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Tumour Size and Age in Early Versus Advanced Breast Cancer in Kuwait

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Abstract Background: In the Middle East, Kuwait in particular, the rate of incidence of breast cancer has increased in the past recent years. The objective of this study was to obtain information about the relationship between tumour size and age in early vs. late stage breast cancer in Kuwaiti female patients. Method: A total of 259 files of Kuwaiti women with breast cancer in 2012 were obtained from the Kuwait Cancer Control Center Registry (KCCC). Data were obtained was evaluated and divided into different prognostic variables including patient characteristics, tumour size, tumour grade, TNM, laterality, and treatments. Results: The results showed that the mean age at diagnosis was 54± 11.2. The mean tumour size was 3.4± 2.1 cm. The most frequent stage observed throughout the study, according to TNM staging, was T2N0M0. One hundred and thirty cases were diagnosed as an early stage while sixty-eight cases were diagnosed as a late stage. Conclusion: Larger tumour size, high lymph node involvement and negative ER/PR receptors were observed more in the older age group compared with other studies. An early-stage disease can present with large tumour size >3 cm and late-stage disease can present with small tumour size. More studies are required to find the aetiologies. Women should be encouraged to do screening programs.

Keywords: *Breast cancer, age, Cancer registry, Kuwait, Middle East, Early Stage, Late stage, Chemotherapy, Radiotherapy, Mastectomy, TNM, Lobular, Ductal, Tubular*

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1. Introduction

Breast Cancer is the most common cancer in women worldwide [1]. In 2012, 1.7 million new cases were diagnosed with breast cancer which represented nearly 25% of all cancers in women [1]. The highest incidence of breast cancer was in Northern America and Oceania and the lowest incidence was in Asia and Africa [1]. It was also identified as the number one cause of mortality in Kuwaiti women [2]. The number of women who died in 2011 due to breast cancer exceeded 500,000 worldwide [1,4].

Breast cancer is a complicated disease that shares different contributions from environmental and inherited risk factors. The risk of breast cancer doubles after menopause, but the survival rates have improved due to early diagnosis and progressive improvement in treatment strategies [1]. Most of the breast cancer cases were hormone-related. Hormonal therapy, such as oral contraceptives, is one of the risk factors in younger women [1].

Lifestyle changes such as sedimentary life with a lack of physical activity and high fat-containing food might be considered as contributing risk factorsthat increase breast cancer incidences [3]. The lifestyle shift in Kuwait not only changed the way people lived but also changed the types of diseases presented in the population. The shift to a more modern western lifestyle altered the disease burden from communicable diseases into chronic non-communicable diseases [2]. The Ministry of health in Kuwait recognised the direct effects of the new lifestyle with studies showing that 48% of Kuwaiti females were obese (BMI ≥30) [2]. It has also shown that 65% of the population were physically inactive with low prevalence of fruits and vegetables intake and high prevalence of smoking among both males and females [2].

In the Arab world, breast cancer was diagnosed at a younger age in comparison with Western countries. Median age at presentation of breast cancer in the US, Egypt and Kuwait was 61 years, 50-54 years and 54 years, respectively. A population-based study in Switzerland revealed that early-aged women presented with more aggressive tumours [5].

Unfortunately, Statistical data to support this were not publicly available because data may not be gathered consistently or not available to answer questions by most cancer registries in the Arab world [6]. Therefore, treatment strategies that were used to treat breast cancer were more aggressive. Most cases included all chemotherapy, radiotherapy, hormonal therapy and surgery [6].

In the past, when there was no breast imaging available, the control of breast cancer depended entirely on the successful treatment of the palpable disease. Today, the control of breast cancer has been improved by being capable of diagnosing the disease at a more favourable stage such as carcinoma in situ and invasive carcinoma when it has crossed the basement membrane [6].

Population-based screening program showed a significant improvement in mortality rates in Western countries [6]. Therefore, they were with no doubt a must in the Arab countries counting the age differences at the time of diagnosis. Screening programs should be based on two principles, the appropriate age to screen and the method [6].

The Kuwait Cancer Registry was founded in 1971 [4]. KCR is a voting member of the International Association of Cancer Registries (IACR) and was the first Arab country to publish the Kuwaiti data on cancer incidences in "Cancer in Five Continents" since the 5th edition in 1990 [4]. However, the number of researches addressing breast cancer in Kuwait is still minimal.

The primary aim of the study was to portray tumour size and age according to the different stages of disease in Kuwaiti women.

2. Methods

2.1. Participants

This was a case series study in which all Kuwaiti patients diagnosed with breast cancer disease C50.0-C50.9 between January 1, 2012, and the end of December 2012, according to the data provided by the Kuwait Cancer Registry were included. The study was conducted in the Cancer Epidemiology and Registry unit, Kuwait Cancer Control Center (KCCC) between January 10, and February 16, 2018.

2.2. Materials

Ethical approval from the Ministry of Health to access medical records was obtained. Medical records of 259 patients were sorted according to the archiving system of the Medical Record Department at KCCC to facilitate the retrieval of the files.

From the medical records; histopathology reports were used to obtain information about tumour pathology, tumour size, tumour grade, estrogen receptors, progesterone receptors, laterality, date of diagnosis and TNM. In case of insufficient information or missing histopathology reports, cytology, radiology and clinical reports were used respectively.

In case of insufficient information or missing reports from KCCC, external reports from other hospitals and clinics were retrieved. The date of birth was obtained from the civil identification card.

Information about co-morbidities, including hypertension and diabetes mellitus and family history of breast cancer were obtained from history sheets provided in the medical records. Information about treatments including chemotherapy, radiotherapy, hormonal therapy and surgery were obtained from the treatment sheets provided by the chemotherapy unit, the radiotherapy unit, the medical oncology unit and the surgical unit in KCCC.

Information about date of last follow-up, date of recurrence, survival status and disease-free status were obtained from the clinical progress sheets, which was included in the medical records.

International classification of the disease codes ICD-O 3rd-edition - first revision was used to resemble tumour pathology (8500, invasive ductal carcinoma and ductal carcinoma in situ), (8520, invasive lobular carcinoma), (8523, tubular carcinoma, mucinous carcinoma), (8530, inflammatory carcinoma), (8522, lobular carcinoma in situ, (8575, metaplastic carcinoma) and (8453, intraductal papillary-mucinous carcinoma) [7].

The staging system used was based on Cancer Staging Handbook [8]. The TNM staging obtained from the charts was recoded into stages 1, 2 and 3 with reference to the handbook. The staging was divided into early and late where stage 1 and 2 were considered early and stage 3 and 4 were considered late. A single case of a patient diagnosed with non-Hodgkin's lymphoma was excluded.

Two cases of male patients diagnosed with breast cancer were excluded. Bilateral breast carcinoma cases where each breast had a different histological type were recorded down as two separate cases. Bilateral breast carcinomas where both breasts had the same histological type of carcinoma were recorded as one single case. The number of cases available for analysis was 198.

Data on malignant neoplasm were collected according to the recommendations of the International Agency for Research on Cancer (IARC) and mortality data were collected from the Vital and Health Statistics Division, MOH, Kuwait [4].

2.3. Statistical Methods

Statistical package for social sciences (SPSS) version 24 and two MacBook Air were used for data management and analysis. Quantitative variables were summarized using mean and SD, median minimum and maximum values. Qualitative data were summarized using frequencies and percentages.

Comparison between the two groups (early and late disease), was done by using the student t-test. The association between two independent qualitative variables was done by Chi2 test or Fisher's exact test whenever appropriate. Differences were considered significant when p was < 0.05 and highly significant when $p < 0.01$ [11].

2.4. Limitations

Medical records were short on some data. Some cases did not have the TNM staging and some did not have the tumour size. Some clinical data were hard to understand due to poor handwriting.

Another limitation was the inability to retrieve medical records from the Mortality Medical Record Department due to the lack of easy access and the short duration of this study.

3. Results

A total of 198 women diagnosed with primary breast cancer at KCCC in 2012 were included in this study (median duration of follow up was 60 months (range 0-84 months) (Table 1). The mean age at diagnosis was 54 ±11.2 years (range23-83 years), around 89.9% of the cases aged above 40 years (Table 1).

About 20.7% of the cases had positive family history of breast cancer and 75.3% had negative family history (Table 1). Nearly 35.9% were diabetic patients and 39.9% were hypertensive (Table 1). The majority of the patients (82.32%) were married while 1.52% were single (Table 1). The right breast was the topographic site in 85 cases (42.9%), 104 cases (52.5%) had left breast cancer and 9 cases (4.5%) presented with bilateral disease (Table 1).

According to the TNM staging, the most frequent stage that was observed among the studied group was T2 with 100 cases (50.5%), and the least observed was T0 with 7 cases (3.5%) (Table 1). The commonest N stage that was observed among the group was N0 represented by 93 cases (47%) and the least observed was N3 in 16 cases (8.1%) (Table 1). Lastly, seven cases out of 198 showed metastasis with M1 (3.5%) at the time of the diagnosis (Table 1).

The analysis illustrated significant differences between early and late stages in patients, tumour characteristics and treatment.

The mean tumour size was 3.4±2.1 cm cm (Table 1). For patients who were above 40 years old, the percentage of those with tumour size less than 3 cm was 41.4% (Table 2). Around 25% of the same age group presented with a tumour size of 3 cm, then about 23% presented with tumour size larger than 3cm.

Forpatients who were 40 years old or less, about 5.1% had tumour size less than 3 cm. Within the same age group, about 1% hada tumour size of 3 cm and 4% hadtumour size greater than 3 cm (p value= 0.425) (Table 2).

For patients aged above 40 years, 118 cases (59.6%) were diagnosed as an early-stage, while 60 cases (30.3%) were diagnosed as a late stage (Table 3). Among the group aged ≤ 40 years, 12 cases (6.1%) were diagnosed as an early-stage, while 8 cases (4%) were diagnosed asa late-stage (Table 3).

There were 39.4% of the cases diagnosed as an early-stage disease who had tumour size smaller than 3cm, 17.2% of the cases had a tumour size of 3 cm and 9.1% had tumour size larger than 3 cm. Patients who were diagnosed with late-stage disease, around 7.1% of the patients had tumour size less than 3cm, 9.1% had a 3cm tumour and 18.2% had tumour size larger than 3cm (Table 3) (Figure 1).

Comparing late and early stages of the disease; early-stage patients were more likely to have positive oestrogen and progesterone receptors, however; the observation was not proved to be of statistical significance (p-value 0.335 and 0.420 respectively) (Table 3).

Within a variety of morphologies, 107 cases (54%) were diagnosed with anearly-stage invasive ductal carcinoma while 56 cases (28.3%) were diagnosed as alate-stage disease with no statistical significance (p-value >0.05) (Table 3).

In the early-stage, 58 cases (29.3%) and 51 cases (25.7%) were diagnosed as grade 2 and 3 respectively while in the late-stage, 39 cases (19.7%) were diagnosed as grade 3, the association proved to be of statistical significance (p-value 0.03) (Table 3).

Treatments between late and earlystages were the same. Among the early-stage cases, 126 women underwent a mastectomy, conversely; three women did not perform surgery (Table 3). There were 94 patients had chemotherapy, radiotherapy and hormonal therapy (Table 3). The number of women who had no chemotherapy, radiotherapy nor hormonal therapy was 29, 32 and 32 respectively (Table 3). The total number of patients in the late-stage who had chemotherapy, radiotherapy and hormonal therapy was 61,50 and 46 cases, respectively compared with 6, 15 and 20 cases who did not have the treatments (Table 3).

Table 1. Patients' characteristics of studied group

Patient characteristics:	Freq(%)
Marital status (Freq %)	
Single	3 (1.52%)
Married	163 (82.32%)
Divorced	9 (4.54%)
Widowed	20 (10.1%)
Not available	3 (1.52%)
Hypertension [HTN] (Freq %)	
No	113 (57.1%)
Yes	79 (39.9%)
Not available	6 (3%)
Diabetes Mellitus [DM] (Freq %)	
No	122 (61.6%)
Yes	71 (35.9%)
Not available	5 (2.5%)
Familial Breast Cancer (Freq %)	
No	149 (75.3%)
Yes	41 (20.7%)
Not available	8 (4%)
Tumor [T] (Freq %)	

0	7 (3.54%)
1	43 (21.72%)
2	100 (50.5%)
3	24 (12.12%)
4	24 (12.12%)
Node [N] (Freq %)	
0	93 (47%)
1	62 (31.3%)
2	27 (13.6%)
3	16 (8.1%)
Metastasis [M] (Freq %)	
0	191 (96.5%)
1	7 (3.5%)
Tumor size/cm (mean±SD)	3.4 ± 2.1
Age / years (mean±SD)	53.8± 11.2
Duration of follow up / months (median + (minimum + maximum))	60 (range 0+84)
Morphology (Freq %)	
Intraductal papillary-mucinous carcinoma	1 (0.5%)
Invasive ductal carcinoma	163 (82.3%)
Ductal carcinoma in-situ	7 (3.5%)
Lobular carcinoma	19 (9.6%)
Lobular carcinoma in-situ	2 (1%)
Invasive tubular carcinoma	2 (1%)
Inflammatory carcinoma	3 (1.5%)
Metaplastic carcinoma	1 (0.5%)
Grade (Freq %)	
0	1 (0.5%)
1	11 (5.6%)
2	77 (38.9%)
3	90 (45.4%)
Not available	19 (9.6%)
Treatments	
Chemotherapy (Freq %)	
No	35 (17.7%)
Yes	155 (78.3%)
Not available	8 (4%)
Radiotherapy (Freq %)	
No	47 (23.7%)
Yes	144 (72.7%)
Not available	7 (3.5%)
Hormonal Therapy (Freq %)	
No	52 (26.3%)
Yes	140 (70.7%)
Not available	6 (3%)
Surgery (Freq %)	
No	8 (4%)
Yes	187 (94.4%)
Not available	3 (1.5%)
Receptors	
Estrogen Receptor [ER] (Freq %)	
No	47 (23.7%)
Yes	149 (75.3%)
Not available	2 (1%)
Progesterone Receptor [PR] (Freq %)	
No	54 (27.3%)
Yes	138 (69.7%)
Not available	6 (3%)
Laterality (Freq %)	
Right	85 (42.9%)
Left	104 (52.5%)
Bilateral	9 (4.5%)

Table 2. Distribution of tumor size, lymph node, ER/PR receptors and comorbidities according to age in studied group.

	Age ≤ 40 yrs Freq (%)	Age > 40 yrs Freq (%)	P Value
Tumor size			
<3cm	10 (5.1%)	82(41.4%)	
3 cm	2 (1%)	50 (25.3%)	0.425
>3 cm	8 (4%)	46 (23.2%)	
Lymph Node			
0	6 (3%)	87 (43.9%)	
1	9 (4.5%)	53(26.8%)	0.425
2	3 (1.5%)	24 (12.1%)	
3	2 (1%)	14 (7 %)	
Receptors			
Estrogen Receptor +ve	11 (5.6%)	138 (69.7%)	0.028
ER -ve	9 (4.5%)	38 (19.2%)	
Progesterone Receptor +ve	10 (5%)	128 (64.6%)	0.033
PR -ve	10 (5%)	44(22.2%)	
Comorbidities			
Hypertension [HTN] (Freq %)			
No	19 (9.6%)	94 (47.6%)	<0.001
Yes	0	79 (39.9%)	
Diabetes Mellitus [DM] (Freq %)			
No	17 (8.6%)	105 (53%)	0.022
Yes	2 (1%)	69 (34.8%)	
Family history of BC (Freq %)			
No	16 (8.1%)	133 (67.2%)	0.579
Yes	3 (1.5%)	38 (19.2%)	

Table 3. Distribution of tumor size, age, ER/PR receptors, morphology, grade, marital status, treatments and laterality according to stage of breast cancer

	Early Freq (%)	Late Freq (%)	P Value
Tumor size			
<3cm	78 (39.4%)	14 (7.1%)	
3 cm	34 (17.2%)	18 (9.1%)	<0.001
>3 cm	18 (9.1%)	36 (18.2%)	
Age			
≤40	12 (6.1%)	8 (4%)	0.623
>40	118 (59.6%)	60 (30.3%)	
Receptors			
Estrogen Receptor +ve	99 (50%)	50 (25.2%)	0.335
ER -ve	29 (14.6%)	18 (9.1%)	
Progesterone Receptor +ve	88 (44.4%)	50 (25.2%)	
PR -ve	36 (18.2%)	18 (9.1%)	0.420
Morphology			
Invasive ductal carcinoma [IDC]	107 (54%)	56 (28.3%)	
Others	23 (11.6%)	12 (6.1%)	>0.05
Grade			
(0-1)	9 (4.5%)	3 (1.5%)	
2	58 (29.3%)	19 (9.6%)	0.03
3	51 (25.7%)	39 (19.7%)	
Marital status			
Single	2 (1%)	1 (0.5%)	
Married	109 (55.1%)	54 (27.3%)	
Divorced	6 (3%)	3 (1.5%)	
Widowed	13 (6.6%)	7 (3.5%)	
Treatments			
Chemotherapy			
-ve	29 (14.6%)	6 (3%)	0.018
+ve	94 (47.3%)	61 (30.8%)	
Radiotherapy			
-ve	32 (16.2%)	15 (7.3%)	0.859
+ve	94 (47.3%)	50 (25.3%)	
Hormonal therapy			
-ve	32 (16.2%)	20 (10.1%)	
+ve	94 (74.3%)	46 (23.2%)	0.497
Surgery			
-ve	3 (1.5%)	5 (2.5%)	0.123
+ve	126 (63.6%)	61 (30.8%)	
Laterality			
Right	60 (30.3%)	25 (12.6%)	
Left	66 (32.8%)	38 (19.2%)	0.231
Bilateral	4 (2%)	5 (2.5%)	

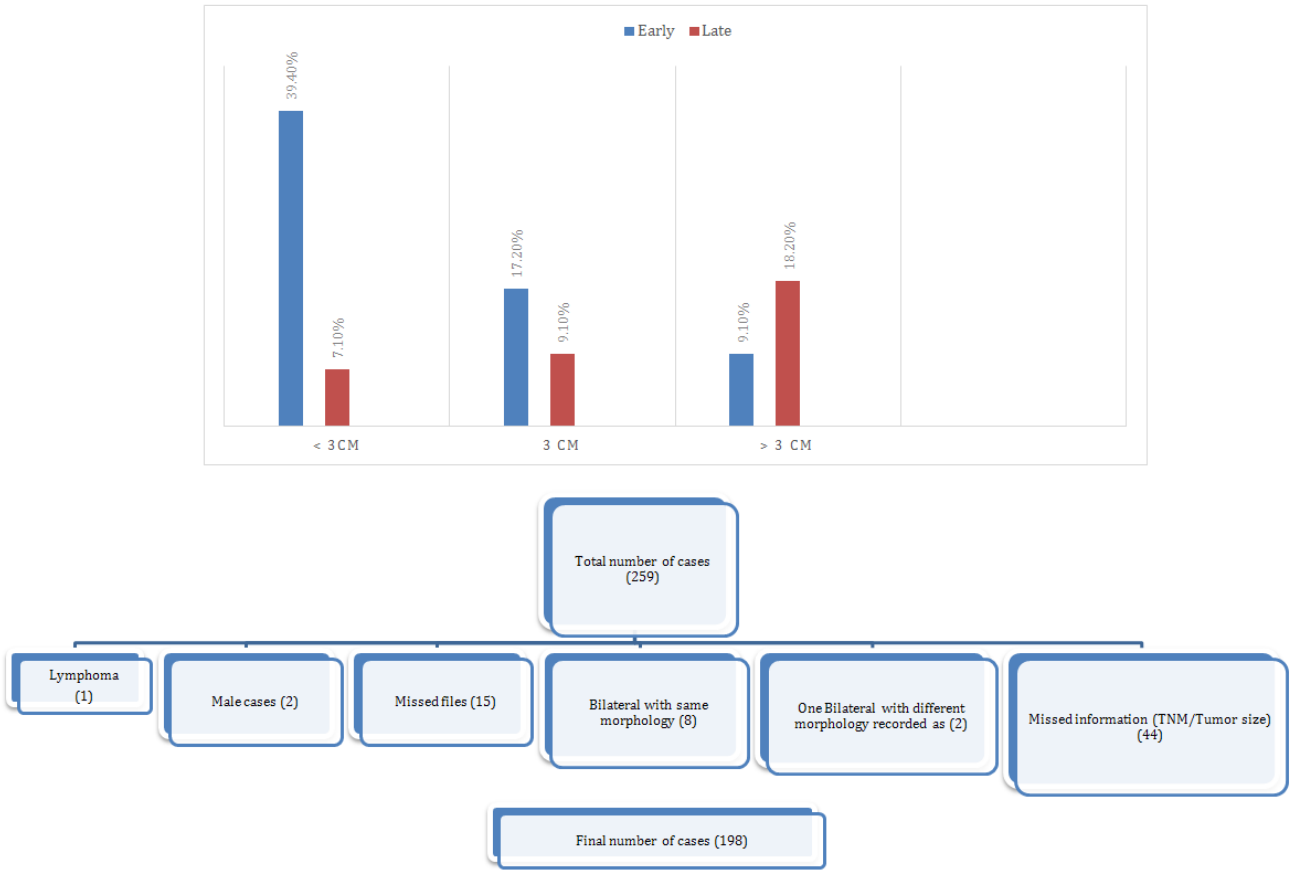

Figure 1. Tumour size (cm) in early vs late stage breast cancer

4. Discussion

This study was the first to portray tumours size and age according to different stages of disease in Kuwaiti women. A total of 259 cases of breast cancer patients between 23 to 83 years were reviewed in this study. Sixty-two files were excluded and these included forty-four files with insufficient information about the TNM staging, fifteen files were not available to be retrieved from the medical records, two files were men breast cancer and one lymphoma case. All were Kuwaiti women and the majority was married.

Age at diagnosis of breast cancer varied considerably among different populations. In Kuwait, the median age was 54 years old; conversely, it was 63 years in the US and it was below 50 years in Saudi Arabia [3]. This study showed that the median age at diagnosis in Kuwait was similar to other Middle Eastern countries and one decade younger than Western countries. There are various risk factors for developing breast cancer. It can be divided into two groups the first one is genetic factors: age, race, family history, early menstruation (before age 12), late menopause (after age 51), reproductive history, and dense breast tissue [12]. The second one is lifestyle factors: number of births, use of birth control or hormone therapy after menopause, breastfeeding, alcohol use, being overweight or obese, and lack of exercise and diet [12]. These findings could be related to the young age structure, racial differences, use of HRTs, family history, the degree of obesity and lack of exercise [5,10,13]. The exact causes were not well-known and more studies should be conducted to reduce the rate and mortality of breast cancer in Kuwait.

Tumour size showed different variations in relation to age. Female cases with breast cancer in Switzerland showed larger tumour size with younger age [5]. This distinction was induced due to possible differences in tumour biology, risk factors and treatment characteristics that demand additional examinations among young women in Switzerland [15]. Breast cancer cases in the Arab world showed that the majority of cases with poor clinicopathologic variables was in younger patients [3,10]. Younger patients tend to have larger tumour size, higher ER and PR receptors negativity and more lymph node positivity which indicate an aggressive behaviour [3].

Based on this study findings, the data revealed contradictory findings with breast cancer patients in Kuwait than those in the surrounding Arab world where Kuwait is considered to be part of it. The data findings showed that older patients tend to have larger tumour size than younger patients. This was based on comparing 46 cases of older patients with large tumour size to 8 cases of younger patients with large tumour size. It also showed that nearly 38 and 44 cases of older patients, when compared with 9 and 10 cases of younger patients, had negative ER and PR receptors, respectively. Moreover, 91 cases of the older group had lymph node positivity while 14 cases of the younger group. This confirmed a more aggressive picture in older patients.

"Possible reasons for these significant findings were that older patients might deny the fact of having breast cancer which leads to a late presentation with a tumour that grows in size by time, lack of screening programs in Kuwait in 2012 and might be due to cultural and psychosocial biases that were presented among Kuwaiti

patients." Said by Dr Hana Alkhawari, The Head of Kuwait National Mammography Screening Program, following a personal communication, Feb 05, 2018.

In 2007, a breast cancer study in Kuwait concluded that most cases of lobular carcinoma were bilateral [10]. With the data that was were collected in this study, 9 cases were bilateral and 5 cases out of 9 were invasive ductal carcinoma. The other 4 cases shared by other different histological types and thus having different findings than what the previous study stated [10]. Bilaterality was independent of the morphology of the tumour; however, maybe a more extended population was needed to test this hypothesis.

Most of the cases were diagnosed with invasive ductal carcinoma (82.3%) (Table 1). A study in 2007, supported this percentage as 83% of cases were diagnosed with invasive carcinoma [10]. In 2007, the study included 166 cases, while this study included 198 cases diagnosed in 2012, which showed a small rise in the number of cases.

5. Conclusion

Though it has limitations, the results of this study shed light on the difference regarding the size of tumour in relation to age and stage among Kuwaiti women. Larger tumours presented with older patients, which was the opposite of what other studies concluded. The reason may be related to women who ignored their disease at the beginning. More studies should be conducted to find the exact causes of these findings. Further genetic research should be carried out regarding biological and pathological features of breast cancer in Kuwaiti women.

Early screening programs started in Kuwait in 2014; nevertheless, general practitioners must be made aware of psychosocial and cultural biases. Awareness campaigns emphasising the importance of screening and stating the risks, symptoms and outcomes of breast cancer must be encouraged and supported to provide awareness and education with specific attention the age group >49 years. Moreover, awareness should be directed to people within 40 years and older through national calls, GPs, geriatric clinics and also to facilitate communication with the mammography screening program in Kuwait.

Mortality data must be preserved in an organised matter to allow sufficient access for all needed files. Doctors should provide details about preformed physical examination and accurate clinical documentation with the correct usage of TNM staging to allow easy access to data for researchers and investigators for future purposes.

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