

Iraqi Breast Cancer: A Review on Patients' Demographic Characteristics and Clinico-Pathological Presentation.

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Summary:

Background: Breast Cancer is the commonest type of malignancy in Iraq. The Iraqi Cancer Registry displays an obvious trend for the disease to affect younger women with advanced stages at the time of presentation. This report presents a review on the main demographic characteristics and clinico-pathological parameters in Iraqi patients diagnosed with breast cancer.

Patients & Methods: The study was carried out on 721 out of a total of 5044 patients (14.3%) who complained of palpable breast lumps that were diagnosed as cancer. The procedure for tumor nuclear DNA Ploidy assessment was performed by means of Image Cytometry. Immunocytochemical and histochemical assays were applied for the determination of Estrogen and Progesterone receptor (ER/PR) contents and Her-2/neu expression of the tumor tissues.

Results: Approximately one third of the breast cancer patients were diagnosed in the age period (40-49 years), 71.9% came from urban areas and 75% were married. History of lactation and hormonal therapy was reported in 63.1% and 29% respectively, while positive family history was recorded in 16.2%. Although the lump was detected by the patient herself in 90.6%, yet only 32% sought medical advice within the first month. Accordingly 47% of these patients presented in advanced stages (III and IV). The main histological type was invasive ductal carcinoma; in which pathological changes of grade II and III were observed in 56.6% and 39.9% respectively. Cytophotometric DNA analysis showed that 80.3% of Iraqi mammary carcinomas were aneuploid. ER and PR positive tumor contents were demonstrated in 65.1% and 45.1% of the examined specimens respectively while Her-2/neu over expression was displayed in 46.4%.

Conclusions: The aforementioned data justifies increasing efforts for establishing comprehensive breast cancer control programs in our country. Further interventional research studies using molecular biomarkers should be promoted to address the factors contributing to the illustrated aggressive tumor behavioral forms

Keywords: Breast Cancer, Iraq, Clinical, Pathological Diagnosis, Aneuploidy, Hormone Receptors, Her-2/neu.

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Introduction:

Globally, breast cancer is the most common cancer among women comprising 23% of the 1.1 million female cancers that are newly diagnosed each year (1,2). It is also the leading cause of cancer-related deaths worldwide; case fatality rates being highest in low resource countries. Approximately 4.4 million women diagnosed with breast cancer in the last 5 years are still alive making breast cancer the most prevalent cancer worldwide (1). In Iraq, breast cancer is the commonest type of female malignancy accounting for approximately one third of the registered female cancers according to the results of the latest Iraqi Cancer Registry (3). The latter shows as well that the breast is the leading cancer site among Iraqi population in general surpassing even bronchogenic cancer. Of the recorded approaches to breast cancer control, as proposed by the World Health Organization (4), early detection and screening, especially when combined with

adequate therapy, offer the most immediate hope for a reduction in breast cancer mortality. That was the basis of the Iraqi national program for early detection of breast cancer which was initiated in Iraq in the year 2001 in an attempt to down stage this disease at the time of presentation. Since then specialized centers and clinics for early detection of breast tumors were established in the major hospital of all Iraqi provinces. This report reviews the main demographic characteristics and clinico-pathological presentation in 721 Iraqi female patients who were diagnosed as having breast cancer within the Main Referral Training Center for Early Detection of Breast Tumors in Baghdad.

Patients & Methods:

Case recording and clinical examination: The present study comprised a total of (5054) female patients who visited the Main Training Center for Early Detection of Breast Tumors in the Medical City Teaching Hospital in Baghdad complaining of palpable breast lumps. Patients were clinically

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Table (2): The recorded Demographic characteristics and Clinico-pathological parameters in 721 patients diagnosed with Breast Cancer.

Studied Parameter	No. of Cases	(%)
Age Group (years)		
20-29	15	2.1
30-39	145	20.1
40-49	230	31.9
50-59	190	26.4
60-69	120	16.6
70 & >	21	2.9
Marital Status		
Married	541	75
Unmarried	161	22.3
Widow/Divorced	19	2.6
Residence		
Urban	526	72.9
Rural	195	27.1
History of Breast Feeding		
Positive	455	63.1
Negative	266	36.9
History of Contraceptive Pills		
Positive	209	29
Negative	512	71
Positive Family History		
Positive	177	16.2
Negative	604	83.8
The Mass was Detected by:		
Patient	653	90.6
Examining Physician	51	7.1
Others	17	2.3
Nodal Status		
Positive	527	73.1
Negative	194	26.9
Clinical Stage *		
Stage I	51	7.6
Stage II	301	45.1
Stage III	210	31.5
Stage IV	105	15.7
Tumor Grade		
Grade I	25	3.5
Grade II	408	56.6
Grade III	288	39.9
Nuclear DNA Ploidy Tumor Content **		
Euploid	27	19.7
Aneuploid	110	80.3
Hormone Receptor Tumor Content ***		
ER +	166	65.1
PR +	115	45.1
Her-2/neu Tumor Expression ****		
Positive	89	46.4
Negative	103	53.6
Total	721	

* Total number of patients classified according to the AJCC Staging system = 667.
 * Total number of specimens analyzed for nuclear DNA Ploidy tumor content = 137.
 * Total number of specimens analyzed for HR content = 255.
 * Total number of specimens analyzed for Her-2 neu expression = 192.

Table (3): The demonstrated DNA Histogram types and Nuclear DNA Ploidy content distribution in pathological specimens belonging to (137) Breast Cancer patients

DNA Histogram Type	No. of Cases	(%)
I (Diploid)	16	11.6
II (Tetraploid)	11	8.1
III (Aneuploid)	68	49.6
IV (Aneuploid)	42	30.7
Total	137	

Table (4): Distribution of Hormone Receptor (ER and PR) Phenotypes in pathological specimens belonging to (255) Breast Cancer patients.

Hormone Receptor Phenotype	No. of Cases	(%)
ER+/PR+	104	40.8
ER+/PR-	62	24.3
ER-/PR+	11	4.3
ER-/PR-	78	30.6
Total	255	

Discussion:
 According to WHO mortality estimates, cancer is the fourth ranked cause of death in the Eastern Mediterranean Region (EMR), after cardiovascular diseases, infectious/parasitic diseases and injuries (9). The largest increase in cancer incidence among the WHO regions in the next 15 years is likely to be in the EMR, (10) within which breast cancer is recorded as the commonest type of female malignancy in almost all national cancer registries.In Iraq, in addition to being the most important cancer, there are other features that justify increasing efforts for breast cancer control; including the tendency for this disease to affect younger women, the obvious rise in its incidence rates and the prevalence of advanced stages at presentation associated with more aggressive tumor behavior resulting in greater fatality rates. In the present study, breast cancer was diagnosed in 14.3% of patients presenting with apparent breast lumps. Approximately one third of the patients were diagnosed in their forties, where the peak frequency occurred, while an obvious decline was displayed after the age of 60 years. That continuous trend for this disease to affect younger generations has been comprehensively illustrated within the results of the Iraqi Cancer Registry (3) and other documented reports from neighboring countries. (11,12) WHO estimates revealed that approximately half of the cancers in the EMR occur before the age of 55 and that the age standardized incidence rates of all cancers in this region is expected to double as risk factor exposure increases (9). On the other hand, this picture differs from that displayed in reports from western and developed countries; where the peak incidence rates project decades later (13).
 In a WHO collaborative project it has been proposed that the younger age distribution in the Arab population could be a

reflection of the younger demographic profile (14). Marital status, history of lactation, history of hormonal therapy and/or contraceptive pill intake did not seem to impose an apparent impact on the studied population. The relative high frequency of patients with positive family history observed in this study compared to others (15, 16) could be attributed to the customary consanguineous marriages which are known to be traditionally common throughout the region (17). Although 90.6% of the patients detected the lumps by themselves, regrettably, only 32% sought medical advice within the first month after detection. That finding was illustrated by the fact that 73% of the studied group had positive axillary nodal metastasis at the time of diagnosis; thus placing 47.2% within stages III and IV. Higher advanced stages at presentation have been documented in published surveys from other developing countries (12,18). The IARC Working Group indicated that survival from this cancer in middle and low income countries remains poor mainly because of the late presentation (19). These observations obviously reflect the poor health education of the general population and their ignorance regarding the significance of clinical breast examination, breast self examination and early medical consultation. In a critical evaluation of the role of early detection and screening of breast cancer in developing countries, the late stage at presentation has been attributed to be a reflection of the cultural norms which downplay women's health problems in these areas (14). It is believed that the improved survival rates in many cancers in the USA and Europe are more related to the earlier stage at presentation rather than to improved treatment (20). Pathologically, in accordance with the results of other cancer registries (13), the leading tumor type was infiltrative ductal carcinomas. A direct relationship was noted between the pathological nodal status and the histological grade; where 17 out of 25 patients (68%) diagnosed as having well differentiated carcinomas (Grade I) in this study presented with negative axillary nodes while all patients with poorly differentiated breast carcinomas (Grade III) had nodal metastasis at the time of diagnosis. Thus confirming that the nodal status might be predicted, at least from the statistical point of view, from the histological grade of the tumor (21). At the molecular level, it has been documented that complex genomic alterations as reflected by altered DNA content is involved in tumor development and progression. In this respect, nuclear DNA ploidy content of breast cancer cells has been used to predict the outcome of the disease. In general, patients with genetically stable breast cancer exhibiting DNA diploid or tetraploid profiles have a better prognosis and more favorable clinical course than those with genetically unstable aneuploid cancer (22). The demonstrated frequency of aneuploid mammary carcinomas in this study (80.3%) is considerably higher than the range reported by other investigators from the western world (23). To explain the observed differences in ploidy pattern distribution, one should consider the possible variations in the biological behavior of the tumor and the differences in demographic characteristics and clinico-pathological presentations of the studied populations. However, earlier reports (7, 22)

documented that DNA ploidy content generally remains stable during cancer progression; thus providing additional significant prognostic information superior to that displayed by other clinical and histomorphological variables. The lower frequencies of hormone receptor (HR) positive mammary carcinomas among Iraqi patients that we reported in this study and others (24,25) compared to those observed among western societies (26) are probably expected in a population of predominantly middle-aged patients harboring considerable rates of poorly-differentiated carcinomas. In general, there is a more uniform loss of these receptor contents as the tumor becomes more anaplastic; indicating that hormone receptor status could represent one aspect of tumor cell differentiation. Following the same rationale, the relatively high rate of positive Her-2/neu protein expression illustrated in this review, and similar reports from the Arab world (27), correlated significantly with the histological tumor grade; whereby 92% of grade I mammary ductal carcinomas showed negative Her-2/neu expression, whereas 61.7 % and 73% of grade II and grade III carcinomas respectively were positive. The coexistence of HER-2/neu over expression, hormone receptor negative and nuclear aneuploid tumor contents in the examined tissue could serve as a strong prognostic indicator for the progress of the disease process.

Conclusion:

The expanding burden of cancer in the EMR in general and Iraq in particular, justifies the demand for establishing comprehensive national cancer control programs. Early detection of breast cancer, as a major approach to control the disease, could be achieved by raising the awareness of the general population about its symptoms and signs, educating the health personnel, and ensuring the provision of readily accessible diagnostic services. The Breast health Global initiative provided guideline implementation for breast health care in low and middle-income countries (28). Pilot projects from Egypt and South Asia demonstrated provisional evidence for the value of these programs (29, 30). The illustrated high frequencies of poorly differentiated, aneuploid mammary carcinomas and ER-/PR- phenotypes, as objective biological markers of tumor aggressiveness, emphasize the urgent need for initiating comprehensive clinical, interventional and Molecular research studies (31). By combining clinical, pathological, hormonal and morphological determinants, the prognosis of breast cancer patients might become more predictable; thus permitting judicious selection of the most effective therapeutic protocols.

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