%, 69.2% received chemotherapy either adjuvant, neoadjuvant or both, 82.5% received adjuvant radiotherapy, 68.6% received hormonal therapy. Metastatic disease developed in 51.3%, with 31% having more than one site of metastases. After a median follow up period of 66 months, the median DFS of patients was 60 months. The median DFS was significantly shorter among patients with positive lymph nodes ($P < 0.0001$), ER negative disease ($P = 0.045$) and stage III disease ($P < 0.0001$).
Conclusion: Breast cancer in young women is aggressive from the time of diagnosis. Our results provide baseline data of young BC in the Middle East & North Africa region; thus, contributing to future epidemiological and hospital-based researches.

Introduction

Breast cancer (BC) is the second most common cancer in the world and, by far the most frequent cancer among women. Incidence rates vary nearly fourfold across the world regions, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe [1]. In USA about 19% of breast cancers are diagnosed in women ages 30–49 years, and 44% occur among women who are age 65 years or older [2]. In Japan, BC in women aged younger than 35 years old comprises approximately 3% of Japanese breast cancer patients [3]. In most African countries, BC among young women comprises a high proportion of cases than among older women. This is a demography driven phenomenon rather than a true intrinsic biologic significance, because the African population has a low median age; generally 20 years and below [4]. Nevertheless in North Africa, the incidence among women aged 15–49 is lower than in Western countries, but the very low incidence among women aged more than 50, combined to the young age pyramid of North-Africa, makes the relative proportions of young patients substantially higher (50–60% versus 20% in France). Such epidemiological features result mainly from peculiar risk factor profiles, which are typical for many developing countries and include notably rapid changes in reproductive behaviors [5]. In Arab women the average age at presentation of BC is a decade earlier than in US and European women. The median age at diagnosis in Arab populations, is about 48 years, and about two-third of women with BC are younger than 50 years [6]. In Egypt the incidence rate of breast cancer is 29.9/100,000 population in the age

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group of 30–34 years [7]. In a study comparing Egypt's Gharbia Cancer Registry (GCR) and the United States Surveillance, Epidemiology, and End results (SEER) registries, Egyptian GCR cases were, on average, over 10 years younger than US SEER cases, with nearly 19% of GCR cases ≤40 years of age as compared to only 6% of US SEER cases [8].

Although many studies considered young age as an independent prognostic factor with worse outcome the reasons are still controversial [9]. Many reports showed that breast cancer at young age carries more aggressive features as lymphovascular invasion, grade 3 histology, HER2 oncogene over expression, absence of the estrogen receptors, higher triple negative subtypes and more advanced presentation [10,11]. While other studies have supposed that breast cancer in young patients is unique biologically with gene expression that is different from the older patients [12,13]. Several reports showed higher rates of local recurrence and lower survival when young women with breast cancer are compared with older patients [14].

In addition to considerations related to presentation of disease and prognosis, young patient population less than 35 years face some specific problems that are less relevant for older patients. These issues may include disruption of career in its early phase, child bearing and ongoing family responsibilities, impact of therapy on sexuality and body image, and the psychosocial stress of facing a life threatening illness at a young age [15]. Fertility, genetics, psychological and emotional factors are particularly important in young patients while taking treatment decisions [16].

In the current retrospective study we document the clinicopathological features & treatment outcome of breast carcinoma in a relatively large cohort of young women originating from a region where BC in young women is very high. There is very limited published literature on experiences of treating BC in young Middle East or North Africa population. It isn't clear whether the disease is different than that reported in the west? Some studies have argued that but not yet confirmed [17]. In our analysis, we had two objectives [1]: to identify the epidemiological and clinicopathological features associated with young BC patients and [2] to discuss factors affecting tumor recurrence and disease free survival.

Patients and methods

This is a retrospective study that included young female patients with primary breast cancer aged ≤35 years treated at NCI, Cairo University from January 2008 to December 2010. The study received approval from ethical committee of NCI. Early, locally advanced and metastatic breast cancer cases were included. The analyses were based on 5408 cases of invasive breast carcinomas who were diagnosed and/or treated at NCI. Five hundred and fifty four cases were ≤35 years. Subjects with non-invasive cancer (2 cases) other non carcinoma histology (53 cases) or unspecified malignancy (2 cases) were excluded. In 39 patients record no data but the histopathology are found so finally 458 are included.

Data collection

Data were collected jointly by 2 team members (LS & AA) and reviewed jointly by two other members (AD & AH). To avoid inconsistencies, all the study members discussed the abstraction items and had them written in a data collection sheet. Data sheet used for data extraction included the following information:

- Patient's identifiers (name-hospital number-phone number-date of entry).
- Patient's demographics including (age – marital status – parity - number of children).
- Family history, oral contraceptive pills intake history
- Tumor related data including laterality, presenting symptoms, histopathological data of the tumor (size-histological type-grade-lymph node status-number of positive nodes –metastasis status-site of metastasis (if any) – staging according to AJCC system-ER status-PR status-HER 2neu status-recurrence (if any) and its site).
- Breast cancer subtypes were identified based on immunohistochemical surrogates for ER, PR & HER2 status.
- Treatment (Surgery type, chemotherapy, radiotherapy & hormonal therapy).
- Time related data including date of entry, date of diagnosis, surgery date, chemotherapy starting and ending date, date of recurrence, date of last follow up and date of death if any and mentioned.

Statistical analysis

All analyses were performed using SPSS version 17.1IL Chicago. A code book was created to keep different categories for each variable. Every effort was done to avoid missing data. Survival was estimated using the Kaplan–Meier method and groups were compared using the log-rank test. Univariate analysis was done of clinicopathological factors &treatment modalities (patient age, pathological type, tumor grade, tumor stage, ER status, PR status, lymph nodes, IHC based subtype, type of surgery, adjuvant &/or neoadjuvant chemotherapy) through the time-to-event endpoints. Time to distant metastases (TDM) was defined as the time between surgery and first documented distant metastases. Time to local recurrence (TLR) was defined as the time between surgery and the first documented local recurrence. Disease free survival was defined as the time interval between surgery and the first documented relapse, death, or last follow-up, which ever occurred first. A probability (P) < 0.05 is considered statistically significant.

Results

This retrospective cohort study included 458, representing 9.2% of the 5408 cases of pathologically proven breast cancer who presented to NCI Cairo at the period of the study.

Patients' characteristics

The patients' characteristics are outlined in (Table 1). The median age at diagnosis was 32 years. About two thirds of patients aged >30–35 years.

Tumor characteristics

The most common pathological type was invasive duct carcinoma presented in 340 patients (83.7%), other types (including papillary carcinoma, mucinous carcinoma, medullary carcinoma, metaplastic carcinoma, tubular carcinoma, invasive cribriform carcinoma were encountered in 31 cases (7.7%)). Tumor grade was documented in 370 cases and grade 2 was the most common grade (83.3%). Almost 2/3 of our patients had positive ER receptors and positive PR receptors (68%, 62.7%) respectively. From 183 patients, HER2 was over expressed in 55 patients (30.1%). On reviewing the files, almost 2/3 of patients (62.1%) presented with (T2) followed by 23.5% (T3). Four percent presented with Stage I, 39.6% with stage II, 45.9% stage III. Thirty six patients (10.2%) presented at first by metastatic disease, 12 patients had bone only metastasis while 6 patients had bone and visceral metastasis, 8 patients had liver metastasis, 6 patients had lung and only one patient presented

Table 1
Clinical & tumor characteristics of female breast cancer patients ≤35 years.

Variables	No. of patients (%)
Age (n = 458)	
Median (range)	32 (23–34)
≤25	34 (7.4%)
>25–30	137 (29.9%)
>30–35	287 (62.7%)
Marital status (n = 458)	
Single	52 (11.4%)
Married	406 (88.6%)
Parity (n = 458)	
Nulliparous	86 (18.8%)
≤3 children	299 (65.3%)
>3 children	73 (15.9%)
OCP (n = 430)	
Median duration of use	9 months
No	402 (93.5%)
Yes	28 (6.5%)
F/H (n = 337)	
No	307 (91.1%)
Yes	30 (8.9%)
Presenting symptom (n = 169)	
Lump	155 (91.7%)
Mastalgia	9 (5.3%)
Others	5 (3%)
Laterality (n = 415)	
Left	203 (48.9%)
Right	206 (29.6%)
Bilateral	6 (1.5%)
Pathological type (n = 406)	
IDC	340 (83.7%)
ILC	15 (3.7%)
IDC + ILC	20 (4.9%)
Others	31 (7.7%)
Grade (n = 353)	
1	1 (0.3%)
2	294 (83.3%)
3	58 (16.4%)
ER status (n = 286)	
+ve	193 (67.5%)
−ve	93 (32.5%)
PR status (n = 287)	
+ve	180 (62.7%)
−ve	107 (37.3%)
HER2 status (n = 183)	
Non over expressed (0–2)	128 (69.9%)
Over expressed [3]	55 (30.1%)
IHC based subtypes (n = 181)	
Luminal cases (A or B)	129 (71.2%)
HER2 +ve	28 (15.5%)
Tripple −ve	24 (13.3%)
TNM stage at diagnosis (n = 350)	
I	15 (4.3%)
II	140 (39.6%)
III	160 (45.9%)
IV	36 (10.2%)

initially with brain metastasis. Axillary nodes involvement was found in 63.9% (Table 1).

Treatment modalities

Local disease

From the 422 who had localized disease, 339 patients underwent surgery. Mastectomy was offered to 74.1% while conservative breast surgery to 26%. Patients with advanced tumors or inflammatory breast cancer received neoadjuvant chemotherapy with 72 patients had anthracycline based chemotherapy (AC, FAC and FEC 100) and 7 patients had anthracycline & taxane protocol. From the 292 patients who received adjuvant chemotherapy 54.3% had anthracycline based chemotherapy. From the 130 patients who didn't receive adjuvant chemotherapy 24 (32%) received previous neoadjuvant chemotherapy. Adjuvant radiotherapy was offered to 82.5%, 68.6% received hormonal treatment & more than half of patients (62%) received multimodality treatment. Only 56 out of 273 patients had ovarian ablation (Table 2).

Metastatic disease

Among 36 patients with metastatic disease, only 28 patients received chemotherapy with anthracycline combined with taxanes in 7 cases. Two patients had only endocrine treatment and 9 patients had palliative surgery.

Tumor recurrence

Tumor recurrence could be assessed only in 230 patients because some data were missing in our patients' records. After a median follow up of 66 month (range of 1–79 month), the tumor recurred in half of the patients, locally and/or distant, and one third of patients with distant metastasis had more than one site of recurrence.

Time to local recurrence (TLR)

After a median follow up period of 66 months, the impact of various factors on time to local recurrence was explored. Although not statistically significant, patients younger than 25 years old, HER2 positive and those who didn't receive chemotherapy have shorter time to local recurrence. Time to local recurrence in patients who underwent BCS was not significantly different from that of patients who underwent mastectomy. Patients with ILC combined IDC & ILC, stage I, grade 1, and triple negative showed no local recurrence at 1 & 3 years (Table 3).

Time to distant metastases (TDM)

The 3 year TDM was 70.2% ± 3.05. Patients with negative lymph nodes and those with stage I disease were found to have statistically significant longer time to distant metastasis (Figs. 1 and 2). Those who were offered BCS had statistically significant longer time to distant metastasis compared to those who were offered

Table 2
Treatment characteristics in young BC patients with local disease.

Characteristics	No. of patients (%)
No. of patients	422 (100%)
Surgery	
Yes	339 (80.4%)
No	83 (19.6%)
Surgery type (n = 339)	
MRM	251 (74.1%)
BCS	88 (25.9%)
Neoadjuvant chemotherapy	
Yes	79 (18.7%)
No	343
Adjuvant chemotherapy	
Yes	292 (69%)
No	130 (31%)
Chemotherapy type	
Anthracycline	229 (54.3%)
Anthracycline/taxanes	87 (20.6%)
Hormonal therapy	
Yes	289 (68.5%)
No	132 (31.5%
Radiotherapy (n = 342)	
Yes	283 (82.7%)
No	59 (17.3%)
Ovarian ablation (n = 273)	
No	217 (79.5%)
Yes	56 (20.5%)

Table 3
Univariate analysis of factors affecting TLR, TDM and DFS in female breast cancer patients ≤35 years.

Variable	Year	TLR		TDM		DFS	
		Estimate	P value	Estimate	P-value	Estimate	P-value
Age							
<25	One	81.7 ± 8.4	0.0884	77.9 ± 8.9	0.4273	60.5 ± 10.5	0.0922
	Three	81.7 ± 8.4		77.9 ± 8.9		60.5 ± 10.5	
≥25–30	One	95.1 ± 2.4		80.4 ± 4.5		76.1 ± 4.8	
	Three	92.2 ± 3.7		59.7 ± 6.3		53.3 ± 6.4	
>30–35	One	94.7 ± 1.8		84.6 ± 2.8		81.9 ± 3.0	
	Three	89.0 ± 2.7		70.6 ± 4.0		65.3 ± 4.1	
OCP							
No	One	94.2 ± 1.5	0.8108	83.1 ± 2.5	0.8491	78.7 ± 2.6	0.7523
	Three	89.3 ± 2.3		67.1 ± 3.4		60.6 ± 3.5	
Yes	One	89.7 ± 6.9		79.7 ± 9.2		74.6 ± 10.0	
	Three	89.7 ± 6.9		63.8 ± 16.1		55.9 ± 17.8	
Pathological types							
IDC	One	93.3 ± 1.8	0.1969	82.1 ± 2.7	0.8418	78.3 ± 2.8	0.9614
	Three	88.2 ± 2.5		66.1 ± 3.7		60.2 ± 3.8	
ILC	One	100 ± 0.00		82.2 ± 11.4		82.2 ± 11.4	
	Three	100 ± 0.00		62.8 ± 14.8		62.8 ± 14.8	
IDC + ILC	One	100 ± 0.00		80.2 ± 10.3		76.1 ± 10.6	
	Three	100 ± 0.00		61.1 ± 14.4		57.9 ± 14.0	
Others	One	85.9 ± 7.6		89.1 ± 7.5		75.3 ± 9.9	
	Three	85.9 ± 7.6		80.2 ± 10.8		67.8 ± 11.4	
Grade							
1	One	100 ± 00	0.4695	80 ± 7.9	0.9482	73.3 ± 17.6	0.8416
	Three	100 ± 00		53.3 ± 24.3		48.9 ± 23.2	
2	One	94.5 ± 1.6		81 ± 2.9		78.0 ± 3.0	
	Three	88.9 ± 2.6		64.3 ± 4.0		59.4 ± 4.1	
3	One	88.6 ± 5.5		86.4 ± 5.7		78.2 ± 6.9	
	Three	84.7 ± 6.5		71 ± 8.5		60.6 ± 8.8	
ER status							
−ve	One	96.4 ± 1.5	0.1041	72.9 ± 5.9	0.1839	68.1 ± 6.1	
	Three	93 ± 2.2		64.8 ± 6.9		58.1 ± 7.0	0.0453
+ve	One	96.4 ± 1.5		87.5 ± 2.6		85.1 ± 2.7	
	Three	93 ± 2.2		68.4 ± 4.0		64.7 ± 4.1	
PR status							
−ve	One	91.8 ± 3.3	0.1841	73.6 ± 5.2	0.0726	70.4 ± 5.3	
	Three	89.6 ± 3.9		63.7 ± 6.1		60.7 ± 6.1	0.0512
+ve	One	96.6 ± 1.5		88.5 ± 2.6		85.9 ± 2.9	
	Three	92.1 ± 2.5		68.2 ± 4.2		63.4 ± 4.4	
Lymph node status							
−ve	One	97.4 ± 1.9	0.1443	95.6 ± 2.5		93.5 ± 2.8	
	Three	94.6 ± 3.3		90.6 ± 3.7	0.0000	85.9 ± 4.6	0.0000
+ve	One	94.6 ± 1.8		76.9 ± 3.3		73.6 ± 3.4	
	Three	89.5 ± 2.6		56.9 ± 4.4		51.8 ± 4.3	
IHC based subtypes							
Luminal (A/B)	One	95.3 ± 2.1	0.0829	85.7 ± 3.4	0.0672	83.0 ± 3.7	0.1966
	Three	89.5 ± 3.6		66.8 ± 5.5		61.2 ± 5.7	
HER2 +ve	One	81.5 ± 10		56.5 ± 12.7		56.5 ± 12.8	
	Three	69.9 ± 13.8		46.2 ± 13.9		46.2 ± 14.0	
Triple −ve	One	100 ± 00		94.6 ± 5.2		89.5 ± 7.0	
	Three	100 ± 00		80 ± 14.1		75.7 ± 14.0	
Stage							
I	One	100 ± 00	0.4974	1.00 ± 00		100.0 ± 00	
	Three	100 ± 00		1.00 ± 00	0.0000	100.0 ± 00	0.0000
II	One	96.0 ± 2.0		95.4 ± 2.0		93.6 ± 2.4	
	Three	91.1 ± 3.4		79.0 ± 4.9		74.3 ± 5.2	
III	One	95.9 ± 1.8		72.9 ± 4.0		69.1 ± 4.2	
	three	92.6 ± 2.6		54.8 ± 4.4		50.4 ± 4.9	
Surgery type							
MRM	One	94.5 ± 1.6	0.0908	81.1 ± 2.8		77.8 ± 3.0	0.0663
	Three	91.2 ± 2.3		65.1 ± 3.8	0.0350	60.8 ± 3.9	
BCS	One	96.0 ± 2.8		87.7 ± 4.4		84.7 ± 4.8	
	Three	89.0 ± 4.6		74.1 ± 6.9		67.1 ± 7.2	
Chemotherapy							
No	One	84.6 ± 8.3	0.0908	86.5 ± 8.0	0.3018	73.5 ± 9.4	0.4070
	Three	68.5 ± 12.2		86.5 ± 8.0		59.5 ± 11.7	
Yes	One	94.7 ± 0.1		82.0 ± 2.5		79.0 ± 2.6	
	three	91.0 ± 0.		65.7 ± 3.4		61.3 ± 3.5	

TLR: time to local reccurence. TDM: Time to distant metastases. DFS: Disease free survival.

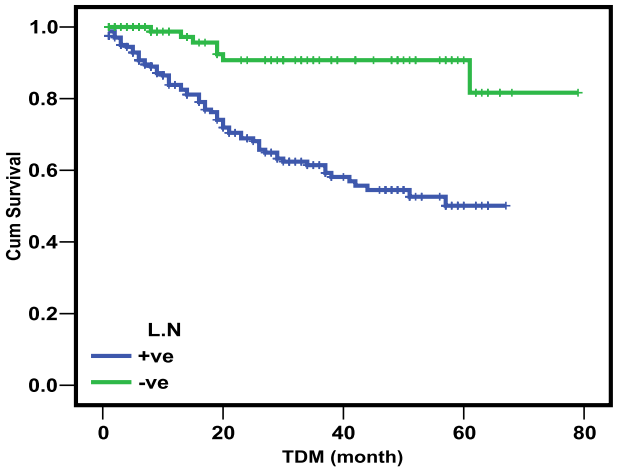

Fig. 1. Relation of lymph node status to TDM in young females <35 years with breast cancer ($P = 0.0000$).

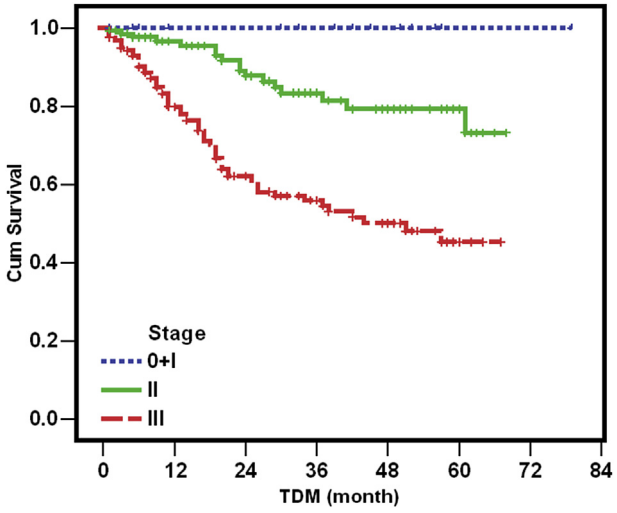

Fig. 2. Relation of tumor stage to TDM in young females <35 years with breast cancer ($P = 0.0000$).

mastectomy (Fig. 3). Although there was no statistical significance encountered, TDM was found to be shorter in patients with HER 2neu enriched disease (Table 3).

Disease free survival

The median DFS was 60 months. Patients younger than 25 years old, single, grade I disease, HER2 enriched disease and who did not receive chemotherapy had non significant shorter DFS. Negative lymph nodes, ER positivity were the factors associated with significantly longer DFS while stage III had very highly significant shorter disease free survival (Table 3**)**, (Figs. 4 and 5).

Discussion

Aided by the founding of the GCR in 1998 as part of the Middle East Cancer Consortium (MECC) recent breast cancer studies in the region have focused on Egypt. To the best of our knowledge this is the first report from the Egyptian NCI and the second from Egypt that systematically examined younger onset BCs in an Egyptian

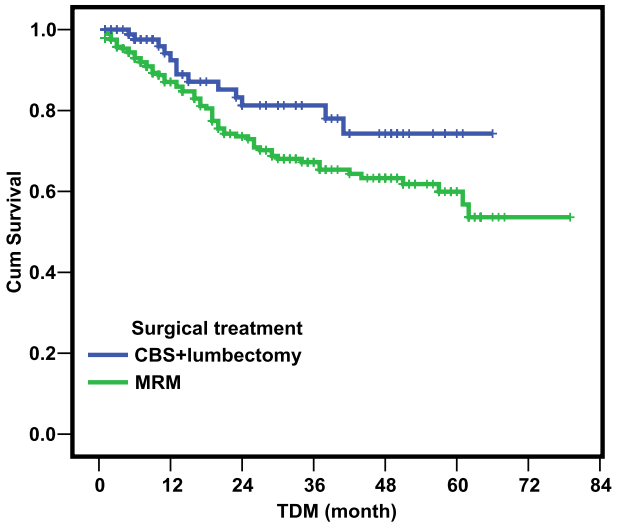

Fig. 3. Relation of surgery type to TDM in young females<35 years with breast cancer ($P = 0.0350$).

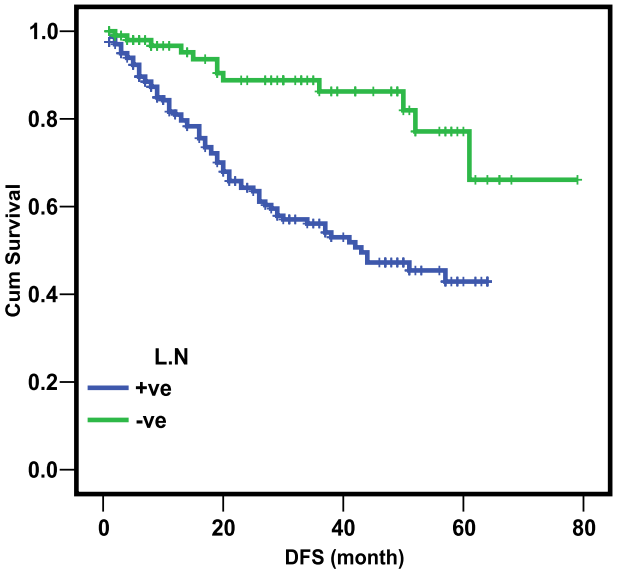

Fig. 4. Relation of lymph node status to DFS in young females <35 years with breast cancer ($P = 0.0000$).

population. The previous report by Farouk et al. [18] commented on patients diagnosed in 2006 through 2015. During those 9 years a lot of advances have been introduced either in the treatment or the procedures & techniques of pathological diagnosis making the group not homogenously diagnosed or treated. Our study analyzed the epidemiological, clinico-pathological factors affecting the prognosis& treatment outcome of breast cancer in women aged 35 years and younger. Although no consensus has been reached about the definitions of young age breast cancer [19], a systematic analysis of a large number of Korean patients found that age <35 years was a reasonable cut-off for defining young age breast cancer in terms of disease outcome [20].

Of 5408 patients diagnosed with breast cancer at NCI between 2008 & 2010, 9.2% of cases were aged ≤35 years and this is almost

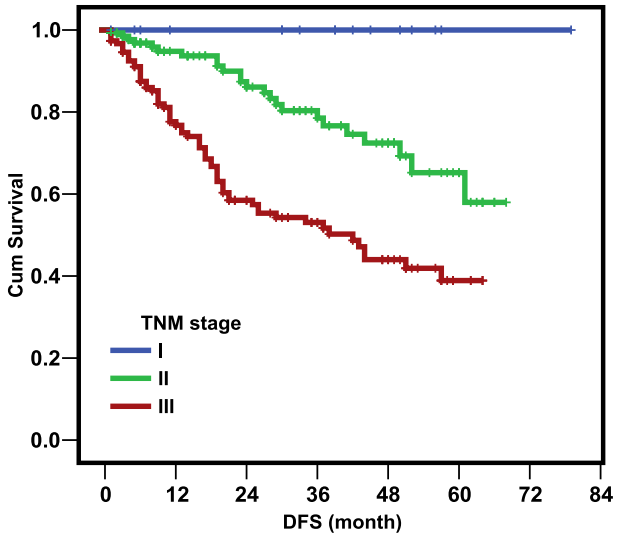

Fig. 5. Relation of TNM stage to DFS in young females <35 years with breast cancer ($P = 0.0000$).

similar to that reported by a Moroccan study [21] and an Indian study [22]. However this is higher than that reported in USA (2.4%) [23]. In Saudi Arabia, the proportion of breast cancer patients ≤40 years at diagnosis is dramatically larger with 25.1% of breast cancer cases [24]. In Asian series, this number varies between 10% in developed and up to 24% in developing countries [25].

Only 19% of our patients were nulliparous and 81% had at least one child which is comparable to Gabriel & Domchek [26] who stated that early childbearing seems to be a risk factor for developing breast cancer before the age of 35. In addition nothing was documented about discussing the issue of fertility preservation in these patients in spite that fertility is an important issue that could significantly affect the decision of the treatment and the quality of life in young cancer patients. The systemic treatment for breast cancer could lead to permanent amenorrhea in 33%–76% in patients younger than 50 years of age [27]. Only 28 patients in this study (6.5%) reported use of oral contraceptive pills. None of large prospective cohort studies with prolonged follow-up has observed an increased overall risk of cancer incidence or mortality among ever users of OC [28]. However this is on the contrary to that reported by Abahssain et al. [21].

The family history was reported in the records of 337 patients of whom only 30 patients (8.9%) had positive family history. This goes with that reported by Abahssain et al. [21] and lower than that reported by Loman et al. [29], Collins et al. [30], Rudat et al. [24] and Kallel et al. [31].

In the upcoming table (Table 4) we compare the clinicopathologic features & treatment modalities of our group of patients together with 5 other studies discussing BC in young women in developing world [9,21,24,31,32]. The finding in these studies support our results that BC in young women have larger tumor size, positive lymph nodes, advanced stage, grade 2–3 more common, predominance of invasive ductal carcinoma, HER2 overexpression.

However we found a higher percentage of grade 2 tumors (83.3%) than is reported in the aforementioned series. Other western studies including a UK-based study evaluating the pathological features and outcome of women who were aged <40 years at diagnosis reported grade 3 tumors in 58.9% cases [33]. Moreover in the analysis presented by Schlichting et al. [8] the majority (56%) of younger (≤40 years of age) SEER cases were diagnosed with grade 3 tumors.

We reported high percentage of stage III disease on the contrary to western studies that reported lower prevalence of stage III disease [8,30,33]. This could be mainly due to lack of the awareness in developing countries and the misconception that cancer breast is the disease of only old women. Moreover, an advanced stage at diagnosis may reflect a rapidly growing tumor. The percentage of estrogen receptor-negative tumors is high (>30%). This is similar to El Saghir et al. [34] and several other studies from western countries [30,33,35,36].

Being a retrospective study, Ki67 was not available in our cohort and HER 2neu overexpression was evaluated in only 183 patients. We divided the patients into Luminal, HER2 enriched and Triple negative groups. We noticed that 71.2%, 13.3% of patients had luminal and triple negative disease (TNBC) respectively. This is in agreement with that reported by Lin et al. [37]. Our results differ from other studies [22,32,38], that reported lower rate of luminal disease (although still the most prevalent subtype) and higher rate of TNBC. Also from this table we found that young BC women are more likely offered mastectomy. This could be partially due to advanced disease at presentation and partially due to the misconception that young age by itself is an indication for radical surgery.

Ovarian suppression (medical, irradiation, and/or oophorectomy) was documented in 56 patients with ER-positive tumors. Although chemotherapy-induced amenorrhea has been associated with improved prognosis, the use of ovarian suppression in addition to chemotherapy and tamoxifen remains controversial [39].

In our study, we focused on some clinical and pathologic factors that may affect the prognosis of young BC patients in univariate analysis. We present one of the few studies exclusively addressing patient, tumor and treatment related factors important for disease free survival. We couldn't prove that very young age less than 30 years compared to those aged from 30 to 35 years is a significantly poor prognostic factor for DFS unlike the study by Zhao et al. [9]. In the current study patients with ER and or PR positive disease had longer DFS than those with HR negative BC. This finding was also reported by Abahssain et al. [21] and Zhao et al. [9]. However, Kim et al. [40] and Yang et al. [41] reported that HR positive disease in young patients (especially PR + ve) had worse prognosis than older group.

In our study the subtypes of breast cancer were introduced to reflect the biology of tumors and mark differences in patient prognosis. Although insignificant, the shortest TLR, TDM and DFS were for HR negative/HER2neu positive subtype with P value = 0.0829, 0.0672 and 0.1966 respectively. HER2 positivity usually correlates with a lack of ER/PR expression, worse nuclear and histologic grades, aneuploidy and a high rate of proliferation which confers higher local recurrence and poorer prognosis especially in young women [42]. We showed that node negative patients had both longer TDM and DFS than those with positive nodes (P value = 0.0000 for both) which is comparable to Alieldin et al. [43], Zhao et al. [9] and Rudat et al. [24].

Stage III in our cohort carried very highly significant shorter TDM and DFS, which was consistent with the study reported by Rudat et al. [24].

In our study TLR didn't differ significantly between patients who were offered MRM and those who were offered BCS (P value = 0.7218). But we demonstrated a significant longer TDM (P value = 0.0350) and a longer although insignificant DFS (P value = 0.0663) for patients treated with BCS compared to those treated with MRM. These results are consistent with that of Rudat et al. [24]. However quite different from other published data that reported higher risk for local recurrence among young patients under the age of 35 following BCS compared to mastectomy Zhou et al. [44] and Abahssain et al. [21]. In spite of these data, young age alone up till now is not a contraindication to BCS because the

Table 4
Comparison between studies from developing countries investigating young onset breast cancer.

Parameter	Our study	Kallel et al. [31]	Thapa et al. [32]	Abahassain et al. [21]	Rudat et al. [24]	Zhao et al. [9]
Number/Total	458/5408	83/781	263/944	427/5309	55/213	132/1931
%	8.46%	10.6%	27.9%	8%	25.8%	6.8%
Median age	32 (23–35)	31.7 (19–35)	34.6 mean	32 (15–35)		32
Histology						
IDC	340 (83.7%)	73.5%	245 (93.1%)	360 (88.2%)	49 (89%)	114 (86.4%)
Grade						
1	1 (0.3%)	3 (3.6%)	II or III	17 (4.1%)	2 (3.6%)	9 (6.8%)
2	294 (83.3%)	35 (42.2%)	147 (55.9%)	206 (50.4%)	17 (30.9%)	74 (56%)
3	58 (16.4%)	25 (30.1%)		155 (37.9%)	22 (40%)	31 (23.48%)
UK	105			31 (7.6%)	14 (25.5%)	18 (13.64%)
T						
T1	29 (11.3%)	6%	–	48 (13.5%)	16 (29.1%)	35 (26.5%)
T2	139 (54.3%)	31.3%	–	161 (45.2%)	22 (40%)	73 (55.3%)
T3	73 (28.5%)	26.5%	–	71 (19.9%)	4 (7.3%)	21 (15.9%)
T4	15 (5.9%)	19.3%	–	76 (21.3%)	6 (10.9%)	3 (2.3%)
N						
−ve	116 (36.1%)	18 (25.7%)	71 (27%)	107 (30%)	18 (32.7%)	65 (49.2%)
+ve	205 (63.9%)	23 (32.9%)	192 (73%)	249 (69.9%)	34 (67.3%)	67 (50.9%)
M						
M0	314 (89.7%)	70 (84.3%)	–	356 (87%)	–	–
M1	36 (10%)	13 (15.7%)	–	53 (13%)	–	–
Stage						
I	15 (4.3%)	–		30 (7.3%)	6 (10.9%)	–
II	140 (39.6%)	–	III or IV	140 (34.2%)	19 (34.5%)	–
III	160 (45.9%)	–	145 (55.1%)	186 (45.5%)	23 (41.8%)	–
IV	36 (10.2%)	–		53 (13%)		–
ER						
−ve	93 (32.5%)	ER & or PR	ER & or PR	160 (39.1%)	17 (30.9%)	43 (32.6%)
+ve	193 (67.5%)	46 (55.4%)	34.7%	220 (53.8%)	33 (60%)	89 (67.4%)
UK		UK: (6%)		29 (7.1%)	5 (9.1%)	
PR						
−ve	107 (37.3%)	–	–	128 (31.3%)	23 (41.8%)	46 (34.8%)
+ve	180 (62.7%)	–	–	252 (61.6%)	7 (49.1%)	86 (65.2%)
UK				29 (7.1%)	5 (9.1%)	
HER2						
−ve	128 (69.9%)			29 (7.1%)	33 (60%)	91 (68.9%)
+ve	55 (30.1%)	5/17 (29.4%)		28 (6.8%)	12 (21.8%)	37 (28.0%)
UK			13/49 (26.5%)	352 (86.1%)		4 (3%)
Subtypes						
Luminal	129 (71.2%)	–		–	29 (52.8%)	35 (26.5%)
Her2	28 (15.5%)	–	22.4%	–	3 (5.5%)	66 (50%)
Triple −ve	24 (13.3%)	–		–	14 (25.5%)	10 (7.58%)
Surgery						
Yes	348 (80.4%)	73	–	347 (97.5%)	100%	–
No	85 (19.6%)	10	–	9 (2.5%)		–
Surgery type						
MRM	251 (72.1%)	62	197 (74.9%)	265 (76.8%)	33 (60%)	–
CBS	97 (27.9%)	11	66 (25.1%)	80 (23.2%)	22 (40%)	–
Neoadjuvant CTH						
Yes	79 (18.7%)	–	–	21.3%	9%	–
No	343 (81.3%)	–	–	78.7%	46	–

observed higher local failure is not associated with an impact on survival [16].

Our study also has some limitations. Firstly detailed information on BC patients such as the exposure risk factors was not fully captured. Secondly there were no immunohistochemical results of ER& PR for a little proportion of patients; also analyses of tumor subtype and HER2 status, were limited by missing data. Thirdly some patients couldn't be contacted and their survival status couldn't be included in the analysis. Lastly, there was no genetic testing for BRCA1 & BRCA2 mutations.

Conclusion

The results of this present study are highly important, as they provide baseline data of young BC in the Middle East & North Africa region; thus, contributing to future epidemiological and hospital-based researches. It is of utmost importance to refine our understanding of the biology of the disease in young patients in an attempt to optimize their management. We recommend further epidemiological & genetic studies along with educational campaigns and screening programs to address the increasing BC problem in the region.

Conflict of interest statements

The authors disclose no conflict of interest.

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