



Profiles of Breast Cancer among Young Premenopausal Females Under the Age of 40 Years

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Received: February 23, 2021

Published: March 08, 2021

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Abstract

Breast cancer, the most registered female malignancy, is mainly diagnosed among women in their postmenopausal age. Recent statistics display an increase in the incidence of the disease in young patients under the age of 40 years.

Aim: To describe the demographic, clinical and pathological profiles of breast cancer diagnosed in a series of Iraqi women under 40 years of age; comparing the findings with those observed among older age groups.

Material and Methods: This retrospective descriptive study was based on the analysis of data collected from medical records belonging to 1173 Iraqi females who were diagnosed with breast cancer. Patients were categorized into two groups according to age: <40 years versus those aged 40 years and over. The analyzed variables included patients' age, marital status, educational level, parity, age at first child birth, family history of cancer, side of the affected breast, histological type, pathological grade, clinical stage and breast cancer subtypes according to the immunohistochemical assessment of Estrogen, Progesterone and HER2 tumor contents.

Results: The total number of young patients presenting with breast cancer under 40 years was 150 (12.8%); versus 1023 patients (87.2%) aged 40 years and older. Significant differences were noted between the two groups with respect to the educational level, age at first delivery and parity ($p < 0.05$). Patients under 40 years gave birth at earlier ages and had less number of children whereas illiteracy was more common among older patients. Younger patients <40 exhibited as well significantly higher rates of Triple Positive, Triple Negative and HER2 Enriched subtypes (18.7, 17.5 and 16.3 respectively versus 12.5, 12.9 and 9.6 respectively in patients over 40). Whereas no statistical differences were illustrated among the age groups regarding the marital status and family history of cancer; there was a higher propensity for the disease to present at advanced stages in the younger group with lower preponderance of well differentiated grades..

Conclusions: The propensity of breast cancer to affect young Iraqi females, with the preponderance of advanced stages at presentation and aggressive tumor subtypes, emphasize the urgent need to strengthen early detection of the most common cancer in the community and to establish multidisciplinary strategic guidelines for its optimum management and control.

Keywords: Profiles; Breast; Cancer; Young; Premenopausal; 40 Years

Introduction

In Iraq, breast cancer has been the main registered malignancy among the population since four decades [1]. In spite of the striking achievements in the field of oncology research, breast cancer control is still considered a major challenge facing health authorities. As the most common cancer among women worldwide and the leading cause of female related mortality, breast cancer currently represents 24% of all newly diagnosed cancer cases and 15% of cancer deaths [1,2]. Although it mainly affects postmenopausal women, yet recent statistics reveal an increase in the incidence of the disease among premenopausal young females under the age of 40 years. Globally, the proportion of patients presenting with breast cancer in the premenopausal age is greatest in developing countries, while the developed societies exhibit a greater burden among postmenopausal women [2-5]. Presently, a growth in the incidence of premenopausal breast cancer is observed in transitioning countries of the world; most probably related to changes in lifestyle and reproductive patterns which are known risk factors for the disease [2,5,6].

Young breast cancer refers to the disease when it presents under the age of 40 and constitutes 4-7% of new cases [7-9]. Whereas only 4% is detected among American women before they reach 40 years [9], numerous studies from Iraq [10-15] and the region [16-18] have clearly illustrated the high propensity of breast cancer to affect younger female generations. In general, it has been claimed that early onset of the disease is often associated with aggressive clinic-pathological behavior and less favorable prognosis [3,19-22] and that young age could play an independent risk factor for disease-free survival among patients with operable breast cancer [23]. In fact, the detection of the disease in females at this age group could be hindered owing to the denser pattern of breast tissues, false negative mammography findings and the lack of screening programs. Such delayed diagnoses are often associated with detection of larger tumors and advanced clinical stages at the time of presentation [24-27].

In light of the above and with the aim of encouraging early detection of breast cancer at younger ages, the current study was designed to describe the demographic, clinical and pathological profiles of breast cancer diagnosed in a series of Iraqi females under the age of 40 years; comparing the findings with those observed among older age groups.

Materials and Methods

This retrospective descriptive study was based on the analysis of data collected from medical records through an information system organized by the author at the National Cancer Research Center of Baghdad University under direct supervision of the International Agency for Research on Cancer, Screening Unit, Lyon in 2012. The data base comprised demographic, clinical and pathological information belonging to 1173 Iraqi female patients who were diagnosed with breast cancer at the Referral Training Center for Early Detection of Breast Tumors, Oncology Teaching Hospital, Baghdad during the period between October 2013 and September 2017.

The study protocol was approved by the institutional Ethical Research Committee in line with the ethical standards of Helsinki Declaration. Female patients were categorized into two groups according to age: those presenting with breast cancer under the age of 40 years versus those aged 40 years and over. Medical records of patients containing valid complete information on the clinical, laboratory, imaging and follow up data were included in the study. Cases diagnosed as carcinoma in situ were excluded.

The analyzed variables involved patients' age, marital status, educational level, parity, age at first child birth, family history of breast cancer or any other malignancy and the side of the affected breast. Paraffin blocks containing breast cancer tissues belonging to 678 patients were available for pathological examination. Whereas breast cancer types were recorded following WHO classification [28], modified Nottingham Bloom-Richardson system was applied to grade mammary carcinoma [29]. Staging of the disease was defined in accordance with the TNM System and the American Joint Committee on Cancer Staging [30]. In 505 patients, immunohistochemical staining of paraffin embedded cancer tissue blocks was used to analyze the breast cancer subtypes [phenotypes] through determining the availability of Estrogen receptor [ER], Progesterone receptor [PR] and HER2 contents of their primary tumors.

Statistical analysis

Statistical program (SPSS), version 23 was used for data entry and analysis. Categorical data were summarized by using digital frequencies and percentages. Findings related to demographic, clinical and pathological profiles among the studied groups were correlated statistically. Chi-Square was considered significant when p-value is < 0.05.

Results

Total	Min	Max	Mean	ST*	Sum	Percentile							
						0.05	0.10	0.25	0.50 Median	0.75	0.90	0.95	
Overall	1 173	24.00	96.00	51.09	10.78	59 923.00	35.00	38.00	44.00	50.00	58.00	65.00	70.00
=/>40 years	1 023	40.00	96.00	53.44	9.38	54 674.00	41.00	42.00	46.00	52.00	60.00	66.00	71.00
<40 years	150	24.00	39.00	34.99	3.44	5 249.00	28.00	30.00	33.00	36.00	38.00	39.00	39.00

Table 1: Distribution of the study population by age groups (<40 versus =/>40 years).

*Standard Deviation

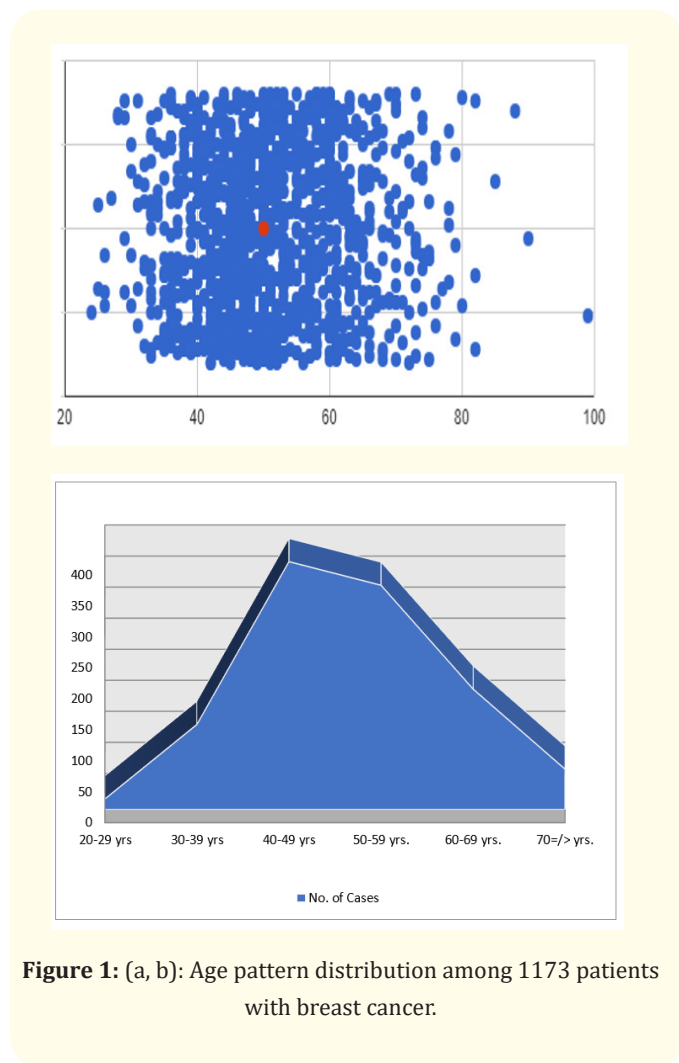


Figure 1: (a, b): Age pattern distribution among 1173 patients with breast cancer.

Studied Variables	Overall 1173 No (%)	=/> 40 years 1023 (87.2) No (%)	< 40 years 150 (12.8) No (%)	Chi Square
Marital Status				0.8067
Unmarried	116 (9.9)	100 (9.8)	16 (10.7)	p= .668087 Not Significant
Marital	1030 (87.8)	898 (87.8)	132 (88)	
Widow/ Divorced	27 (2.3)	25 (2.5)	2 (1.3)	
Education				16.2621. p =.002687 Significant at p<.05
Illiterate				
Primary School	258 (23.3)	239 (24.8)	19 (13.4)	
Secondary School	353 (31.9)	289 (29.9)	64 (45.1)	
University and Higher	271 (24.5)	238 (24.7)	33 (23.2)	
Unknown	66	58	8	
Age at 1 st Delivery#				11.5623 p =.009043 Significant at p<.05
10-19	317 (32.5)	279 (32.8)	38 (30.4)	
20-29	490 (50.3)	412 (48.5)	78 (62.4)	
30-39	158 (16.2)	149 (17.5)	9 (7.2)	
40-49	10 (1.0)	10 (1.2)	0 (0)	

Parity@				
0	81 (7.7)	73 (7.9)	8 (6.0)	12.0277
1-2	199 (18.8)	169 (18.3)	30 (22.4)	p =.007289
3-4	422 (39.9)	355 (38.5)	67 (50.0)	Significant
=>5	355 (33.6)	326 (35.3)	29 (21.7)	at p<.05
Family History				
None	812 (69.2)	716 (70.0)	96 (64.0)	2.7261
Breast Cancer	219 (18.7)	184 (18.0)	35 (23.3)	p= .255877
Other Cancers	142 (12.1)	123 (12.0)	19 (12.7)	Not Significant
Breast Side				
Right	576 (49.1)	498 (48.7)	75 (50.0)	0.5812
Left	546 (46.5)	477 (46.6)	70 (46.7)	p= .747812
Bilateral	51 (4.3)	48 (4.6)	5 (3.3)	Not Significant
Histology Type	*	**	***	
Ductal	572 (84.4%)	495 (83.8)	77 (88.5%)	1.4467
Lobular	46 (6.8%)	(6.9) 41	5 (5.7%)	p= .485135
Others	60 (8.8%)	55 (9.3)	5 (5.7%)	Not Significant
Pathological Grade	*	**	***	
Grade I	42 (6.2)	39 (6.6)	3 (3.4)	2.6703
Grade II	479 (70.6)	420 (71.1)	59 (67.8)	p= .263115
Grade III	157 (23.2)	132 (22.3)	25 (28.7)	Not Significant
Clinical Stage	*	**	***	
Stage I	72 (10.6)	66 (11.2)	6 (6.9)	1.931
Stage II	322 (47.5)	(47.4)280	42 (48.3)	p= .586841
Stage III	230 (33.9)	197 (33.3)	33 (37.9)	Not
Stage IV	54 (8.0)	48 (8.1)	6 (6.9)	Significant

Table 2: Characteristics of Iraqi breast cancer patients verified according to age.

Total Number = 975 excluding Nulliparous and Unmarried; @ Total Number = 1057 excluding Unmarried.
 *Total Number = 678; **Total Number = 591; ***Total Number = 87.

STAGE	Overall No (%)	>=40 Years No (%)	<40 Years No (%)
Stage I	72 (10.6)	66 (11.2)	6 (6.9)
Stage IIA	167 (24.6)	142 (24.0)	25 (28.7)
Stage IIB	144 (21.2)	128 (21.7)	16 (18.4)
Stage II UN	11 (1.6)	(1.7) 10	(1.1) 1
Stage IIIA	103 (15.2)	0 (15.2)9	(14.9)13
Stage IIIB	55 (8.1)	48 (8.1)	7 (8.0)
Stage IIIC	(7.7) 52	42 (7.1)	10 (11.5)
Stage III UN	20 (2.9)	17 (2.9)	(3.4)3
Stage IV	54 (8.0)	48 ((8.1)	(6.9)6
Total	678	591	87

Table 3: Staging of breast cancer among patients < 40 years versus =/>40 years.

SUBTYPE*	Overall No (%)	>= 40 years* No (%)	< 40 years* No (%)
Luminal A (E+/P+/H-)	253 (50.1)	224 (52.7)	29 (36.3))
Luminal B (TP) (E+/P+/H+)	68 (13.5)	53 (12.5)	15 (18.7)
Triple Negative (E-/P-/H-)	69 (13.7)	55 (12.9)	14 (17.5)
HER2-Enriched (E-/P-/H+)	54 (10.7)	41 (9.6)	13 (16.3))
Other Subtypes	61 (12.1)	52 (12.2)	9 (11.3)
Total	505	425	80

Table 4: Immunohistochemical breast cancer Subtypes analyzed in tumor tissues of the studied groups.

*Chi Square =0.051121; Significant at p <0.10.

The total number of young premenopausal patients who were diagnosed with breast cancer under the age of 40 years was 150 (12.8%); versus 1023 patients aged 40 years and older (87.2%). Figures representing the minimum, maximum, mean and median age among the young patients were 24, 39, 34.9 and 36 respectively; whereas the corresponding figures among the older patients

were 40, 96, 53.4 and 52 respectively (Table 1). Overall, the peak age frequency in the studied sample occurred in the period "40 - 49 years" (34%) followed by the period "50 - 59 years" (30.7%) – (Figure a and b).

Table 2 shows the demographic and clinical profiles in the two studied groups (verified as <40 versus ≥40 years). Whereas no statistical difference between the two categories was noted with respect to the marital status, significance variations were demonstrated regarding the educational level, age at first delivery and parity ($p < 0.05$). Illiteracy was more prevalent in older patients aged 40 years and over. Young patients under 40 years delivered their first babies at earlier ages and had less number of children.

No statistical differences were illustrated among the age groups regarding family history of cancer, the affected breast side and the histologic type of breast cancer. Although advanced stages (III and IV) at presentation were more common among younger patients than those aged 40 years and older (44.8% versus 41.4%) with a lower preponderance of well differentiated grades in the younger group (3.4% versus 6.6%), yet these differences were not statistically significant. Detailed classification of clinical breast cancer staging is presented in table 3.

Immunohistochemical staining for ER, PR and HER2 contents of the primary breast cancers revealed four main receptor-defined subtypes:

- **Luminal A:** HR Positive/HER2 Negative; ER/PR (+) and HER2 (-).
- **Luminal B (Triple Positive):** HR Positive/HER2 Positive; ER/PR (+) and HER2 (+)
- **HER2 Enriched (Non-Luminal):** HR Negative/HER2 Positive; ER/PR (-) and HER2 (+)
- **Triple Negative (Non-Luminal):** HR Negative/HER2 Negative; ER/PR (-) and HER2 (-).

In this study, younger patients <40 years exhibited lower rates of Luminal A phenotypes but statistically higher frequencies of Triple Positive (Luminal B), Triple Negative and HER2 Enriched subtypes than older patients (36.3%, 18.7%, 17.5% and 16.3% respectively versus 52.7%, 12.5%, 12.9% and 9.6% respectively). The differences were statistically significant at $p < 0.10$ (Table 4).

Discussion and Conclusion

Age at diagnosis has been considered an important factor in the management and prognosis of patients with breast cancer [19,20]. Globally, a significant rise in breast cancer has been recently observed among young premenopausal women. That is claimed to be related to changes in lifestyle attitudes, exposure to hormones, having no or fewer children and late age at first pregnancy [2,22]. Although breast cancer in women under 40 years of age accounts for a small proportion of the total incidence, yet it has a great impact on the society due to its related mortality, outcome on fertility and psychosocial consequences; specifically in low and middle income countries. In the present work, 12.8% of breast cancers affected females under 40. That seems significantly higher than the 4-7% range reported in the literature [7-9].

In general, age standardized incidence rates and cumulative risks of breast cancer in women under 40 years vary between different populations emphasizing the heterogeneity and the complex nature of this type of cancer [5]. While the median age at diagnosis of breast cancer in American women is 62 years [31], the median age at diagnosis among Iraqi patients in this study was 50 years. In 2020 the Global Cancer Observatory of the International Union against Cancer registered an age standardized incidence rate for breast cancer in Iraq equivalent to 144 and an age standardized mortality rate approaching 81 [32]. The recorded statistics from WHO [1,32,33] as well as studies from the Arab region [16-18] and Iraq [10-15] have highlighted the young age at presentation of breast cancer in patients from developing countries; attributing that to the younger age structure of the populations and associated social and economic factors. Nevertheless, in a recent population-based survey on the global burden and trends of breast cancer it has been displayed that the incidence in young premenopausal women started to increase steadily in high income societies; especially following the implementation of the screening programs [1,2].

In this study the demographic and clinical profiles of patients diagnosed with breast cancer, before reaching the age of 40 years, is represented by females aged 24 - 39 years with a mean age of 34.9. The majority [88%] was married, 18.4% were University graduates, almost one third [30.4%] delivered their first child before the age of 20 while 21.7% had more than four children, approximately two thirds [64%] recorded negative family history of cancer, and clinically 44.8% presented in stages III and IV. Comparing these

findings with those observed among older patients [aged 40 years and over], the younger group registered statistically lower rates of illiteracy, less number of children and earlier ages at first delivery. Close figures were demonstrated in previous studies from Iraq [10,11].

Young patients in this study recorded a relatively higher frequency of positive family history of breast cancer than the older category [23.3% versus 18%]; though not reaching a significant level. In an earlier descriptive study that focused on 204 Iraqi patients who had breast cancer and family history of the same disease, the first degree relatives were involved in 43.7%, yet no significant differences were observed in the demographic and clinical profiles among the different age groups [34]. Randomized trials indicated that family history has an independent effect on the risk of invasive breast carcinoma [35,36] and that it could act as a non-modifiable risk factor in premenopausal women when there are genetic mutations [37]. The data of the present study did not register any significant association between bilateral breast cancers and age; contrary to other studies which pointed out that early age at first diagnosis could be a predictor of contralateral breast cancer specifically among those who are BRCA1 carriers and have strong family history [38,39].

Pathologically, there was no significant difference in the rates of histological types and grades of breast cancer when correlating the findings among younger versus older patients apart from a higher propensity to ductal carcinomas and a lower preponderance of well differentiated tumors in the <40 group. That was consistent with previous studies [40-42], whereas other reports indicated that breast carcinoma tends to be remarkably less differentiated in younger women [5,19-21]. An earlier survey displayed significantly higher rates of aneuploidy mammary carcinomas among patients from Iraq when compared to the Swedish counterparts suggesting a more aggressive tumor potential [43]. Clinically, relatively higher rates of advanced stages were encountered in this study among patients < 40. It has been found that young patients are more likely to present with larger tumors and nodal involvement owing to the lower index of suspicion and denser breast tissues that yield delayed and false negative diagnoses [22,24-27,39]. In fact, many studies have affirmed the tendency of breast cancer to be detected at late stages in Iraq and developing countries; emphasizing the necessity to raise the level of awareness among the

society to the significance of early detection of the disease [10-16,26,42,44]. A comparative study on the behavior of breast cancer among Iraqi and British women revealed that our patients presented at significantly younger ages and advanced stages, yet there was no statistical correlation between age and stage at diagnosis among the Iraqi cohort [12].

Numerous studies in the literature reported that breast cancers detected in young women are more likely to exhibit potentially aggressive biological features represented by poorly differentiated grades, lower hormone receptor contents, HER2 overexpression and worse subtypes recommending intensive therapy and closer monitoring [3,5,19-22,45,46]. It is believed that the prognostic significance of young age differs according to the subtypes and that the worst recurrence-free survival is associated with the luminal phenotypes [41,47]. Among women with luminal breast cancer age seems to be an independent prognostic factor [48]. In the current study, the rates of Triple Positive, Triple Negative and HER2 breast cancer subtypes were significantly higher among patients aged <40. Comparable findings were recorded in other studies [40,48]. Previous research on Iraqi patients disclosed higher prevalence of aggressive breast cancer phenotypes compared to the western studies emphasizing that variations in the expressions of these molecular markers could be attributed to the differences in racial backgrounds, demographic characteristics or tumor cell heterogeneity [12,49,50]. Another recent study demonstrated that patients exhibiting the Triple Negative breast cancer expression were significantly younger in Iraq and presented with larger size tumors than those who had other subtypes [51].

Nevertheless, a preceding report enrolling a series of young Irish women diagnosed with breast cancer concluded that the disease could be less aggressive than anticipated, as they found no significant differences in its clinical behavior among the various studied age groups [40]. In general, it has been proclaimed that strategies in the management of breast cancer are not age specific [5,22,52-54]; apart from consideration to preserve fertility in younger patients [7,8].

In conclusion the propensity of breast cancer to affect young Iraqi females, with the preponderance of advanced stages at presentation and aggressive tumor subtypes, emphasize the urgent need to strengthen early detection of the most common cancer in

the community and to establish multidisciplinary strategic guidelines for its optimum management and control.

Conflict of Interest

The author declare that there is no conflict of interest that competes with any of the contents of the manuscript

Acknowledgement

The author would like to thank the health staff working at the Main Referral Center for Early Detection of Breast Tumors and the National Cancer Research Center in Baghdad.

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