

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. Immuno-cytochemical 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 interviewed and examined according to the Triple Assessment Technique (i.e., clinical breast examination, mammography and/or ultrasonography, and fine needle aspiration cytology - FNAC). Out of the relevant data recorded within the patients' file sheet questionnaire, the main studied parameters included patient's age, marital status, and residence, history of lactation,

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contraceptive pills and/or hormonal therapy and family history of breast cancer. Data on tumor size and nodal status were obtained by examination of the tissue biopsies. Abdominal U/S and Chest X rays were carried out to exclude metastasis and when indicated a skeletal survey was performed.

Pathological diagnosis: Patients were scheduled for complete diagnostic work-up which comprised FNAC, excisional biopsy and/or mastectomy. FNA technique was carried out using disposable 10 ml syringes attached to 22-or 23 gauge needles and the aspirated material was stained by Papanicolaou. All reports with positive FNAC results were confirmed histopathologically after excision of the lesions. Tissue sections of the formalin fixed paraffin embedded blocks were stained by Hematoxylin and Eosin. The type of mammary carcinoma was determined following the WHO classification while the TNM staging system of the American Joint Committee on Cancer (AJCC) staging was used in recording the clinical stage of the disease (5). Ductal carcinoma was graded following the recommendations of Scarff, Bloom and Richardson (6).

Assessment of nuclear DNA Ploidy content: The procedure for quantitative cytophotometric DNA analysis and nuclear DNA Ploidy assessment was applied on 137 pathological specimens by means of Image Cytometry and according to the Feulgin technique (7). In the protocol for each slide, there was an emphasis upon the availability of adequate tumor cells (at least 200) and upon the admixture with normal lymphocytes which were used as an internal controls of the normal diploid (i.e., 2C) DNA content in all specimens. All tumor values were expressed in C units in relation to the corresponding internal controls. The DNA histogram patterns were classified according to the criteria described by Auer et al (7) into type I (Diploid), type II (Tetraploid), or types III and IV (Aneuploid).

Determination of Estrogen and Progesterone Receptor (ER & PR) contents: For the determination of ER and PR contents, a semi-quantitative immunocytochemical assay (ERICA/PRICA) was applied on 125 cases using Abbott reagents. Briefly, the method included incubation of breast cancer cells with the primary antibody (which is an IgG fraction of monoclonal rat antibody to human ER or PR) and a bridging goat antibody. The reaction of peroxidase with hydrogen peroxide yielded an insoluble reddish brown product which was visualized by light microscopy. The receptor cells, located inside the nuclei of hormone receptor positive tumor cells, stained reddish brown when positive and light grey when negative. During analysis both the staining intensity and the fraction of positively stained cells were incorporated as primary parameters using a threshold value of 20 (8).

Her-2/neu Immuno-histochemical staining:

Five microns-thick sections obtained from formalin fixed-paraffin embedded tissue blocks belonging to 192 patients were stained immuno-histochemically through streptavidin biotin peroxidase complex technique using anti-Her-2/neu monoclonal antibody (rabbit anti-human Her-2 protein / Dakocytomation). The intensity of the cancerous cell membrane staining of Her-2 neu protein expression was graded through a score of 0 to 3+ recording the intensity of the staining reaction in more than 10% of tumor cells.

Results:

FNAC revealed cellular changes consistent with mammary carcinoma in smears belonging to 721 patients (14.3% of total – Table 1, Figure 1). The peak frequency of breast cancer increased with age until menopause, thereafter it started to decline. More than half of the patients were in their premenopausal age (54.2%); 31.9% were diagnosed in the age period (40-49) years and 22.2% were under 40 – Table 2).

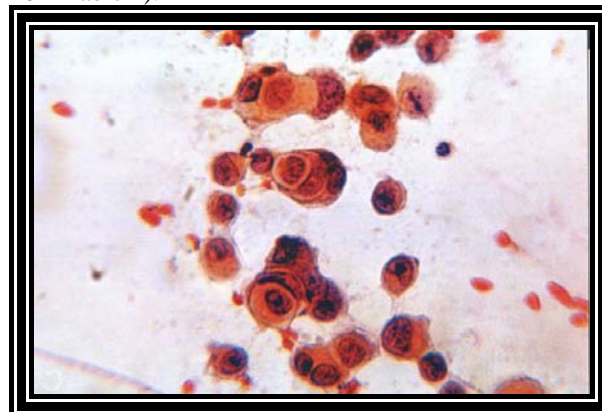


Figure (1): FNAC from a breast mass of a 47 year old woman showing cellular changes consistent with poorly differentiated (Grade III) mammary ductal carcinoma (Papanicolaou Stain X 400).

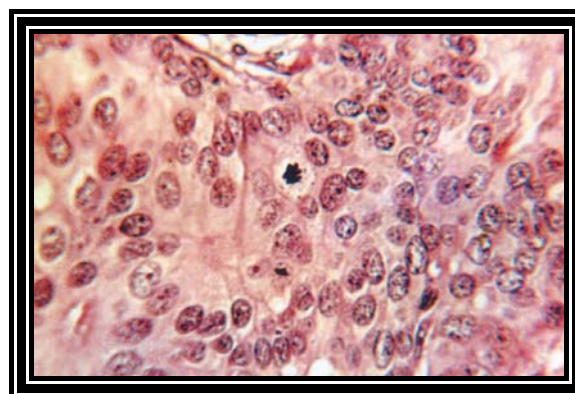


Figure (2): Tissue Biopsy (mastectomy specimen) from the same patient confirming the cytological diagnosis of Grade III invasive ductal carcinoma (H & E X 400).

Cytophotometric DNA analysis showed that 80.3% (111 out of 137) examined mammary carcinomas were aneuploid (Table 3). According to Auer et al

histogram classification 11.6% were diploid, 8.1% were tetraploid, 49.6% were aneuploid and 30.7% were highly aneuploid (Figure 3).

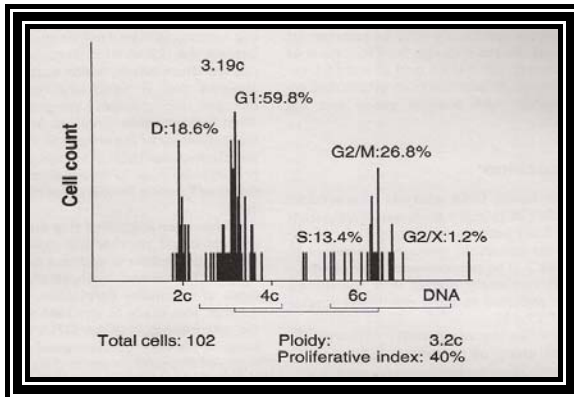


Figure (3): Cytophotometric DNA analysis of the case above showing highly Aneuploid (Auer Type IV) histogram pattern with high proliferative index.

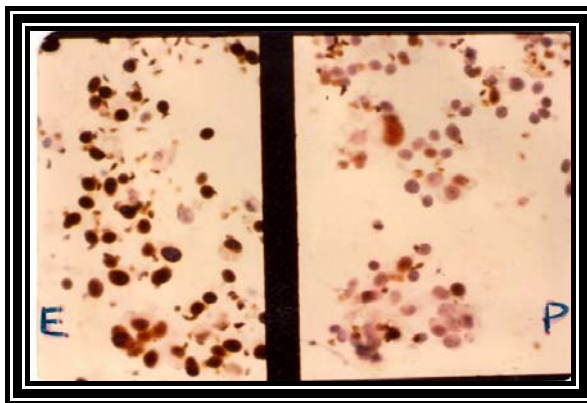


Figure (4): ERICA/PRICA immunocytochemical staining of FNAC specimen from the same malignant breast mass exhibiting strongly positive ERICA (left) and rather moderate-weak PRICA (right) staining reactions (ERICA/PRICA X 250)

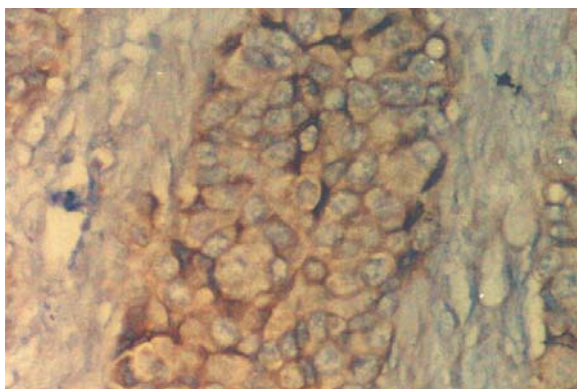


Figure (5): Invasive ductal carcinoma, moderately differentiated (Grade II), showing faint to moderate membrane staining: "positive reaction" score 2+ (Immuno-histochemical staining for HER-2/neu, x400)

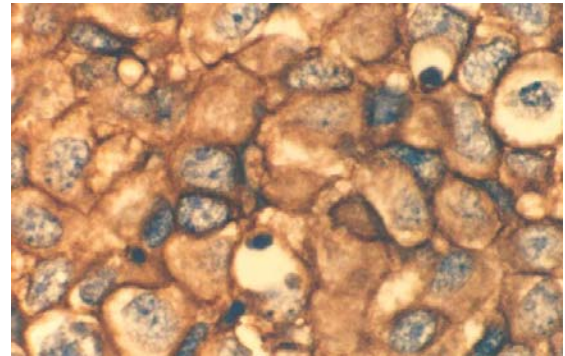


Figure (6): Invasive ductal carcinoma, poorly differentiated (Grade III), showing strong complete membrane staining: "positive reaction" score 3+ (Immuno-histochemical staining for HER-2/neu, x400)

Table (1): Pathological diagnosis of Breast Cancer in 5054 patients presenting with apparent breast lumps.

Pathological Diagnosis	No. of Cases	(%)
Benign	4333	85.7
Malignant	721	14.3
Total	5054	

The same Table displays that 526 patients (72.9%) came from urban Iraqi areas, 541 (75%) were married, 455 (63.1%) gave history of lactation while no history of using contraceptive pills and/or hormonal treatment was Obtained in 512 (71%). Family history of breast cancer was reported in 16.2%; 19.8% of those (i.e., 35 of 177 patients) had an affected first degree relative. Although the malignant lump was detected by the patient herself in 653 patients (90.6%), yet only 32.5% sought medical advice within the first month after detection while 16.2% did so after one year. Following the WHO classification, the most common histological type determined microscopically was invasive ductal carcinoma (655 patients: 90.8% - Figure 2). Seventy-three percent (527 patients) had axillary nodal involvement at the time of initial diagnosis. According to the AJCC system, the displayed frequencies were 7.6%, 45.1%, 31.5% and 15.7% for stages I, II, III and IV respectively. The Scarff Bloom Richardson classification revealed that 3.5%, 56.6% and 39.9% of ductal carcinomas were graded as I, II and III respectively.

ER and PR positive tumor contents were demonstrated in 65.1% and 45.1% respectively (166 and 115 out of 255 examined specimens); namely the ER+/PR+ phenotype being recoded in 40.8% of the studied cases (Figure 4), while the ER-/PR-variant was displayed in 30.6% (Table 4).

Immunohistochemical staining for Her-2/neu protein over expression revealed a positive reaction in 46.4% (89 out of 192 examined tissue blocks) - (Figures 5, 6).

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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