

Family History among Iraqi Patients Diagnosed with Breast Cancer

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Abstract: Breast cancer is the most common cancer affecting women in Iraq. Although a positive family history is a well established risk factor for the disease, yet the clinical and pathological characteristics of familial breast cancer remain a controversial issue. **Aim:** To correlate the family history of breast cancer with the clinico-pathological characteristics among Iraqi patients diagnosed with the disease. **Patients and Methods:** This comparative retrospective study involved 204 female patients who reported a family history of breast cancer out of 1081 diagnosed with the disease. All data was extracted from an established information system database, developed by the Director of the National Cancer Research Center/Baghdad University, over a 2-years period from July 2014 to June 2016. The recorded information included relevant data pertaining to family history, clinical presentation, diagnostic, clinical and pathologic findings. The family history was considered positive when the patient had one or more relatives diagnosed as breast cancer within three generations. **Results:** Family history of cancer was registered in 30% of Iraqi patients affected with breast cancer; in 18.5% the involved site was the breast. Among those 156 patients had one affected relative (76.5%), 39 had two involved relatives (19.1%) while a first degree relative was noted in 43.7%. The peak age frequency at the time of diagnoses was in the fifth decade of life. About 88% were married, 18.1% were nullipara and 15% had their first child born after the age of 35 years. History of lactation and hormonal intake was demonstrated in 54.5% and 22.5% respectively. Bilateral breast cancer was detected in 7.4%; the main histological type was infiltrative ductal carcinoma (77.8%). Positive lymph node involvement was observed in 65% of the patients in whom 42% presented at stages III and IV. Estrogen and Progesterone receptor positive activities were diagnosed immunohistochemically in 63.2% and 65% of tumor specimens respectively, 29.1% exhibited Her2 over expression. **Conclusions and Recommendations:** The characteristics of patients with positive family history of breast cancer did not reveal distinct clinical markers for their identification. Careful screening and regular follow up of the target population along with promoting public education on breast health care seem to be essential approaches to identify high risk groups for breast cancer control in Iraq.

Keywords: Breast, cancer, clinico-pathological characteristics, family history, Iraqi patients

1. Introduction

Breast cancer is the most widespread cancer among women worldwide (1). It is the most commonly diagnosed malignancy among the Iraqi population in general constituting about one third of the registered female cancers and the leading cause of death from malignant neoplasm among women (2). The complex etiology of the disease comprises an interaction between genetic, hormonal and environmental factors where family history represents a documented risk for its onset. It has been illustrated that the severity of the risk depends on the degree of family involvement, the age and the number of the affected relatives; probably reflecting the interaction between multiple genetic variants and shared environmental exposures among relatives (3).

About 5-10% of patients with breast cancer carry a genetic familial predisposition due to highly penetrant germline mutations (4). Breast cancers resulting from familial or genetic predisposition account for 15% to 20% of all diagnosed cases (5). Research focusing on family history assessment has become a potential tool for emphasizing the relevant importance of screening as a major approach to control breast cancer (6).

While earlier studies highlighted the clinico-pathological features of breast cancer among Iraqi patients (7-9), the characteristics of familial breast cancer remain a controversial issue. In the literature inconsistent results were reported regarding the relationship between that type of breast cancer and the corresponding clinical and

pathological parameters at the time of initial diagnosis (10,11). Understanding this association aid in paving the way for designing appropriate screening guidelines for patients with the disease; where local protocols for the care and referral of women at risk could be promptly developed.

The aim of this study is to estimate the frequency of familial breast cancer among Iraqi patients diagnosed with the disease and to evaluate its relationship with the displayed clinico-pathological characteristics.

2. Material & Methods

This comparative retrospective study involved 1081 female patients diagnosed with breast cancer. All data was extracted from an established information system database established by the author, under supervision of the International Agency for Research on Cancer, over a 2-years period from July 2014 to June 2016. That data-based system comprised all relevant data pertaining to patient identification including family history, clinical presentation, diagnostic (clinical and pathological) findings along with treatment outcomes.

The study was approved by the local ethical committee of our institution Data regarding family history were based on interviews with the patients from whom written consents were obtained at the time of diagnosis. The family history was considered positive when the patient had one or more relatives with breast cancer within three generations. In this study, family history was evaluated in those having up to three relatives.

The assessed parameters included the number of affected relatives, age at diagnosis, marital and educational status, parity, age at first child birth, history of lactation and hormonal intake, tumor localization, its histological type, grade, stage at presentation, hormone receptor contents (Estrogen and Progesterone) and Her2 over expressions. Malignant tumors were typed according to WHO classification of the disease, graded according to Scarff Bloom Richardson and staged following UICC classification system. Tumor characteristics were obtained from the diagnostic pathology reports.

3. Results

Table 1: Distribution of patients according to family history of cancer

	Organ involved	No	%
1	None	771	70.00%
2	Breast	204	18.50%
3	Colon	12	1.10%
4	Endometrium	8	0.70%
5	Ovary	3	0.30%
6	Leukemia/Lymphoma	12	1.10%
7	Lung	9	0.80%
8	Bladder	42	3.80%
9	Brain	20	1.80%
Total		1081	100%

Out of the total 1081 patients included in the study, no family history of any cancer was declared by 771 (70%), while **204 (18.5%)** recorded a positive family history of breast cancer. Among the remaining patients, history of colonic, ovarian and endometrial cancer was demonstrated in 1.1%, 0.3% and 0.7% respectively (Table 1).

Table 2: Distribution of family history of breast cancer according to the involved relatives

Number of Involved Relatives	Family History	%
1 Relative	156	76.5
2 Relatives	39	19.1
3 Relatives	9	4.4
Total	204	100

Among those with positive family history of breast cancer, Table (2) reveals that 156 patients had one affected relative (76.5%), 39 had two involved relatives (19.1%) while nine reported a positive history of breast cancer in three family members. (4.4%).

Table 3: Relationship of the affected family members among patients with positive history of breast cancer

Degree of Relation	Total		2 Relatives		3 Relatives	
	No	%	No	%	No	%
Mother	30	14.7	1	2.6	0	
Sister	56	27.5	8	20.5	1	11.1
Daughter	3	1.5	0		0	
Grandmother	9	4.4	3	7.7	0	
Aunt/Cousin	92	45.1	20	51.3	6	66.7
Others	14	6.9	7	17.9	2	22.2
Total	204	100	39	100	9	100

In general, a positive family history in a first degree relative (mother, sister or daughter) was noted in 43.7% (14.7%, 27.5% and 1.5% respectively). A positive history in aunts or

cousins was displayed in 45.1%. Among those declaring the involvement of two relatives the sisters and aunt/cousins were affected in 20.5% and 51.3% respectively. The aunt/cousins were effected in 2/3rd of those with three affected family members (Table 3)..

Table 4: Association between family history of breast cancer and the clinical parameters of the disease

Clinical Parameter	Studied Variable	Total No (204)	%
Age	>20	3	1.5
	20-29	6	2.9
	30-39	23	11.3
	40-49	59	28.9
	50-59	40	19.6
Marital status	>60	73	35.8
	Single	24	11.8
	Married	177	86.8
Education	Divorce/Widow	3	1.5
	Illiterate	31	15.2
	Primary School	65	31.9
	Secondary School	56	27.5
Parity	University	52	25.5
	0	37	18.1
	1-2	31	15.2
	3-5	95	46.6
Age at 1 st Child Birth	> 5	41	20.1
	<20	29	17.4
	20-29	88	52.7
	30-39	38	22.8
Lactation	>40	12	7.2
	Yes	91	54.5
Hormonal Intake	No	76	45.5
	Yes	46	22.5
Involved Breast Site	No	158	77.5
	Right	100	49.0
	Left	89	43.6
	Bilateral	15	7.4

Table 5: Association between family history of breast cancer and the pathologic characteristics of the disease

Clinico-Pathological Characteristics	Studied Variable	Total No (117)	%
Histologic Type	Ductal	91	77.8
	Lobular	10	8.5
	In Situ	3	2.6
	Others	13	11.1
Tumour Size	T0/Tis	5	4.3
	T1	18	15.4
	T2	72	61.5
	T3	11	9.4
	T4	7	6
Lymph Node status	Tx	4	3.4
	N -	41	35.0
	N +	76	65.0
Stage	I	14	12.0
	II	54	46.2
	III	39	33.3
	IV	10	8.5
Grade	I	11	9.4
	2	75	64.1
	3	31	26.5
ER	ER+	74	63.2
	ER-	43	36.8
PR	PR+	76	65.0
	PR-	41	35.0
Her2	Her2 +	34	29.1
	Her2 -	83	70.9

Tables 4 and 5 illustrate that the peak age frequency (28.9%) at the time of diagnosing breast cancer among Iraqi patients with positive family history was in the fifth decade of life. About 88% were already married, 53% were educated above secondary school, 18.1% were nullipara, while 70% had their first child before the age of 30 years. History of lactation and hormonal intake was demonstrated in 54.5% and 22.5% respectively.

Bilateral breast cancer was detected in 7.4%; the main histological type was infiltrative ductal carcinoma (77.8%) followed by lobular (8.5%), Positive lymph node involvement was noted in 65% while 61.5% of the tumors had diameters ranging between 2-5 cm. The majority of the breast cancers were moderately differentiated (64.1%); merely less than 10% exhibited well differentiated features. TNM system classified 58% of familial breast cancer as Stages I and II versus 42% as III and IV. Estrogen and Progesterone positive receptor activates (ER, PR) were diagnosed immunohistochemically in 63.2% and 65% respectively, while 29.1% exhibited positive Her2 over expression.

4. Discussion

The latest Iraqi Cancer Registry (2) estimated that 4,115 cases of breast cancer were reported in 2013 accounting for 19.5% of all newly diagnosed malignancies and 34% of the registered female cancers. The incidence rate was approximately 22 per 100,000 female population; the peak frequency being observed among middle aged women in their fifth decade of life. Very close age related findings were illustrated in the present work and within earlier reports from Iraq (7-9) reflecting the deficient knowledge on the significance of screening among families with affected relatives.

Breast cancer screening programs are usually designed for women aged 50 years and over since screening among female population under that age has been proved to be cost ineffective (6,12). Nevertheless, it has been estimated that 13% of women aged 30–50 years among the general population documented a family history of breast cancer (13). IARC indicated that females reporting a family history of that disease, with or without a known genetic predisposition, are at increased risk and therefore may benefit from intensified monitoring at earlier ages and shorter intervals than those at average risk (12). Consequently, early detection of breast cancer through screening might be advisable and cost effective in younger age groups.

The data base analysis of this survey highlighted that a family history of cancer was registered in 30% of Iraqi patients affected with breast cancer; in 18.5% the involved site was the breast. In general, it has been illustrated in the literature that 10–30% of patients complaining of breast cancer have a relative with the same disease (3,14). Previous studies from Iraq demonstrated relevant frequency rates ranging between 16 and 18% (7,9). Among those recalling a positive family history of breast cancer, 76.5% had one affected relative, 19.1% had two, while 4.4% reported a positive history in three family members. Interestingly, a

Moroccan study reported close frequencies of affected relatives who presented at relatively younger ages (11).

Among the remaining patients, positive history of colonic, ovarian and endometrial cancers was observed in 1.1%, 0.3% and 0.7% respectively. Hereditary breast, ovarian, and endometrial cancers comprise a significant portion of cancers affecting women. It has been emphasized that women with such genetic susceptibility have a much higher risk of developing cancer than the general population, accordingly recommending prompt thorough screening (15). In Turkey, a family history of cancer was reported in 57.4% of patients with breast cancer and among those the breast and ovaries were involved in 24% (10).

In this study, a positive family history in a first degree relative was noted in 43.7%; the mother, sister or daughter being involved in 14.7%, 27.5% and 1.5% respectively. Among those declaring history in two relatives, the sisters and aunt/cousins were affected in 20.5% and 51.3% respectively. A Turkish study illustrated that 54.1% of breast cancer patients under the age of 50 years reported a family history of the disease in a first degree relative while 71% had a second degree relative; in 21% of their patients the mother was affected with breast or ovarian cancer and in 3.9% she was affected with both (10). The breast cancer risk could be predicted by accurate calculation using the Tyrer-Cuzick model of the International Breast Cancer Intervention Study program (16). In Canada, it has been analyzed that cancer-related distress is often high among sisters of newly diagnosed patients with breast cancer; those showing a perceived lifetime risk of > 20% required future interventions (17).

Breast cancer, as a heterogeneous disease, is susceptible to genetic, hormonal and environmental risk factors that reflect a variety of characteristics which correlate with its prognosis. Women with a strong family history of breast cancer could inherit genetic alterations that modify their risk and clinical presentations. Accordingly, the second part of this study was designed to evaluate the clinico-pathological characteristics of patients with positive family history of breast cancer.

It was observed that the frequency of premenopausal patients versus postmenopausal in the studied group was equivalent to 44.6% versus 55.4%; rather close to that reported in a recent survey on Iraqi patients with breast cancer. Nevertheless, younger age groups at the time of presentation were recorded in earlier cohort studies from Baghdad (8,9). Other investigators emphasized that patients with familial breast cancer often present at younger ages (10,11,18); supporting the urgent need to initiate the cancer screening programs in their relatives at least a decade earlier than the general population.

Compared with what has been reported on the risk factors for breast cancer (3,4,19), it was interestingly displayed in this study that about 88% of the patients were married, 18.1% were nullipara, 15% had their first child after the age of 35 years while history of hormonal intake was demonstrated in 22.5%. A previous Iraqi report on the same population of patients with breast cancer, regardless of their

family history, documented that only 8.5% did not have children and 7% delivered their first child after 35 years; illustrating the obvious knowledge gaps on the risks of breast cancer among the Iraqi community in general and in those having a relative with breast cancer in particular. In the literature, the relationship of familial breast cancer with reproductive factors among affected patients has been found to be controversial (3,19-22). Evidence suggests that this association could vary by tumor subtypes as defined by their hormone status (19). Some studies proposed that first full-term pregnancy at a young age offers significant protection in familial breast cancer while others denied any protective role (20). Higher rates of hormonal use among patients with family history of breast cancer were recorded in other studies (11). Others concluded that long duration of oral contraceptive pills might be inversely associated with the risk of breast cancer (21). In this study the rate of patients who breast fed their children was 54.5%, slightly higher than that demonstrated among those with no family history of the disease in a previous research (7); disregarding the protective role of lactation (22).

Among the studied group bilateral breast cancer was observed in 7.4% of patients exhibiting family history of the disease; higher than what was revealed in other studies (10,11). In a survey on the characteristics of breast cancer among Iraqi women, 4.6% of patients had contra lateral involvement (7). It has been proposed that bilateral cases are more frequently associated with familial breast cancer where the risk of the contra lateral breast disease is higher (23). However, it has been recommended that the clinical management should not differ when the underlying mutation is unknown (24).

Positive lymph node involvement was noted in 65%; approximately 42% of patients in the current study were diagnosed in Stages III and IV. Preliminary findings from an Iraqi breast cancer research project published recently demonstrated that 9.8% of the patients presented in Stage I, while 46% were diagnosed in Stages III and IV (7). That insignificant difference in the stage of disease at presentation, between patients recording positive family history and those without, was noted by other investigators (11,25). Nevertheless, inconsistent relevant results were documented in other studies varying from the prevalence of smaller tumors (10, 26) or more advanced stages at the time of presentation (27). Histological examination of the tumor specimens illustrated in other studies that lobular carcinomas were often encountered among patients with positive family history (10,11, 28), however, our findings did not reveal any significant difference in the type of carcinoma compared to earlier reports on breast cancer patients in Iraq (7,9).

Likewise, in line with the results illustrated in previous studies from Iraq (7,9) and other countries (10, 11,29), no significant differences were noted concerning the distributions of tumor grade, ER, and PR among patients with and without family history of the disease. On the other hand, other investigators reported that tumors of patients with familial breast cancer tend to exhibit a more aggressive biology and are likely to be ER/PR negative (10, 30, 31).

Nevertheless, it was noted that the rate of Her2 positive tumors (29%) was lower than what was previously reported

in Iraq (7,9), in agreement with other studies (11,31,32), which illustrated a lower prevalence of that tumor marker among patients with familial breast cancers.

5. Conclusions and Recommendations

The characteristics of patients with positive family history of breast cancer did not reveal distinct clinical markers for their identification. Careful screening and regular follow up of the target population along with promoting public education on breast health care seem to be essential approaches to identify high risk groups for breast cancer control in Iraq.

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