Imaging and clinicopathological characteristics of breast cancer among women under the age of 40 years

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Abstract:

Background: although breast cancer in young women is less common and often overlooked, it is still considered a major health concern.

Objectives: to evaluate the demographic, clinical, radiological and histopathological characteristics of breast cancer among a sample of Iraqi women diagnosed under the age of 40 years.

Patients and methods: a retrospective study enrolled 73 females below the age of 40 years with a history of breast cancer. All data was extracted from an established information system database designed by the Principal Investigator of the Iraqi National Breast Cancer Research Project under supervision of the International Agency for Research on Cancer (IARC) over a 4-years period from 2011 to 2014.

Results: seventy three women under the age of 40 years with breast cancer were included in the study out of 625 diagnosed cases at different ages (11.68%). The age at presentation ranged from 25 to 39 years, the peak age frequency (63%) was recorded in the period between 35-39 years (n=46). Family history of breast cancer was noticed in approximately 31.5% of cases (n=23). Early menarche (less than 12 years old) was detected in 78.1% (n=57) of cases. On examination, 90.4% (n=66) of patients had painless palpable breast lump. By Sonography, the lesions were spiculated margins in 52% (n=38) of patients and echogenic halo around the mass was detected in 57.5% (n=42) of cases. Stage-II disease was recognized in 54.8% (n=40) of sample of the study and majority of the tumor (98.6%) were ductal in origin. According to Scarf-Bloom-Richardson method, 60.3% (n=44) of the tumors were moderately differentiated (i.e. grade- II). Eight patients (10.9%) were presented with triple receptor-negative breast cancer and recurrence of tumor was encountered in 17.8% (n=13) of cases.

Conclusions: The current study suggest that breast cancer among young Iraqi women under 40 years had high incidence rate but might be less aggressive than what is reported in western countries despite of high recurrence rate.

Key words: breast, cancer, young age, Iraq.

Introduction:

It has been demonstrated in many studies that breast cancer in young women exhibit more aggressive behavior and poor outcomes in comparison with older patients.1,2,3 Other authors displayed that breast cancer in women before age 40 years differs biologically from that encountered in the older generations 4 and that only 5 % of breast cancer cases occur in women at that age.5 Since breast cancer occurs at a much lower rate among young women than in the older counterparts, it remains less emphasized in many research studies. According to the latest Iraqi Cancer Registry, breast cancer is the most common malignancy among the Iraqi population constituting about one third of the registered female cancers; 17.8% are diagnosed in patients under 40.6 In fact, worldwide, no effective breast-cancer screening tool yet exists for females aged 40 or younger. Accordingly, most of

the patients diagnosed at this age group in our country usually present subsequent for discovering the lump accidentally or following either breast self-examination (BSE) or clinical breast examination (CBE) by their examining doctor. The Iraqi National Breast Cancer Research Program of the Ministry of Higher Education and Scientific Research (MoHESR) established in 2009 a comprehensive information system database under supervision of the International Agency for Research on Cancer (IARC). That data-based system comprise all relevant data pertaining to patient identification, family history, clinical presentation, diagnostic findings (including radiological and pathological), hormone receptor status of the tumor, treatment options, possibility of recurrence and survival rates at 2 and 5 years interval following the diagnosis. The main purpose of this study was to analyze the characteristics of breast cancer among a sample of Iraqi population diagnosed with the disease at age period below the 40 years; focusing on the demographic, clinical and radiological profiles.

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Patients and methods:
This is a retrospective analysis of the data extracted from the information system database belonging to the Iraqi National center for cancer Research-Baghdad University-MoHESR during a 4-year period starting from January 2011 until December 2014. Overall 625 patients were enrolled in this survey. The evaluated variables included data pertaining to patient identification, family history, clinical presentation, diagnostic findings (including imaging, radiological and pathological), and hormone receptor status of the tumor, treatment options, and possibility of recurrence and survival rates at 2 and 5 years interval following the diagnosis. Data belonging to all patients recorded below the age of 40 years (73 patients) were analyzed and tabulated separately. Verbal and/or written consent was obtained from each of the patient at each visit during which their database was updated. The assessed parameters included age at diagnosis, marital status, educational level, age at first delivery, and age at menarche, number of parity, history of lactation and hormonal intake and family history of the disease. Other data pertaining to clinical and radiological diagnoses were also recorded comprising method of detection, tumor size (mm), and tumor site, number of lesions, presenting symptoms and signs and characteristics of the malignant lesion by Ultrasound. Malignant tumors were typed according to WHO classification of the disease, graded according to Scarff Bloom Richardson method and staged following UICC (Union for International Cancer Control) classification system. Statistical analysis was performed and different variables were analysed.

Results:
Demographic characteristics: Over a period of 4 year, 73 patients with breast cancer were included in the study; the age at presentation ranged from 25 to 39 years. The mean age was 36 years and the maximum numbers of patients (63%) affected belong to the age group of 35-39 years (table 1). Majority of our patients were referred to breast clinic in the National Center of Early Detection of Cancer by consultant surgeon in same center following patient concern upon self-examination while the minority of the patients were referred from private clinic after clinical evaluation by their doctors. Wide differences in the education status were evident among patients; however, more than half of the women had primary school education and majority of them were housewives. The results shows 87.7% (n=64) of patients were married or had history of marriage while only 12.3% (n=9) were single. 67.1% (n=49) of women reviewed in this study had 3 or more children while 15.1% (n=11) were nulliparous and only three patients (4.1%) were using combined oral contraceptive pills. 80.8% (n=59) of patients had age less than 30 years at first child birth and menarche age below 12 years noted in 78.1%

(n=57). 95.9% (n=70) of patients had history of menstruation in last 12 months and 30.1% (n=22) of women had history of lactation for at least 6 months for the last child. 31.5% (n=23) of patients revealed reported family history of breast cancer or related malignancy as shown in (table 1).

Table (1) patients' characteristics of breast cancer in women under the age of 40 years

Variable	Category	No.	%
Age at diagnosis	25-29 years	3	4.1
	30-34 years	24	32.9
	35-39 years	46	63.0
Marriage status	Married	62	84.9
	Divorced or widow	2	2.8
	Single	9	12.3
Number of delivery	0	11	15.1
	1-2	13	17.8
	3 or more	49	67.1
First delivery age (years)	< 30	59	80.8
	30 or more	3	4.1
	Negative	11	15.1
Menarche age	<12	57	78.1
	12	9	12.3
	13	5	6.8
	14	2	2.8
	15 or more	0	0
Hormonal intake (OCP)	Yes	3	4.1
	No	70	95.9
Family history	Negative	50	68.5
	Positive	23	31.5
Education level	Illiterate	8	11.0
	Primary school	37	50.6
	Secondary school	14	19.2
	University equivalent	14	19.2
Menstruation in the last 12 months	Yes	70	95.9
	No	3	4.1
Lactation for at least 6 months for the last child	Yes	22	30.1
	No	51	69.9

Clinical presentations: Following the clinical assessment, 90.4% (n=66) of patients had presented with a lump whereas

only 23.3% (n=17) complained from breast pain and 13.7% (n=10) had skin changes. Only 4.1% (n=3) of patients suffered from bloody nipple discharge and ulceration detected in 2.7% (n=2) of patients. 15.1% (n=11) had axillary lumps (lymphadenopathy). At first time of examination, 9.6% (n=7) of patients presented with symptoms or signs of distant metastasis. On examination, 90.4% (n=66) of patient had a palpable breast lump detected either by breast self examination or by clinician while remaining minority of patients (9.6%) with non-palpable breast lesions detected by ultrasound examination (table 2).

Table (2) clinical presentations of breast cancer in women under the age of 40 years

Variable	Category	No.	%
Method of detection	BSE +/-Clinical examination (palpable)	66	90.4
	Ultrasound (non-palpable)	7	9.6
Presenting symptoms and signs	Asymptomatic	0	0
	Pain	17	23.3
	Lump	66	90.4
	Skin changes	10	13.7
	Ulceration	2	2.7
	Bloody nipple discharge	3	4.1
	Axillary nodes	11	15.1
	Symptoms and signs of distant metastasis	7	9.6

Ultrasound findings: High resolution ultrasound with Doppler facility applied on all patient and results are categorized according to breast imaging and reporting data system (BIRADS) and category- 4 & 5 were ended by fine needle aspiration cytology with or without ultrasound guidance according to size of the tumor; subsequently the histopathology was done. 56.2 (n= 41) of patients had right-sided lesion whilst 41.1% (n=30) had left-sided lesion and only 2.7% (n=2) presented by bilateral disease. 42.5% (n=31) of these patients demonstrated the lesion in the upper outer quadrant, 15% (n=11) of the lesions were retroareolar in location and only 4.1% (n=3) of the lesions were detected in more than one quadrant. The majority (95.9%) of women displayed single lesion and multiple masses detected in the 4.1% (n=3) of patients. Maximum diameter of the tumor at time of presentation measured by millimeter (mm), 52% (n=38) of the lesions were ranged from 10-19 mm and 5.5 % (n=4) of lesions were less than 10 mm; 37% (n=27) of the lesions were measured from 20-29 mm and 5.5% (n=4) had 30 mm or more diameters. Edge characterization of the tumor by ultrasound had spiculated margin in 52% (n=38) of the patients, microlobulated margin were detected in 28.8%

(n=21) of patients, macrolobulated were detected in 4.1% (n=3) of patients and tissue distortion without definite mass lesion was noticed in 15.1% (n=11) of cases. Echogenic halo around the mass was detected in 57.5% (n=42) of patients. Quantitive Doppler ultrasound measurement of vascularity and Resistive Index (RI) of the tumor were high RI figure in 71.2% (n=52) of patients as shown in (table 3). Internal calcifications within the breast mass were detected by ultrasound examination only in 9.6% (n=7) of cases.

Table (3) ultrasound findings of breast cancer in women under the age of 40 years

Variable	Category	No.	%
Tumor size (mm)	<10	4	5.5
	10-19	38	52
	20-29	27	37
	30 or more	4	5.5
Tumor site	UOQ	31	42.5
	UIQ	10	13.7
	LOQ	14	19.2
	LIQ	4	5.5
	Retroareolar region	11	15
	More than one quadrant	3	4.1
Laterality	RT	41	56.2
	LT	30	41.1
	Bilateral	2	2.7
Tumor number	Single	70	95.9
	Multiple	3	4.1
Edge characterization of the lesion by Ultrasound	Smooth	0	0
	Macrolobulated	3	4.1
	Microlobulated	21	28.8
	Spiculated	38	52.0
	Tissue distortion without mass	11	15.1
Resistive index on Doppler ultrasound	<0.7	21	28.8
	Equal or >0.7	52	71.2
Echogenic halo	Positive	42	57.5
	Negative	31	42.5
Calcification	Positive	7	9.6
	Negative	66	90.4

Histopathological outcomes: Pathological analysis of sample of study revealed that 54.8% (n=40) of patients had stage-II, 28.8% (n=21) of cases had stage-III, 9.6% (n-7) of patients had stage-IV and 4.1% (n=3) of patients had stage-I. 60.3%

(n=44) of patients were grade- II; 32.8% (n=24) were grade-III and 6.9% (n=5) were grade-I. 98.6% (n=72) of patients had tumor of ductal origin and only one tumor was lobular in type. Estrogen receptor was negative in (15%) of patients (n=11) and Progesterone receptor was negative in (13.7%) of patients (n=10) and Her2 Neu growth factor over expression was negative in 24.7% of women (n=18).

The majority (98.6%) of the patients included in the study treated by total mastectomy aside from a single patient had breast conserving surgery. Over four years period of study, 13 patients (17.8%) had tumor recurrence during regular-interval follow up investigations and survival rate cannot be applied on all women in this study and prescription of chemotherapy, radiotherapy and hormonal therapy as well as the biological therapy also cannot be specified in most of the patients.

Table (4) histopathological parameters of breast cancer in women under the age of 40 years

Variable	Category	No.	%
Stage	0	2	2.7
	I	3	4.1
	II	40	54.8
	III	21	28.8
	IV	7	9.6
Histology	Ductal	72	98.6
	Lobular	1	1.4
	Other	0	0
Grade	I	5	6.9
	II	44	60.3
	III	24	32.8
Estrogen receptor	Negative	11	15
	Positive	18	24.7
	Unknown	44	60.3
Progesterone receptor	Negative	10	13.7
	Positive	19	26
	Unknown	44	60.3
HER 2 status	Negative	18	24.7
	Positive	10	13.7
	Unknown	45	61.6
Recurrence		13	17.8

Discussion

Breast cancer in women under 40 years of age is infrequent but on the other hand it has significant consideration since various studies show poor disease outcome 5,6,7 and unfortunately remains the most commonly diagnosed cancer in young women under 40 in Iraq.8 There are few studies considers the young age group as independent adverse prognostic indicator of survival in breast cancer.2,9,10 The national center for early detection of cancer at medical city in Baghdad receives about 3500 patients per year where a total of 134 new breast cancer patients from all age groups are diagnosed annually and approximately 11% (15/134) of these new breast cancer patients are below 40 years of age. This incidence is dissimilar to the incidence in other studies reported 4% as in Winchester et al from the US 11 and McAree et al from Belfast city at the UK 12 while the incidence is higher in the north Ireland (7%).13 In this study the individual incidence in women below 35 years of age was 32.9% and less than 4.1% before age 30.The American cancer society estimates that 6.6% of all breast cancer cases diagnosed before age 40, 2.4% diagnosed before age 35, and 1% diagnosed before 30.4 Currently, there is no routine screening program in Iraq for women less than 40 years for that reason most women in this age group are symptomatic and presented mostly with palpable lump. The examination findings in this study were a palpable lump (90.4%), pain (23.3%), axillary node (15.1%) and skin changes (13.7%); no breast cancer was diagnosed in asymptomatic women, which is in agreement with Agnese et al that reported that younger patient under 40 were much more likely to present with a palpable mass (70%).14 Foxcroft et al stated that only 7% of breast cancer below 40 years were diagnosed in asymptomatic women.15 In this study most our patient were married or had married (84.9%) and 67.1% of patients had 3 or more child and 80.8% of these women had first child delivery before age of 30 years. Rodriquez et al found that women aged less than 35 year, early childbearing and multiparity are risk factors, due to short-term elevation in breast cancer risk for several months immediately following a birth.16 Also married women were more likely to have received a breast exam and received mammograms within the last years than single (never married) or no longer married women.17 78.1% of our sample of this study had early menarche before age of 12 years, which is considered one of possible risk factor for breast cancer while only 17.6% had early menarche in Najmeh et al.18 Although recent oral contraceptive use is a risk factor for early onset breast cancer particularly for estrogen (ER)-negative tumors as stated in Rodriquez et al study 16; only 3 (4.1%) patients in this study had history of combined oral contraceptive pills intake. A positive family history of cancer in first degree relative was 31.5% while McAree et al study reveals only 10.5% of patient had a first degree relative affected by breast cancer and Foxcroft et al study also shows only 13.4% had a positive family history.12, 15 Antoniou et al found that breast cancer at an early age is more likely to be associated with an increased familial risk, especially in women harboring a BRCA1mutation.19 therefore; our patient carry strong family

history of cancer in compared to other aforementioned studies and women over 40 years that only 18.7% in Foxcroft et al.15 but in Italy, patient under 40 years old more frequently had a family history of breast cancer, more often used oral contraceptives and on average they had experienced menarche 1 year earlier than did older patients as reported in Sidoni et al.20 Lalloo et al found that half of women with breast cancer diagnosed before age 30 had positive BRCA1, BRCA2 and TP53 mutations in those who had strong family history of breast cancer and less than 10% of women with non-familial breast cancer 21; however, BRCA 1 analysis was not available in our center at time of this study, therefore the relationship between positive family history and positive BRCA 1 mutation not properly assessed. This study found that breast cancer affected the women with low education level [primary school and illiterate] although the likelihood of having a breast examination and receiving mammograms within the last years increased with education.17 Women under age 40 were no longer eligible for breast cancer screening, with the exception of women in that age group who are at high risk for breast cancer or with clinically significant findings for breast cancer; for that reason majority of the breast cancer in this study were symptomatic presented by palpable mass and detected by clinical examination while only 9.6% of patients have no palpable mass and detected only by ultrasound. Most of breast cancer in this study presented as hypoechoic spiculated mass with great value of resistive index in characterization of malignant lesion because of 71.2% of lesions display high resistive index. Histopathological review of sample of the study revealed that 98.6% of breast cancer I n young women were ductal in origin (invasive ductal carcinoma) in contrast to McAree et al who found that 85.5% of breast cancer were invasive ductal type and 71.5% in Foxcroft et al.12, 15 while, there is preponderance for invasive ductal carcinomas in older patient.15 In our review, 29 patients from 73 women with breast cancer investigated for estrogen [ER], progesterone receptors [PR] and HER2 status; 8 patients (10.9%) of them were triple negative results; however, estrogen receptor status is widely reported as predominantly negative in younger women.2, 22, 23 In this study, 60.3% (n=44) of tumors were graded as grade-II and 32.8% (n=24) were grade-III. These results were slightly higher than results obtained by McAree et al study which found that 54.4% were grade-II and 40.7% were grade-III 12 and lower than results obtained by Fernandopulle et al study that indentified a 60% grade-III in young Asian women.22

Over a 4-year period, 13 (17.8%) of patients had breast tumor recurrence in women under 40 years which is in agreement with Van Nes et al reported that recurrence rate of breast cancer up to 4 times higher in women less than 40 years when compared with older women.24

Conclusions

The current study suggest that breast cancer among young Iraqi women under 40 years had high incidence rate but might be less aggressive than what is reported in western countries despite of high recurrence rate.

Author contributions:
Abdullateef Aliasghar: Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.
Nada abdelsahib, Enam Azez: Authors participate in drafting the article or revising it critically for important intellectual content; authors give final approval of the version to be submitted.

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