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Kingdom of Saudi Arabia Ministry of Health Agency of Public Health Assistant Agency for Preventive Health Field Epidemiology Training Program Breast cancer in women aged 40 and below reported to Sultan Qaboos Cancer Care Comprehensive Center: 20 Years Retrospective cohort study

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Background: Breast cancer is considered a public health concern worldwide. In 2020, 11·7% of all cancers diagnosed in the world were female breast cancer, making it the most common cancer reported around the globe. Breast cancer comprises 22·36% of all diagnosed cancers among Omani women. Breast cancer in young women has not been studied in Oman, for which, this study was conducted. Also, to understand the histological and molecular pattern of BC in this age group, as well as to estimate the overall (OS) survival of these patients.

Methods: We conducted a retrospective cohort study. Electronic data was collected from women aged 40 and below treated at Sultan Qaboos Cancer Care Comprehensive Center (SQCCCRC), from 2002-2022. Secondary data for socio-demographics, family history of BC, BC histological subtypes, immunohistochemistry (PR, ER, and HER2), and TNM staging were collected. SPSS was used to analyze the data. Appropriate statistical tests were used for descriptive and inferential analysis. The Kaplan-Meier estimator and log-rank test were used for the survival analysis. Differences were considered statistically significant at p-value < 0·05.

Results: A total of 418 patients were included in the study. The reported cases' mean age at the time of diagnosis was (34·7 ±4·3 years), with a mean BMI of (28· 47±6·6). 16·7% of patients had a positive family history of BC. Out of all cases, 84·7% of cases were ductal, while 3·3% were lobular. On diagnosis, the majority of patients (39·1%) were in the T2 stage, while 14·1% were in the Metastatic stage, and 37·6% had axillary lymph node metastases. Whereas, 68 (16·3%) were in the early stage, and 213(51%) of the patients reported a locally advanced stage of BC. Positive PR, ER, and HER2 immunostaining were 61·6%, 70%, and 42·2% respectively. Early-stage (T1,2 and N0, M 0) patients had 89% five-year overall survival (OS), while locally

advanced (T0-1-2, N1-2-3, M0) patients had 80% five-year OS, and metastatic (T0-1-2-3, N1-2, M1) patients had 40% five-year OS (p=0·001).

Conclusion: Our study showed that BC has the same pathological characteristics as the neighboring countries but it differs from other developed countries, and this requires further study. Reviewing the screening program and maintaining a well-organized cancer registry would help in dealing with breast cancer more promptly.

Keywords: Breast cancer, 40 years and below, women aged 40, Sultan Qaboos Cancer Care Comprehensive Center

Introduction:

Breast cancer (BC) is a major public health concern that affects people globally. In 2020, 11·7% of all cancers diagnosed in the world were female breast cancer, making it the most common cancer worldwide.[1] In 2020, there were 2·26 million women diagnosed with breast cancer and 685,000 deaths globally.[1] Breast cancer is responsible for roughly 15% of all cancer deaths among women worldwide.[2]

The rising incidence of breast cancer is affecting both developing and developed countries.[1] For example, in 2019: Breast cancer became the most common cancer and accounting for 30% of all cancers in the United Kingdom.[1] Although the rate of breast cancer in women has doubled over the past 50 years, it has remained stable in men over the past two decades.[1] 86% of breast cancers in women are diagnosed at stage I or stage II (early-stage breast cancer which has not spread beyond nearby lymph nodes).[1]

In the Gulf Cooperation Council (GCC) region, BC is the most commonly diagnosed cancer among women, accounting for 13%–35% of all cancers; moreover, approximately half of patients with BC are under 50 years of age at the time of diagnosis, with a median age of 49–52 years compared with the age of 63 years in the Western countries.[2] As breast cancer is becoming a leading cause of cancer death worldwide, this needs proper planning and resource management in prevention, early detection, treatment, follow-up and palliative care.

Breast cancer incidence in Oman is increasing. In 2010, breast cancer was the most common cancer diagnosed in Oman, comprising 22·36% of cancers among women, and mostly reported in women aged 40–59 years.[3] In 2019, a total of 338 (29·19%) cases of BC were reported among women in Oman.[3] Among these 338 cases, 56 cases were reported in women 35–39 years, 25 cases were reported in women aged 30–34 years, and 12 cases among 25–34 years old women.[3] Breast cancer incidence rose from 301 cases in 2018 to 350 cases in 2019.[3] This indicates that 27·5% of breast cancer affect Omani women aged below 40 years. These figures are similar to other countries in the region.[4]

The Sultanate of Oman has recently established the Sultan Qaboos Comprehensive Cancer Care and Research Centre (SQCCCRC). This new center, along with already operating cancer centers in the capital Muscat, the National Oncology Center has become a primary site for receiving and treating cancer patients in Oman.[5]

We aim to study the breast cancer patients reported to the Sultan Qaboos Comprehensive Research Center in women aged 40 years and below, associated with the type of tumor, positive family history, and smoking. The study provides a descriptive analysis of this population. This analysis can provide demographical and clinical data to the healthcare providers and policymakers; which provide insight to improve screening protocols, early detection, treatment goals, and to improve the health care provided for women aged 40 years and below diagnosed with BC. The study also aims to examine the prognosis (overall survival) of these patients and its association with receptor status, family history, and cancer stage.

Methods

Study design

This is a retrospective cohort study, a patient-based study using secondary data from the SQCCCRC and Sultan Qaboos University Hospital SQUH. Electronical data was collected from 2002–2022. The following variables, age, gender, body Mass Index BMI, histological type (Invasive ductal carcinoma IDC, Invasive Lobular Carcinoma ILC, and Ductal Carcinoma In Situ DCIS) staging TNM, Immune Histochemistry IHC, and family history.

Study population

The study population of this study, are Omani women, diagnosed with Breast cancer in the SQCCCRC and SQUH. The Inclusion criteria were Omani females, aged 40 years and below, with breast cancer diagnosed and treated at SQCCCRC and SQUH between 2002 and 2022. Exclusion criteria was set to exclude all the male patients, women diagnosed with BC but treated in other centers, above 40 years old females diagnosed with BC and none Omani patients diagnosed with BC who are followed at the SQCCCRC.

Variables

BMI was categorized as low (<18), normal (18–24·99), and high (25 or above). [20] Ki67% was divided into two categories, 20 and below were labeled as low and 21–100 as high. Histology types included Invasive ductal carcinoma (IDC), Invasive Lobular Carcinoma (ILC), and Ductal Carcinoma in Situ (DCIS). Based on the TNM criteria, the stage was classified as early (T0,1,2, N0, M0), locally advanced (T3,4, Nx, M0), and metastatic (Tx, Nx, M1,2). Overall survival (OS) was calculated from the date of diagnosis to the date of the last follow-up. Receptor status (estrogen receptor ER, progesterone receptor PR, human epidermal growth receptor 2 HER2), family history, and were examined as predictive factors of OS.

Statistical analysis

Data was extracted from the electronic medical record system and stored as a Microsoft Excel (2019) file. Descriptive analysis was performed using mean and standard deviation for the continuous variables, frequency, and proportions for the categorical variables. The survival analysis will be performed using the Kaplan-Meier estimator and log-rank test. Differences were considered statistically significant at p-value < 0·05. Statistical analyses were performed using the IBM SPSS (Statistical Package for Social Sciences) software version 23.

Ethical consideration

The data is obtained from the SQCCCRC and SQUH, ethical approval obtained from SQCCCRC. For any missing data, patients were contacted to gain further information to have more accurate results. IRB & EC Project ID is (CCCRC-28-2023)

Table 1: **baseline characteristics of the study population.**

	Mean (SD)
Age	34·7 (4·3)
BMI	28·0 (6·6)
	N (%)
PR (Progesterone receptor)	
Positive	242/393 (61·6%)
Negative	151/393 (38·4%)
Total	393
Missing	25
ER (Estrogen receptor)	
Positive	244/394 (70%)
Negative	150/394 (30%)
Total	394
Missing	24
HER2 (Human Epidermal Growth factor receptor)	
Positive	162/384 (42·2%)
Negative	222/384 (57·8%)
Total	384
Missing	34
Ki67 (Protein used as cellular marker for proliferation)	
High	54/314 (17·1%)
Low	260/314 (82·8%)
Total	314
Missing	100
Family history	
Positive	51/304 (16·7%)
Negative	253/304 (83·2%)
Total	304
Missing	114
Histochemistry	
DCIS (Ductal Carcinoma In Situ)	21/418 (5%)
Ductal	354/418 (84·7%)
ILC (Invasive Lobular Carcinoma)	14/418 (3·3%)
Other	19/418 (4·5%)
Total	418
Staging	
Early	68(16·3%)
Locally Advanced	213(51%)
Metastatic	47(11·2%)
Total	418

Results

A total of 1134 patients were diagnosed with breast cancer in the center, out of them 418 (36·8%) patients were included in the study who fulfilled the inclusion criteria. 716 patients were excluded. All 418 patients were diagnosed and treated between 2002–2022 in the SQCCCRC or Sultan Qaboos University Hospital. The mean age at the time of diagnosis was 34·7, ranging from 19–40 years. With a mean BMI of 28 and ranging between 13–49·5. 47 (11·2%) of the reported cases were in late (Metastatic stage). Whereas, 68 (16·3%) were in the early stage and 213 (51%) of the patients reported in the locally advanced stage of BC. Patients were tested for their PR, ER, Her2 receptor status, and Ki67 protein level. The total available data for PR was 393 out of which 242 (61·6%) reported positive and 151 (38·4%) were negative. For ER, a total of 394 patients had available data. 244 (70%) patients reported positive and 150 (30%) reported negative. 384 patients had available data for Her2. 162 (42·2%) patients reported positive and 222 (57·8%) patients reported negative. A total of 314 results were available for Ki67, out of which 54 (17·1%) were high and 260 (82·8%) were found low. Out of the total 418 patients, only 304 patients had available details regarding the family history. 51 (16·7%) patients had a positive family history, and 253 (83·2%) had a negative family history. Histochemistry category a result. 354 (84·7%) had Ductal carcinoma, followed by 21 patients (5%) had DCIS, followed by other types of tumors, as 19 patients (4·5%) had Invasive lobular carcinoma in 14 patients (3·3%).

Table 2: **survival analysis of BC patients <=40 years old, Overall survival (OS) predicted by Receptor status (ER, PR, HER2), family history, and disease stages.**

	N	**5 YR OS (95%CI)**	**Log-rank test p-value**
Overall			-
ER **(Estrogen receptor)**	43		0·024
Positive	18	68% (1.47)	
Negative	25	67% (0.11368)	
PR **(Progesterone receptor)**	43		0·027
Positive	18	68% (0.147)	
Negative	25	67% (0.11368)	
HER2 **(Human Epidermal Growth factor receptor)**	43		0·249
Positive	17	70% (0.14112)	
Negative	26	68% (0.11564)	
Family History of BC	31		0·202
Positive	3	86% (0.16.72)	

Negative	28	70% (0.10388)	
Staging TNM	41		0·001
Early	8	89% (0.12936)	
Locally Advanced	23	80% (0.11172)	
Metastatic	10	40% (0.28616)	

ER was a significant predictor of OS. ER-positive patients had 68% OS at five years, and ER- had 67% OS at five years (p=0·024). PR was a significant predictor for the OS. PR-positive patients had 68% and PR-negative e patients had 67% at five years (p=0·027). HER2 is not a significant predictor for this study (p=0.249), as the HER2-positive patients had 70% and HER2-negative patients had 68% OS at five years. Family history is insignificant to OS. Patients with positive family history had 86% and negative family history had 70% OS at five years (p=0·202). TNM staging categorized as early, locally advanced, and metastatic was a significant predictor of OS. Early stage (T1,2 and N0, M 0) had 89% five-year OS. Locally advanced (T0-1-2, N1-2-3, M0) had 80% five-year OS. While Metastatic (T0-1-2-3, N1-2, M1) had 40% five-year OS (p=0·001).

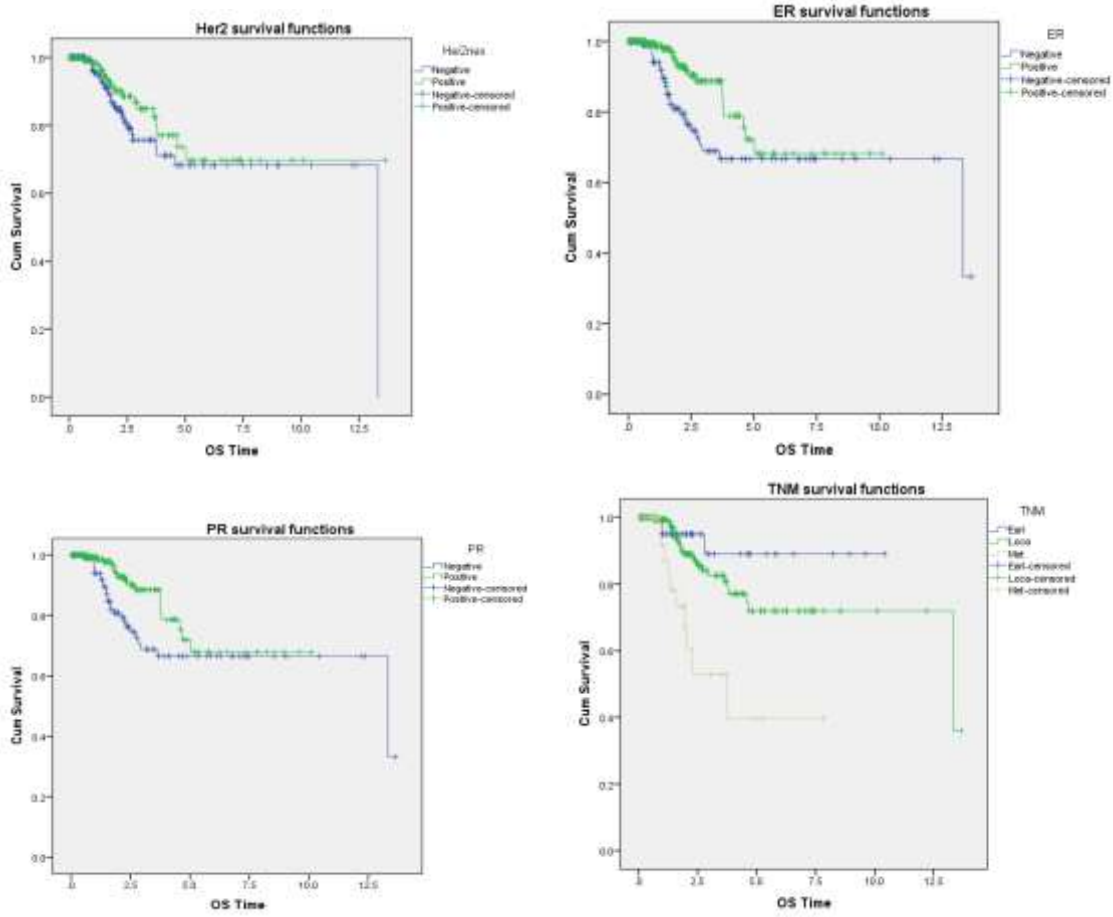

Figure 1: **Showing survival analysis graphs**

Discussion

Breast Cancer is significantly co-related to age at diagnosis and the stage at which the patient presents, as noted in our study and compared to the neighboring countries.

Many studies were conducted in Oman in regards to breast cancer, but very few knowledge is known about BC in this age group (40 years and below).

In the GCC, breast cancer is the most common cancer diagnosed.[6] From 1998–2007 a total of 11,396 BC cases were reported. The most common type of BC is ductal carcinoma which is consistent with our findings.[6]

A study published from United Arab of Emirates (UAE), studying women referred to the University hospital Sharjah between March 2016 to July 2018. A total of 1048 patients were studied. Out of this 1048 patients a total of 94 (10%) patients were diagnosed with breast cancer and 954 (91%) had benign breast lesions. Approximately 1 in 5 of these women were aged 40 or younger than 40 years of age at diagnosis. The variables studied were age, body mass index, menopause status, and women with serum 25-hydroxyvitamin D [25(OH)D] levels lower than 20 ng/mL.[7] In this study it was noted that 84% had Invasive ductal carcinoma, 5% had Invasive Lobar Carcinoma and mixed. 36% were diagnosed with Luminal A (hormone receptor status positive and HER2 status negative), 14% had Luminal B (hormone receptor status positive and HER2 status positive). Also, 16% were Triple positive.[7]

The receptor status has been studied extensively in many different studies around the world and it's a good comparing variable. In Saudi Arabia for instance, a study conducted at King Abdulaziz University Hospital showed that 88% of BC female patients had ductal carcinoma, 78% were ER-positive, 62% were PR-positive, and 39% were HER2-positive.[6]

In contrast with a study conducted in India, which included 1284 women following up in the Department of Medical Oncology at Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India during the period from January 2008 to December 2011, ER and/or PR was seen in 63·4% patients, while 23·8% of tumors were triple negative. Only 23% were HER2 positive. Around 10·0% of tumors were both ER and HER2 positive. ER and PR positivity was significantly associated with negative HER2 status.[5] Whereas, in our study, 42% were triple negative and 58% were triple positive.

Taking an example from an advanced well-developed country, and to compare our study findings with a cohort study conducted in Norway, which included 21384 patients, aged 20–89, between 2005–2015. All of these 21384 patients were diagnosed with BC and listed in the Cancer registry. In the age group of 40 and below, 31·7% reported negative ER, and 68·3% reported positive. 44·3% reported negative and 55·7% reported positive for PR. 72·5% were negative and 27·5% positive for HER2.[8] In contrast, our study showed that the majority of patients tested positive for PR and ER (62%, and 70%), and 42% tested positive for HER2. Similarly, 38·4 % reported negative PR, 30% negative ER and 57·8% negative HER2.

This makes us to reach to conclusion that the pathological characteristics of BC in Omani women could be similar to neighboring countries (like Saudi Arabia), but different from other Asian (e.g., India) and European countries (e.g., Norway).

Limitations:

This study had several limitations. The lack of some fundamental data like smoking history, age at menarche, as this may be associated with the development of breast cancer. Another limitation was that the national data is not accessible to enhance the data analysis for this study, but should be considered for future studies. Another limitation was that not much studies could be found on this age group worldwide, as normally breast cancer is studied in general. Another limitation worth mentioning here is, some cases may be lost as the wrong ICD coded initially in the primary health care first. Second, some patients opt flying abroad for treatment specially for diseases like cancer for social reasons. Another important side was not studied in this study, the correlation analysis of stages with the age at diagnosis and analysis on predicting factors of progress of disease from one stage to another.

Recommendation:

As part of our role in public health awareness and guidance, we would recommend to review the screening program in Oman and the other neighboring countries. One of the suggestions is to reduce the age of screening to help early detection of none symptomatic patients as early as possible. Also, promote self-examination in the community. As its advisable to include the breast self-examination in school health and university health programs, to target the girls at younger age to help early diagnosis and improve the knowledge regarding breast cancer. Far most important recommendation is, maintain one single register for all cancer types in Oman, under the ministry of health umbrella and to have easier and faster excess to screening programs, and encourages more integrated multidisciplinary clinics. As having a single registry with easy accessibility would help in future studies and setting polices accordingly.

Conclusion

This study found that most of the Omani women aged 40 and below reported to SQCCCRC with breast cancer were positive ER and PR but negative HER2 status receptors. At reporting, most of the women were at an advanced stage and ductal cancer as per the histochemistry. Receptor status (ER, PR) and TNM staging were significant predictors of OS in Omani women diagnosed with breast cancer under or at the age of 40 years.

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