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Young age Iraqi Women with Breast Cancer: an overview of the correlation among their clinical and pathological profile

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Globally, breast cancer is the most frequently diagnosed cancer in women. Young women with breast cancer represent a subset of breast cancer with its unique characteristics and outcome compared to older women. To assess Iraqi female breast cancer patients' clinical profile, and evaluate patients' molecular profile. An observational cross-sectional study conducted in the tertiary hospital, Baghdad Medical City, Baghdad oncology teaching hospital. 1349 women with breast cancer of whom 202 had age less or equal to 40 years involved. The prevalence of young with breast cancer (defined as ≤40 years) as 15%, (7.9%, 4.8%, 2.1% and 0.2% for 36 – 40, 31 – 35, 26 – 30 and 20 – 25 years respectively). There was high ER and PR positive status 74.4% and 74%, with 23.1% Her2 positive (+3) while 16.3% were equivocal (+2), and 10.2% as triple negative. Luminal A is the most molecular subtype 50%. There was a slight positive trend of increase ER and PR expression with an increase in age and there was a slight negative trend of increment of Her2 expression and triple negative with increase in age. Lower age associated with increased odds for having stage IV or metastatic disease. The highest age group was 36 – 40 years in the young women, with the highest expression for ER status and the lowest for triple-negative disease, around one-quarter of the patients express her 2 positive diseases, age appear to have the weak effect on hormonal and immune-histochemistry characters of the tumors.

INTRODUCTION

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. In the United States, breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer death in women. In addition, breast cancer is the leading cause of death in women ages 40 to 49 years. Breast cancer is treated with a multidisciplinary approach involving surgical oncology, radiation oncology, and medical oncology, which has been associated with a reduction in breast cancer mortality (1). Annually, it is estimated that approximately 226870 American women will be diagnosed with invasive breast cancer, and 39510 women die from the disease (2). Worldwide in 2008, there were 1,383,500 estimated new cases of breast cancer. Worldwide, breast cancer accounts for 23 percent of the total cancer cases, 14 percent of cancer deaths, and is the leading cause of cancer death in women (3,4).

MATERIALS AND METHODS

This observational cross-sectional study conducted in Baghdad oncology teaching hospital from December 2016 to April 2017 carried on 1349 women with breast cancer of whom 202 had age less or equal to 40 years and was further analyzed with their histopathology reports and immune-histochemical (IHC) results including ER, PR, and HER2/neu. The patients enrolled in this study were already diagnosed with breast cancer either on adjuvant chemotherapy, hormonal therapy or on regular follows up, all of them were females. The data of all the patients were obtained from the laboratory of the Baghdad Oncology Teaching Hospital and form cancer research department of the hospital which included the histo-pathological reports that confirm their diagnosis regarding breast subtypes, grading, and staging. Also, immune-histochemical (IHC) reports that confirm their hormonal status (ER, PR HER2). The patients in this study underwent surgical intervention either by biopsy or mastectomy with axillary clearance, and then the formalin-fixed paraffin-embedded tissue blocks were sent to the hospital laboratory for H&E and IHC. Inclusion criteria: Women with breast cancer, and Age equal of below 40 years, while exclusion criteria: Male with breast cancer and Age above 40 years.

Statistical analysis

All continuous data presented as the mean and standard deviation. T-test, chi-square test used. Binary logistic regression analysis used. Odd ratio (OR) and their 95% confidence intervals, also used. Linear regression analysis performed to assess the relationship between

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different variables if one or both of them follow normal distribution person regression used but if both did not follow normal distribution spearman correlation will be used. Scatter plot used with r (correlation coefficient), r<0.25 weak, 0.25 – 0.5 mild, 0.5 – 0.75 moderate, >0.75 strong correlations. SPSS 20.0.0, Graph Pad Prism 7.0 software package used to make the statistical analysis, p-value considered when appropriate to be significant if less than 0.05.

Informed Consent

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this article.

Ethics Committee Approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS

We examined a sample of 1349 women diagnosed with young age breast cancer of whom 1147 (85%) had age above 40 years, 106 (7.9%) between 36 – 40 years, 65 (4.8%) between the age 31 – 35 years, 28 (2.1%) between the age of 26–30 years, and 3 (0.2%) between the age of 20 – 25 years as illustrated in figure 1.Patients with young women with breast cancer (age <40 years), had mean age of 35.11 ± 3.96 years ranging from 23 – 40 years, 1.5% of them between 20 – 25 years, 13.9% between 26 – 30 years, 32.2% between 32.2% and 52.5% between 36 – 40 years. Mean weight and height was 73.86 ± 12.90 kg and 160.0 ± 6.34 cm respectively, mean BMI was 28.91 ± 4.93 kg/m2 ranging from 18.4 - 39.6, with 0.8% underweight, 23.0% normal weight, 33.3% overweight, and 42.9% as obese. As illustrated in table 1.

ER and PR had similar distribution pattern (25.7% vs. 29.6% negative score), while HER2 had the higher rate of a negative score (45.9%), triple negative had the lower rate (10.2%) as illustrated in table 2.

The molecular subtype of early breast cancer had the following distribution with the majority had luminal A (50.3%), followed by luminal B (27.6%0), HER2 enriched (11.7%) and finally basal-like (10.3%) as illustrated in figure 2.It revealed that as age increase there is the slight tendency for more triple negative women, we used binary logistic regression to assess if a relationship between age and various markers, no significant relationship was found with ER, PR, HER2 and triple negative as in table 3.

Early age weakly increase the risk of stage IV, in which patients aged between 20–25 years had the highest risk (4 folds increase) followed by 26–30 years (2 folds increase). ER and PR positive status decrease risk of stage IV, but the only PR was strongly predicted a low risk of stage IV, in which those with negative PR had 4 folds higher risk of stage IV. Also Her2 positive increase risk of stage IV, in which Her2 negative had a 55.1% lower probability to have stage IV compared to strongly positive Her2 status. Her2 enriched had a higher risk of stage IV compared to basal-like, while luminal A had the lowest risk and luminal B had a similar risk of stage IV. As illustrated in table 1.

DISCUSSION

Age of the women with breast cancer considered an important prognostic factor, in this study we focused on women diagnosed with breast cancer at early age (<40 years) since many studies shown that such women had poorer prognosis when compared to older females. Of notice, a clear definition of a young female with breast cancer had not been clearly defined (which is important for assessing the indication of chemotherapy and the prognosis), many guidelines emphasis on prescribing combination chemotherapy instead of sequential mono-therapy for young women (5-8). In a study involved 5815 patients with age below 50 years that local recurrence in women aged <35 years compared to 35 – 40 years was (21.5% vs. 15.4% p <0.01) and distance metastasis rate (21.8% vs. 12.6% p<0.01), young age ≤40 had OR=2.05, ≤35 had OR=3.86, Her2 over expression had OR=6.58 and nodal involvement had OR=16.91; these were strong predictor for chemotherapy (9). In the current study the prevalence of women with breast cancer aged ≤40 years was 15%; worldwide the prevalence of young women breast cancer is highly variables, in USA is the prevalence is lower 6.4% with breast cancer age <40 years (10), while in UK the prevalence was 4% of women age below 40 years in their study that involved 86,852 women of their 2012 registry of breast cancer (11) the same outcome reported in Italy in which in single center of breast cancer they received 635 cases in 2013 they reported 41 (6.4%) of them to be breast cancer in young patients (BCYP; ≤40 years) (12). However in Albania in a retrospective study from 2011 – 2014 they studied 1158 cases with 11.4% presented with BCYP which is similar to our finding in the current study (13), in Algeria BCYP was found to be 12% which is also similar to our findings (14). In more recent studies; first in Switzerland they reported 23.4% of the cases as BCYP, also in their longitudinal study they found the age-standardized incidence trends between 1996 – 2009 for age group 20 – 39 years (which is BCYP) is increasing from 57.4 to 68.3 cases per 100,000 patients year from 1996 to 2009 and when compared it to the age group 40 – 49 years they found an estimated annual percentage changes to be more significant in BCYP (1.8%, 95%CI 0.6 – 2.9) this indicates that there is a clear increase in population of BCYP however in the current we could not assess this trend due to the cross-sectional nature of our study (15), in Morocco they found 24.9% of the patients to be BCYP which is higher than our findings (16). In France of 5815 patients 24.3% was BCYP which is also higher than our findings (17). These variations in the prevalence of BCYP an important topic because of the increase incidence, also since these women at such young age are in reproductive age so their management demands an integrated multidisciplinary approach, (e.g. oocyte preservation, psychological support), one theory is that the prevalence of breast cancer in young women depend on race, another one is the prevalence depend on who good the screening program in the country since in more develop countries where the overall detection rate of breast cancer in high leading to lower contribution of young age.

In the current study mean age of females was 35.11 ± 3.96 years ranging from 23 – 40 years, 1.5% of them between 20 – 25 years, 13.9% between 26 – 30 years, 32.2% between 32.2% and 52.5% between 36 – 40 years, which is in agreement with (11) with mean age of BCYP of 37 ± 2.8 years, also in agreement with (17) in which 64.2% had age between 35 – 40 years and the ≤35 years with 35.8%. In the current study there was an overall increase in the prevalence of breast cancer 0.2%, 2.1%, 4.8%, 7.9% and 85% (in age groups: 20 – 25, 26 – 30, 31 – 35, 36 – 40 and above 40 years), in this regard our finding was lower than that of (18) in which they reported average crude incidence rate between 2011 to 2008 of 10%, 38.6% and 51.4% in age groups <30, 30 – 44 and ≥45 years. Our finding was similar to previous Iraqi study in 2016 which involved smaller sample (100 patients) with 2%, 10% and 88% (aged: 20 – 29, 30 – 39 and ≥40 years respectively) (19), in another study in Iraq in another proven (Kirkuk) 170 female patients with breast cancer presented as 4.1%, 27.7%, 68.2% with age 20 – 30, 31 – 40 and

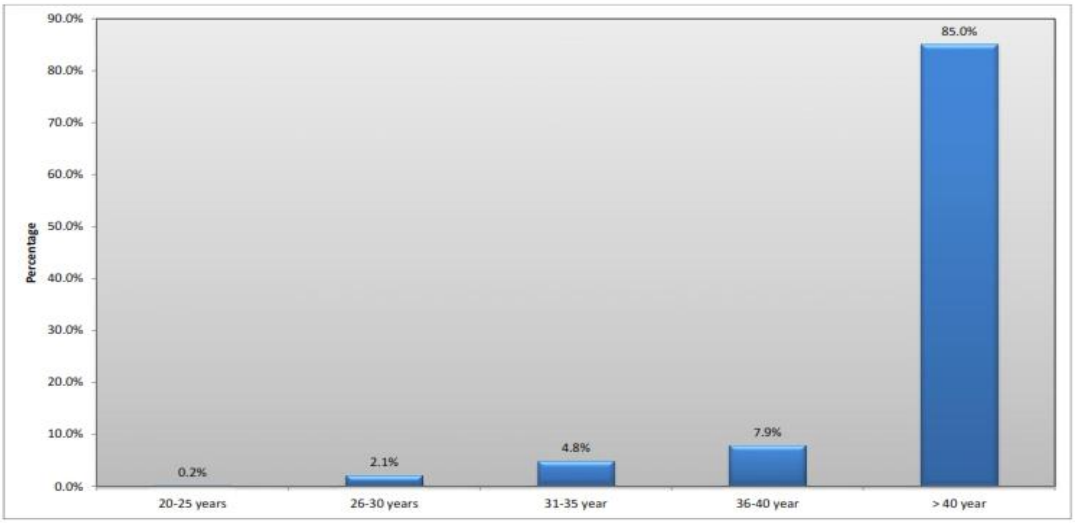

Figure 1 Classification of Iraqi female patients with breast cancer across to their age groups

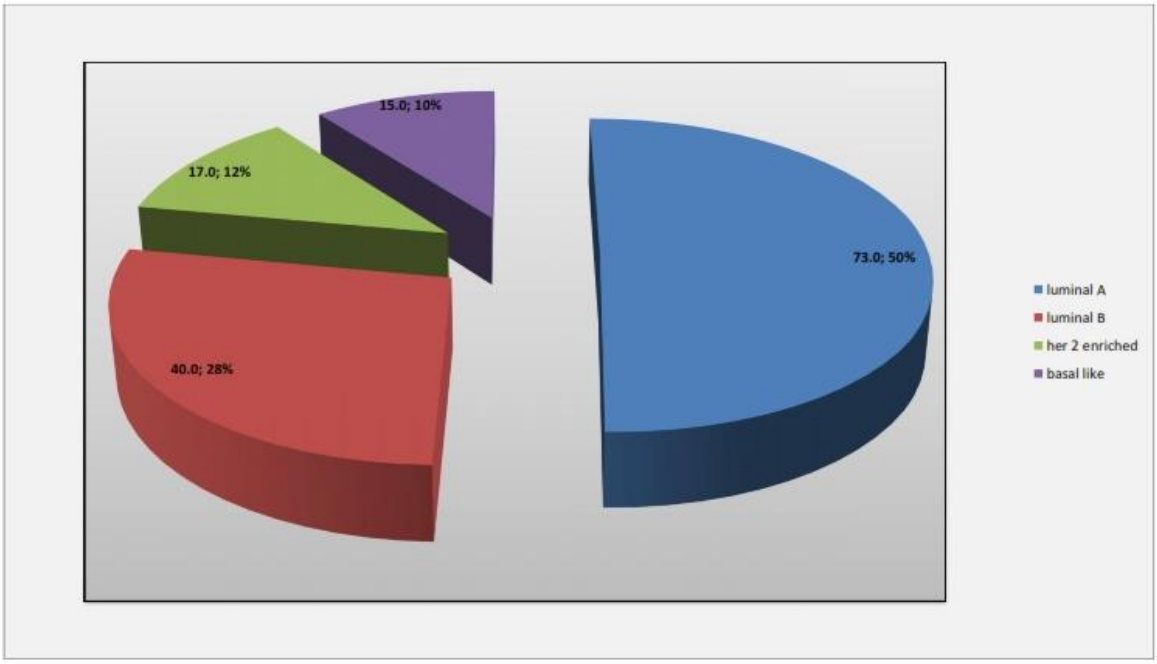

Figure 2 Molecular subtypes of women with young women with breast cancer

Table 1 Demographic data of breast cancer in young women

Variables	Value
Age, (years)*; mean ± SD (Range)*	35.11 ± 3.96 (23 - 40)
Weight, (Kg)*; mean ± SD (Range)*	73.86 ± 12.90 (48 - 105)
Height, (cm)*; mean ± SD (Range)*	160.00 ± 6.34 (145 - 175)
BMI, Kg/m^2*; mean ± SD (Range)*	28.91 ± 4.93 (18.4 - 39.6)
BSA*; mean ± SD (Range)*	1.77 ± 0.15 (1.4 - 2.13)

BMI: body mass index, BSA: body surface area, SD: standard deviation

Table 2 Hormonal and molecular status in breast cancer in young women

Molecular status		Number (%)
ER status	Negative	38 (25.7%)
	Positive	110 (74.3%)
PR status	Negative	42 (29.6%)
	Positive	100 (70.4%)
HER2 status	Negative	68 (45.9%)
	+1	22(24.3%)
	+2	24(16.3%)

	Positive (+3)	34 (23.1%)
Triple negative status	no	132 (89.8%)
	yes	15 (10.2%)

ER: Estrogen receptors; PR: Progesterone receptors; HER 2neo: Receptor tyrosine-protein kinase erbB-2

Table 3 Binary logistic regression analysis of the association between age and various pathological and molecular predictors

	Negative	Positive	OR (95%CI)	P value
ER	34.79 ± 3.96	34.83 ± 4.26	1.002 (0.917-1.095)	0.961
PR	34.40 ± 4.10	34.89 ± 4.31	1.027 (0.944-1.118)	0.533
HER2	35.28 ± 4.02	34.61 ± 4.22	0.961 (0.887-1.041)	0.325
Triple negative	34.89 ± 4.19	34.07 ± 4.08	0.956 (0.844-1.081)	0.471

OR: odds ratio, CI: confidence interval, ER: Estrogen receptors; PR: Progesterone receptors; HER 2neo: Receptor tyrosine-protein kinase erbB-2

Table 4 A predictor of stage IV and metastasis

Variables	OR (95%CI)	P value
Age (by 1 year)	0.933 (0.851 – 1.023)	0.140
20 – 25 years	4.077 (0.239 – 69.599)	0.332
26 – 30 years	2.038 (0.684 – 6.071)	0.201
31 – 35 years	1.631 (0.685 – 3.882)	0.269
36 – 40 years	1.0	0.450
BMI (by 1 unite)	0.949 (0.852 – 1.056)	0.335
ER positive	0.825 (0.321 – 2.122)	0.690
PR positive	**0.344 (0.141 – 0.838)**	**0.019**
Negative	**4.062 (1.146 - 14.402)**	**0.030**
Weak positive	1.339 (0.339 - 5.299)	0.677
Moderate positive	2.083 (0.512 - 8.472)	0.305
Strongly positive	1.0	0.097
Her2 positive	1.071 (0.453 - 2.535)	0.875
Negative	0.449 (0.158 - 1.279)	0.134
Weak positive	0.563 (0.145 - 2.190)	0.407
Moderate positive	0.960 (0.256 - 3.598)	0.951
Strongly positive	1.0	0.418
Triple negative	1.107 (0.278 - 4.403)	0.886
Molecular subtype		
Luminal A	0.635 (0.147 - 2.732)	0.541
Luminal B	1.043 (0.225 - 4.840)	0.957
Her2 enriched	2.143 (0.376 - 12.197)	0.390
Basal-like	1.0	0.328
Tumor size	**1.880 (0.942 - 3.752)**	**0.073**
Lymph node	1.443 (0.923 - 2.256)	0.108
No. of Lymph node involved	**1.068 (1.001 - 1.140)**	**0.047**

OR: odds ratio, CI: confidence interval, ER: Estrogen receptors; PR: Progesterone receptors; HER 2neo: Receptor tyrosine-protein kinase erbB-2, BMI: body mass index, BSA: body surface area, SD: standard deviation

≥40 years respectively which is similar to our findings (20), and similar to another Iraqi study involved 150 patients with 12% between the age 30 – 39 years (21).

The results of the current study showed that 74.3% and 70.4% had positive immune-histochemical ER and PR status in breast cancer tissues, respectively. Our result was in agreement with Slaoui *et al*(15) findings with 73.4% and 79.9% had positive ER and PR status in all the patients, while in their breast cancer patients with metastasis 75%, and 95% had positive ER and PR status (had higher PR status compare to our findings: 72.4% vs. 55.2% ER and PR positive status in metastatic breast cancer patients), also in agreement with Conlon et al (21) with ER-positive status in 68%.

Out findings regarding ER and PR status was similar to Ikonomi *et al*(12) with 80% with positive ER and/or PR status in BCYP, and higher to Villarreal-Garza *et al*(22) with 56% and 52.5% ER and PR positive status, also higher than Farouk *et al*(23) with 49% and 51.7% ER and PR positive status in BCYP. These variations in ER and PR because of indifference in inclusion criteria in which both were considered as major criteria for entering the study.

The results of the current study show that 23.1% had positive Her2 status and 10.7% had triple-negative immune-histochemistry; Slaoui *et al*(15) had a similar rate of Her2 positive compared to the current study 24.8% and similar rate of triple negative 15.8%; also they found that in young women (multivariate analysis) negative Her2 and PR associated with poor EFS (event-free survival while in older women both Her2 and PR did not associate with significant effect on EFS, in study in very young Chinese females (<25 years) they found that ER and PR statuses are significant predictors of overall survival (OS) and disease-free survival (DFS) in univariate analysis and only ER status to be predictor for OS and DFS in multivariate analysis (25); while Her2 did not influence OS and DFS. Our findings were not similar to Ikonomi *et al*(12) with 48% Her2 positive and 14% triple negative status (of notice they reported no significant difference in hormonal status against women aged >40 years).

Sabiani *et al*(16) show in his study that Her2 expression and triple negative decreased with advance in age in which 22.1%, 16.3%, 10.6% and 10.2% had positive Her2 status and 22.2%, 19.1%, 14.3% and 10.4% had triple-negative corresponding to ≤35, 36 – 40, 41 – 45 and 46 – 50 years respectively, they found that Her2 positive status predict poor DFS in patients aged ≤35 against 36 – 50 years (8), this higher rate of Her2 positive status in BCYW was also reported in another study in which 24.3% had Her2 in women aged <40 years and women ≥40 years it was 14.8% and for triple negative the rate also increased from 21.6% to 13% (22). We hypothesized that these variations in hormonal

immune-histochemistry profile can partially explain the reduction in OS, DFR, and EFS in young women with breast cancer, but since this study is cross-sectional we could not examine their effect on survival. An important consideration is the link between genetic and BCYP, despite that we did not study the genetic profile in the current study but previous studies show that link we genetic mutations like BRCA 1 and 2 or even TP53 implication in BCYP, indeed a familiar cause of BCYP should be considered, in a case control study the rate of BRCA1/2 was 9.4% in women aged <35 years, compared to 0.2% in the population (26), high grade of triple negative associated with BRCA 1 mutations (27), in a French study they found the rate of BRCA1 mutations with BCYP aged <35 years 28.6% association with triple negative and poorly differentiated tumors which is regardless of family history of breast cancer (27), in the previous study the authors derived equation to predict the probability BRCA1 carrier mutation depending on ER status, tumor grade and found that women with age between 30 – 34 years, ER negative, and grade III tumor had 26.5% for carrying BRCA1 mutation, while for <30 years it was higher reaching 35%, the probability decline afterward to 6.6%, 3.7%, 2.5% and 0.9% corresponding to age groups 35 – 39, 40 – 44, 45 – 49 and 50 – 59 years respectively (27).

The rate of metastasis in the current study was 17.2%, in the literature metastasis follow two pattern either similar to our findings or lower than them, Slaoui *et al*(15) reported similar findings with 13.8% in BCYP vs. 19.7% in >40 years women, Sabiani *et al*(16) reported 21.8% metastasis rate <35 years and 12.6% between 36 – 40 years, and decline the rate of metastasis afterward with advance in age; these two study show similarity with ours. 4.7% had metastasis in the Egyptian study (24) and 5.4% in USA study (22), while no explanation can be found for these variations in the literature; the difference in the genetic component in the patients included can lead to these variations.

CONCLUSION

In the current study negative PR status had 4 folds increase in the risk of stage IV and metastatic disease [OR= 4.062 (1.146 - 14.402)], also high tumor size, high number of lymph node involved, very young age (20 – 25 years 4 folds, 26 – 30 years 2 folds, 31 – 35 years 1.5 folds compared to 36 – 40 years).

About 15% of the total sample presented with breast cancer of young women, in young women with breast cancer; the age between 36 – 40 represent the highest frequency with breast cancer 52.5% while the lowest in the age group 20 – 25 yours with 1.5%, they were mostly obese 42.9% or overweight 33.3%, high ER and PR positive status 74.4% and 7.4%, with 23.1% Her2 positive, and 10.2% as triple negative, Luminal A is the most molecular subtype 50%, and there was a slight positive trend of increase ER and PR expression with an increase in age, there was a slight negative trend of increment of Her2 expression and triple negative with increase in age. The lower the age the higher odds of having stage IV disease or metastasis

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Breast cancer, Molecular classification, Estrogen receptors, Progesterone receptors, Receptor tyrosine-protein kinase erbB-2, Triple negative

Abbreviations
ER: Estrogen receptors; PR: Progesterone receptors; HER 2neo: Receptor tyrosine-protein kinase erbB-2;IHC:immunohistochemistry; BCYP: breast cancer in young patients

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