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The Stage of Breast Cancer at the Time of Diagnosis: Correlation with the Clinicopathological Findings among Iraqi Patients

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Abstract

Background: Breast cancer is the most frequently diagnosed malignancy and the second leading cause of mortality among women in Iraq forming 23% of cancer related deaths. The low survival from the disease is a direct consequence to the advanced stages at diagnoses.

Aim: To document the composite stage of breast cancer among Iraqi patients at the time of diagnosis; correlating the observed findings with other clinical and pathological parameters at presentation.

Patients and Methods: A retrospective study enrolling the clinical and pathological characteristics of 603 Iraqi female patients diagnosed with breast cancer. The composite stage of breast cancer was determined according to UICC TNM Classification System of Breast Cancer and the American Joint Committee on Cancer Staging. The studied parameters comprised age of the patient, stage of the disease, marital and educational status, history of lactation and hormonal intake (for a minimum period of 6 months), family history of breast or any other cancer, the effected breast side, hormone (Estrogen and Progesterone) receptor (ER, PR) and Her2 contents of the primary cancer. Statistical analysis was performed to correlate the recorded composite stages at diagnosis with the corresponding clinical and pathological data utilizing SPSS version 16.0 statistical program.

Results: Out of 603 patients, seven (1.2%) had ductal carcinoma *in situ* (Stage 0). Stages I, II and III and IV were documented in 9.5%, 47.1%, 33.2% and 9.1% of the patients at the time of diagnoses. Overall 70.8% of patients presented in the age group (40-59 years), 79.3% were married and 32.2% were highly educated. History of lactation, hormonal intake, family breast cancer and contralateral breast involvement was observed in 73.4%, 26.5%, 20.2% and 6.5% respectively. No correlation was elicited between the stage of breast cancer and the age of the patients, history of lactation or contralateral breast involvement. On the other hand, significant associations were demonstrated with respect to the marital and educational status, history of hormonal intake and breast cancer in the family. Immuno-histochemical evaluation revealed ER+PR+Her2+ (Triple Positive/Luminal B), ER-PR-Her2- (Triple Negative), ER+PR+Her2- (Luminal A) and ER-PR-Her2+ (Her2) subtypes in 13.4%, 11.8%, 48.2% and 9.8% of the examined breast samples respectively. When correlating the composite stage at diagnosing breast cancer with the corresponding subtypes the relationship was highly significant at $p<0.01$.

Conclusions and Recommendations: The study reports a regression in Stage IV breast cancer at the time of initial presentation among Iraqi patients specifically in those with family history of the disease; pointing out to the fruitful outputs of initiating the National Program for Early Detection of Breast Cancer in the country. Further professional efforts, endorsed by practical policy decisions, are recommended to down stage breast cancer through promoting evidence based

protocol guidelines and adopting comprehensive well designed diagnostic, screening and cancer control strategies.

Keywords: Breast cancer; Stage; Diagnosis; Iraqi patients; Clinicopathological findings

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Introduction

Cancer burden is increasing all over the world, specifically in in the Eastern Mediterranean region (EMR) where many countries are witnessing demographic and socioeconomic transitions [1-3]. It has been estimated that breast cancer is the second most common malignancy worldwide and the most frequently diagnosed female cancer. It remains the main cause of cancer death among women in developing regions of the world including those within the EMR [4]. The low survival from breast cancer is a direct consequence to the advanced stages at diagnoses prevailing in those settings. That emphasizes the urgent need to strengthen breast cancer control strategies through promoting awareness towards the significance of early detection of cancer, screening and appropriate therapy [5-7].

In Iraq, breast cancer is currently the second leading cause of mortality among women after cardiovascular diseases forming 23% of cancer related death [8,9]. Overall, it is the most common malignancy among the general Iraqi population, the number of registered cases are double those recorded for bronchogenic cancer, the second most frequent cancer. The latest Iraqi Cancer Registry shows that 4,115 cases of breast cancer were registered among an estimated population of about 32.5 million; accounting for 19.5% of newly diagnosed malignancies, 34% of female cancers and an incidence of 22 per 100,000 female populations [8]. Previous surveys have illustrated that the highest frequency of the disease is often displayed among younger women in their fourth and fifth decades of life who often present in advanced stages at the time of diagnosis [8,10,11].

A National Program for Early Detection of Breast Cancer was initiated in Iraq in 2000 in an attempt to down stage the disease at the time of presentation. That was followed by establishing a National Breast Cancer Research Program in 2010 to emphasize the role of research as one of the basic pillars in the adoption of a national cancer control strategy. An online information system data base was developed by the National Cancer Research Center of Baghdad University, for Iraqi patients complaining of breast cancer, under supervision of the International Agency for Research on Cancer (IARC) [6,10,12].

The aim of this study is to document the composite stage of breast cancer at the time of diagnosis among a sample of Iraqi female patients referred to two major breast cancer facilities in Baghdad; correlating the observed findings with other clinical and pathological characteristics at presentation.

Materials and Methods

This retrospective study enrolled the clinical and pathological characteristics of 603 female patients diagnosed with breast cancer at the Referral Training Center for Early Detection of Breast Cancer/Medical City Teaching Hospital and the National Cancer Research Center/Baghdad University during the years 2014-2016. Only cases with complete documented valid data were included in this study. The composite stage of breast cancer was defined according to UICC TNM Classification System of Breast Cancer [13] and the American Joint Committee on Cancer Staging [14,15]. The majority of the data (77% of the cases) were extracted from an established online information system database developed by the principal investigator in collaboration with IARC. Other information belonging to the rest of the cases was directly obtained from the patients' clinical case sheet records which include the pathology reports. The research study protocol was initially approved by the Ethical Committee of the National Cancer Research Program.

The studied parameters comprised age of the patient, stage of the disease, marital and educational status, history of lactation and hormonal intake (for a minimum period of 6 months), family history of breast or any other cancer, the effected breast side, hormone (Estrogen and Progesterone) receptor (ER, PR) and Her2 contents of the primary cancer.

Tumor markers were analysed by immuno-histochemical examination of the stained formalin fixed paraffin embedded tissue sections of the primary breast tumor to evaluate ER, PR and HER2 expressions in 448 cases, through a semi quantitative fashion depending on the staining intensity and the percentages of the positively stained tumor cells utilizing Dako kits™ (Dako, Denmark). Accordingly, the examined breast carcinomas were classified into eight molecular subtypes: E+/P+/H+ (Triple Positive/Luminal B), E-/P-/H- (Triple Negative), E+/P+/H- (Luminal A), E-/P-/H+ (HER2 variant), E+/P-/H+, E-/P+/H+, E+/P-/H- and E-/P+/H-.

Statistical Analysis

Statistical analysis was performed to correlate the reported composite stages with the corresponding demographic, clinical and pathological data utilizing SPSS version 16.0 statistical program. P values less or equivalent to 0.05 were considered significant.

Results

Table 1 shows that out of the 603 patients, seven (1.2%) had ductal carcinoma *in situ* (Stage 0); four (57.1%) were detected in asymptomatic women through opportunistic screening while three (42.9%) were diagnosed during follow up for moderate-severe fibrocystic changes. Overall, stages I, II, III and IV were documented in 57 (9.5%), 284 (47.1%), 200 (33.2%) and 55 patients (9.1%) respectively. Stage II was subcategorized according to the Anatomic Stage/Prognostic Groups [13-15] into IIA and IIB (forming 24.7%, and 16.9% of total respectively) while 5.51% were unspecified. Likewise Stage III was subdivided into IIIA, IIIB and IIIC diagnosed in 12.8%, 5.5%, and 12.9% of the total number of patients respectively.

The correlation between the stages of breast cancer with the age of the patients at the time of presentation was not significant. It was observed that all five patients with carcinoma *in situ*/Stage 0 (71.4%) were diagnosed in their seventh decade of life. Overall 70.8% of patients presented in the age group (40-59 years) versus 13.8% who were diagnosed under the age of 40 years and 15.4% who were 60 years and older **(Table 2)**.

In general, the majority of the patients were married at the time of diagnosis (79.3%) and only 14.3% were single. That applied on almost all stages of the disease with the exception of patients who were diagnosed at advanced Stage IV where 36.4% were not married at all (single). That relationship was statistically highly significant at p<0.01 **(Table 3)**.

It was displayed that almost one third of the breast cancer patients in this study (32.2%) were highly educated (i.e., granted a University degree or higher) while 11.9% were illiterate (72 patients). Among patients diagnosed with Stage I, 38.6% were relatively highly educated versus 7.3% among those presenting at advanced Stage IV. Interestingly carcinoma *in situ* was accidently detected in two illiterate patients who were older than 60 years during examination for symptomatic fibrocystic changes. The correlation between the educational status and the composite stage of breast cancer was highly significant at p<0.01 **(Table 4)**.

No significant relationship was demonstrated when correlating the history of lactation with the stage of breast cancer. Excluding those patients who were not married and nulliparous (87patients), 54.1% confirmed a history of regular lactation for a minimum period of 6 months to each baby (68.2% of married women), while 4.1% had practiced improper breast feeding (5.2% of those were married). **Table 5** reveals that the differences were not significant among patients diagnosed at different stages of the disease.

Overall, 26.5% (160 patients) had history of using contraceptive pills and/or other hormonal manipulation for a minimum period of 6 months. Nevertheless, it is interesting to observe that such history was present in 47.4% of patients who were diagnosed at Stage I versus only 12.7% in those presenting in Stage IV. Such relationship was found to be statistically significant at p<0.05 **(Table 6)**.

Table 1 The composite stages of breast cancer among the study sample.

Stage	No. of Cases	%	Total (%)/Each Stage
0	7	1.2	7 (1.2)
I	57	9.5	57 (9.5)
II A	149	25	--
II B	102	17	--
II Unspecified	33	5.5	--
II (total)	--	--	284 (47.1)
III A	77	13	--
III B	33	5.5	--
III C	78	13	--
III Unspecified	12	1.9	--
III (total)	--	--	200 (33.2)
IV	59	9.8	55 (9.1)
Total	603	100	603 (100)

Table 7 clearly illustrates the highly significant correlation (at p<0.01) between family history of malignancy and breast cancer staging. Approximately 35% of the patients had a family history of breast cancer and/or other malignancies in one or more 1st, 2nd or 3rd degree relatives. History of breast cancer was found in 20.2% among the studied sample; of those 15.6%, 49.2%, 26.2% and 8.2% were registered at Stage I, II, III and IV respectively. One third of patients presenting with Stage I had a positive family history of breast cancer versus 18.2% in those who were diagnosed at Stage IV.

Table 8 displays that the relationship between the composite stages of breast cancer, the effected breast cancer side and contralateral breast involvement was not significant. The latter was encountered in 6.5% of the diagnosed stages in general.

When correlating the composite stages with the corresponding breast cancer subtypes, categorized according to the immuno-histochemical staining **(Table 9)**, and specifically focusing on the main breast cancer phenotypes **(Table 10)**, the demonstrated relationship was highly significant at p<0.01 (The chi-square statistic is 39.3655 and the p-value is 0.00001).

The ER+PR+Her2+ (Triple Positive or Luminal B), ER-PR-Her2- (Triple Negative), ER+PR+Her2- (Luminal A) and ER-PR-Her2+ (Her2) subtypes were detected in 13.4%, 11.8%, 48.2% and 9.8% respectively. Among patients diagnosed in Stage I, 51.9% of their tissue biopsy specimens exhibited the Luminal A subtype while merely 3.7% were Triple Negative. **Table 10** shows that 64.4% and 67.2% of patients with Luminal A and Luminal B breast cancers respectively were diagnosed at stages I and II. Conversely 68% and 62% of those with Triple Negative and Her2+ subtypes respectively presented at advanced Stages III and IV.

Table 2 Composite stages of breast cancer verified according to age.

Stage*	20-29 Years	30-39 Years	40-49 Years	50-59 Years	60 and above	Total (%)/* Each Stage
0	0	0	0	2 (28.6)	5 (71.4)	7 (1.2)
I	0 0	3 (5.3)	23 (40.4)	22 (38.6)	9 (15.8)	57 (9.5)
II A	2	21	51	53	22	149
II B	3	16	25	37	21	102
II Unspecified	0	2	14	10	7	33
II (total)	5 (1.8)	39 (13.7)	90 (31.7)	100 (35.2)	50 (17.6)	284 (47.1)
III A	0	8	42	24	3	77
III B	0	4	15	8	6	33
III C	4	12	26	24	12	78
III Unspecified	0	2	0	6	4	12
III (total)	4 (2.0)	26 (13.0)	83 (41.5)	62 (31.0)	25 (12.5)	200 (33.2)
IV	1 (1.8)	5 (9.1)	23 (41.8)	22 (40)	4 (7.3)	55 (9.1)
Total Number (%)	10 (1.7)	73 (12.1)	219 (36.3)	208 (34.5)	93 (15.4)	603 (100)

*Excluding Stage 0, the relationship is not significant at p<0.05 (p-value=0.131, Chi-square test=13.776)

Table 3 Composite stages of breast cancer verified according to marital status.

Marital Status*					
Stage*	**Single**	**Married**	**Widow**	**Divorced**	**Total (%)/* Each Stage**
0	0 0	6 (85.7)	0 0	1 (14.3)	7 (1.2)
IIA	23	111	14	1	149
IIB	6	93	2	1	102
II Unspecified	6	26	1	0	33
II (total)	35 (12.3)	230 (81.0)	17 (6.0)	2 (0.7)	284 (47.1)
IIIA	11	64	1	1	77
IIIB	6	23	3	1	33
IIIC	9	67	1	1	78
III Unspecified	0	10	2	0	12
III (total)	26 (13.0)	164 (82.0)	7 (3.5)	3 (1.5)	200 (33.2)
IV	20 (36.4)	32 (58.2)	2 (3.6)	1 (1.8)	55 (9.1)
Total Number (%)	86 (14.3)	478 (79.3)	30 (4.9)	9 (1.5)	603

*Excluding Stage 0, the relationship is significant at p <0.01 (p-value = 0.0005, Chi-square test= 29.244).

Table 4 Composite stages of breast cancer verified according to the educational status.

Educational Status					
Stage*	**1**	**2**	**3**	**4**	**Total (%)/* Each Stage**
0	2 (28.6)**	1 (14.3)	3 (42.9)	1 (14.3)	7 (1.2)
I	3 (5.3)	14 (24.6)	18 (31.6)	22 (38.6)	57 (9.5)
IIA	12	30	46	61	149
IIB	6	24	28	44	102
II Unspecified	4	12	7	10	33
II (total)	22 (7.7)	66 (23.2)	81 (28.5)	115 (40.5)	284 (47.1)
IIIA	9	26	28	14	77
IIIB	11	10	6	6	33
IIIC	13	21	14	30	78
III Unspecified	2	2	6	2	12
III (total)	35 (17.5)	59 (29.5)	54 (27.0)	52 (26.0)	200 (33.2)

IV	10 (18.2)	33 (60.0)	8 (14.5)	4 (7.3)	55 (9.1)
Total	72 (11.9)	173 (28.7)	164 (27.2)	194 (32.2)	603

[1] Illiterate; [2] Primary school; [3] Secondary school; [4] University/Equivalent and Higher
*Excluding Stage 0, the relationship is highly significant at p<0.01 (p-value<0.0001, Chi-square test= 58.985). **Percent of total Row.

Table 5 Composite stages of breast cancer verified according to history of lactation.

History of Lactation* No (%)					
Stage*	**1**	**2**	**3**	**4**	**Total (%)/* Each Stage**
0	4 (57.1)	1 (14.3)	1 (!4.3)	1 (14.3)	7 (1.2)
I	31 (55.4)	19 (33.3)	4 (7.0)	3 (5.3)	57 (9.5)
IIA	65	58	21	5	149
IIB	79	13	8	2	102
II Unspecified	16	6	10	1	33
II (total)	160 (56.3)	77 (27.1)	39 (13.7)	8 (2.8)	284 (47.1)
IIIA	40	22	11	4	77
IIIB	13	8	10	2	33
IIIC	42	28	6	2	78
III Unspecified	10	0	2	0	12
III (total)	105 (52.5)	58 (29.0)	29 (14.5)	8 (4.0)	200 (33.2)
IV	26 (47.3)	10 (18.2)	14 (25.5)	5 (9.1)	55 (9.1)
Total	326 (54.1)	165 (27.4)	87 (14.4)	25 (4.1)	603

[1] Regular Lactation
[2] No Lactation
[3] Not applicable
[4] Irregular Lactation for less than 6 months.
*Excluding Stage 0, the relationship is not significant at p <0.05 (p-value = 0.088, Chi-square test= 15.103).

Table 6 Composite stages verified according to history of hormonal intake.

History of Hormonal Intake*No (%)				
Stage*	**1**	**2**	**3**	**Total (%)/* Each Stage**
0	3 (42.9)	3 (42.9)	1 (14.3)	7 (1.2)
I	27 (47.4)	23 (40.4)	7 (12.3)	57 (9.5)
IIA	43	95	11	149
IIB	22	67	13	102
II Unspecified	4	24	5	33
II (total)	69 (24.3)	186 (65.5)	29 (10.2)	284 (47.1)
IIIA	20	42	15	77
IIIB	14	13	6	33
IIIC	18	54	6	78
Unspecified	2	6	4	12
III (total)	54 (27)	115 (57.5)	31 (15.5)	200 (33.2)
IV	7 (12.7)	29 (52.7)	19 (34.5)	55 (9.1)
Total	160 (26.5)	356 (59.0)	87 (14.4)	603

Table 7 Composite stages verified according to family history of cancer.

Family History of Cancer No (%)				
Stage	**None**	**Breast Cancer**	**Other Cancers**	**Total (%)/* Each Stage**
0	5 (71.4)	1 [0.8]* (14.3)**	1 (14.3)	7 (1.2)
I	29 (50.9)	19 [15.6]* (33.3)**	9 (15.8)	57 (9.5)
IIA	78	33	38	149
IIB	70	20	12	102
II Unspecified	20	7	6	33
II (total)	168 (59.2)	60 [49.2] (21.1)	56 (19.7)	284 (47.1)
IIIA	54	18	5	77
IIIB	24	8	1	33

Family History of Cancer No (%)				
Stage	None	Breast Cancer	Other Cancers	Total (%)/* Each Stage
IIIC	69	1	8	78
III Unspecified	7	5	0	12
III (total)	154 (77)	32 [26.2] (16.0)	14 (7.0)	200 (33.2)
IV	37 (67.3)	10 [8.2] (18.2)	8 (14.5)	55 (9.1)
Total	393 (65.2)	122 (20.2)	88 (14.6)	603
*Percent of total Column (Family History of Breast Cancer) **Percent of total Raw (Stage of Breast Cancer)				

Table 8 Composite stages verified according to the affected breast side.

Affected Breast Side* No (%)				
Stage*	Right	Left	Contra-lateral	Total (%)/* Each Stage
0	3 (42.9)	4 (57.1)	0 (0)	7 (1.2)
I	27 (47.4)	25 (43.9)	5 (8.8)	57 (9.5)
IIA	93	50	6	149
IIB	34	62	6	102
II Unspecified	13	19	1	33
II (total)	140 (49.3)	131 (46.1)	13 (4.6)	284 (47.1)
IIIA	31	40	6	77
IIIB	23	8	2	33
IIIC	29	41	8	78
III Unspecified	6	6	0	12
III (total)	89 (44.5)	95 (47.5)	16 (8.0)	200 (33.2)
IV	26 (47.3)	24 (43.6)	5 (9.1)	55 (9.1)
Total	285 (47.3)	279 (46.3)	39 (6.5)	603

Table 9 Composite stages verified according to the breast cancer subtypes.

Composite Stage*											
Breast Cancer Subtypes*	Stage 0	I	IIA	IIB	II unspecified	IIIA	IIIB	IIIC	III unspecified	IV	Total
ER+PR+Her2+	2	5	16	12	6	3	1	8	3	4	60 (13.4)
ER-PR-Her2-	0	1	5	7	4	13	9	9	2	3	53 (11.8)
ER+PR+Her2-	0	14	63	45	17	30	4	29	6	8	216 (48.2)
ER-PR-Her2+	2	7	1	6	2	11	3	8	1	3	44 (9.8)
ER-PR+Her2-	0	2	3	2	0	7	0	4	0	1	19 (4.2)
ER-PR+Her2+	0	1	4	0	0	2	2	2	0	1	12 (2.7)
ER+PR-Her2-	0	3	6	2	3	3	2	6	0	3	28 (6.3)
ER+PR-Her2+	0	1	6	0	0	3	1	4	0	1	16 (3.6)
	4 (8.9)	34 (7.6	104 (23.2)	74 (16.5)	32 (7.1)	72 (16.1)	22 (4.9)	70 (15.6)	12 (2.7)	24 (5.4)	448
*The relationship is highly significant at p<0.01 (p-value=0.00001, Chi-square test=39.365).											

Table 10 Stage classification of the main breast cancer subtypes among the study sample (categorized according to immuno-histochemical staining).

Breast Cancer Subtypes	Stage I	Stage II	Stage III	Stage IV	Total
ER+PR+Her2+ (Triple Positive/Luminal B)	5 (18.5)* [8.6]**	34 (18.5) [58.6]	15 (10.7) [25.9]	4 (22.2) [6.9]	58
ER-PR-Her2- (Triple Negative)	1 (3.7) [1.7]	16 (8.7) [30.2]	33 (23.6) [62.3]	3 (16.7) [5.7]	53
ER+PR+Her2- (Luminal A)	14 (51.9) [6.5]	125 (67.9) [57.9]	69 (49.3) [31.9]	8 (44.4) [3.7]	216
ER-PR-Her2+(Her-2 variant)	7 (25.9) [12.1]	9 (4.9) [21.4]	23 (16.4) [54.8]	3 (16.7) [7.1]	42
Total	27	184	140	18	369
*Percent of total Column **Percent of total raw					

Discussion

The TNM staging system [13] is designed to determine the anatomical extent of cancer on the basis of clinical (cTNM) and pathological (pTNM) criteria depending on the assessment of the primary tumor (T), lymph-node involvement (N) and metastasis (M). It corresponds to the classification of the American Joint Committee on Cancer [AJCC] [14,15]. Both systems are revised

periodically with the advances of diagnosis and treatment to facilitate exchange of clinical information, planning for treatment and provision of prognostic guidance [16].

In this study 1.2% of our patients were diagnosed at Stage 0; 57.1% of those presented as asymptomatic women in whom the neoplastic breast cell proliferation was detected through opportunistic screening while in 42.9% breast cancer was detected during follow up for fibrocystic changes. That probably reflects the advantage of initiating the National Programs for Early Detection and Research in our country [4,6,10-12,17]. Focusing on the composite stage of breast cancer at the time of presentation, among patients attending referral centers in Baghdad, our findings illustrated that 9.5%, 47.1%, 33.2% and 9.1% were diagnosed at Stages I, II, III and IV respectively. The ratio of Stages 0, I and II versus Stages III and IV is equivalent to 57.7:42.3. Compared to an earlier survey conducted in the same Referral Centre for Early Detection of Breast Cancer nine years ago [11], the registered ratio was 52.7:47.3; displaying lower percentage for patients diagnosed at Stage IV (15.7% in the previous report). This relative improvement in the stage of the disease at diagnosis emphasizes the fruitful outputs of the pioneering national breast cancer detection program which was initially established by the Ministry of Health in 2000 and strengthened by the Ministry of Higher Education and Scientific Research through the National Cancer Research Project in 2010 [4,6,10-12].

Nevertheless, the stage distribution of breast cancer in our country is still far beyond those reported in the cancer registries of high resource settings where at least 50% to 60% of breast cancer present in localized stages [18,19]. Changes in the distribution patterns of the stage at diagnosis are important indicators of the success of the awareness campaigns and the effectiveness of any screening program. Earlier studies highlighted the gaps in the knowledge, attitudes and practices among Iraqi women regarding breast cancer [20-24]; and consequently paved the way towards promoting the adoption of a comprehensive national breast cancer control strategy based upon public education campaigns, and early detection and treatment protocol guidelines [6,10-12,25].

No correlation was noted between the age of the patients and the stage of breast cancer at the time of presentation. In fact 71.4% of patients with carcinoma *in situ* (Stage 0) were diagnosed in their seventh decade of life. In accordance with previous studies from Iraq [8-12], the peak age frequency of breast cancer (70.8%) was observed within the period (40-49 years) while only 15.4% of the patients were aged 60 years and over. In general, it has been illustrated that the average age at diagnosis of breast cancer among Arab women is a decade earlier than their western counterparts; attributing that to the younger demographic profiles and social, economic and population variations [3,11,26].

A significant relationship was confirmed with the marital status and the degree of education in this study where 79.3% of the patients were married and 32.2% were highly educated. The observed positive association between the level of literacy and breast cancer diagnosis and awareness should be strongly invested in breaking barriers related to early detection in developing countries [21-24,27]. History of lactation and hormonal manipulation was observed in 73.4% of and 26.5% married patients respectively. While the stage of breast cancer correlated significantly with the history of hormonal intake among the affected patients in this study, no association was elicited regarding the state of lactation.

On the other hand, a highly significant correlation was observed between the composite stages at diagnosing breast malignancy and family history of cancer, whereby 35% of our patients had one or more relatives affected by cancer. Family history of breast cancer specifically was registered in 20.2%; higher than the frequency reported in an earlier study applied in the same centre [11]. One third of patients presenting with Stage I had a positive family history of breast cancer versus 18.2% in those who were diagnosed at Stage IV. Although about 66% of the patients who had a positive family history of breast malignancy sought medical advice at Stages 0, I and II; nevertheless 34% still presented at Stages III and IV. That was consistent with the findings observed following a recent survey on the clinical and pathological characteristics of familial breast cancer in Iraq [28,29]; which indicates the need for further efforts to elevate the level of awareness among the community towards the importance of screening and close follow up of the female population at risk. In accordance with another study [10] a history of contralateral breast cancer was noted in 6.5% of the patients, which was not significantly associated with the stage of the disease.

Traditional molecular markers to predict early-stage breast cancer include ER, PR and Her2; the standard method for their evaluation worldwide is still immunohistochemistry [30,31]. Studies that established the molecular classification of breast cancer were updated to categorize the disease into four main molecular subtypes; Luminal A, Luminal B, Triple Negative and HER2 enriched variants [32,33]. Immunohistochemistry staining of the tissue samples belonging to tumors of the examined patients in this study revealed that ER+PR+Her2+ (Triple Positive/ Luminal B), ER-PR-Her2- (Triple Negative), ER+PR+Her2- (Luminal A) and ER-PR-Her2+ (Her2) subtypes were encountered in 13.4%, 11.8%, 48.2% and 9.8% respectively. The corresponding figures reported in a recent published study on breast cancer subtypes among Iraqi female patients were 14.6%, 15.6%, 42.2% and 11.8% respectively [34].

Interestingly, a highly significant association was noted between the documented breast cancer subtypes in this study and the composite stage of breast cancer at diagnosis. Almost 52% of the biopsy specimens belonging to patients presenting with Stage I exhibited the Luminal A subtype which provides a favorable prognosis, while merely 3.7% were Triple Negative. Focusing on Luminal cancers, we demonstrated that 64.4% and 67.2% of patients with Luminal A and Luminal B breast cancers respectively were diagnosed at Stages I and II, while 68% and 62% of those with Triple Negative and Her2+ subtypes respectively presented at advanced Stages III and IV. It has been displayed in the literature that hormone receptor positive breast cancer expressions are

often associated with earlier stages at presentation and that Her2+ impact on these cancers is reflected by higher tumor grades and advanced stages [34-36]. In a recent retrospective study, where no significant variations were observed in the clinicopathological presentations of patients with Luminal A subtype as compared to Luminal B, the investigators concluded that the latter might be driven primarily by the hormone receptor status [34].

Conclusions and Recommendations

The illustrated regression in Stage IV breast cancer at the time of initial presentation among Iraqi patients, specifically in those with positive family history of the disease, points out to the fruitful outputs of initiating the National Program for Early Detection of Breast Cancer in Iraq that is currently strengthened by the National Cancer Research Project. Further professional efforts, endorsed by practical policy decisions, are recommended to down stage breast cancer through promoting evidence based protocol guidelines and adopting comprehensive well designed diagnostic, screening and cancer control strategies.

Conflict of Interest

The authors declare that they have no conflict of interest that competes with any of the contents of the manuscript.

Authors Contribution

The principal author, Founding Director of the Iraqi National Cancer Research Center/Program, designed the study, analyzed the results, wrote the manuscript and presented the final version. Other co-authors supported in providing relevant information, assisted in data entry and statistical analysis.

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