

The Correlation of Age with Various Prognostic Factors in Breast Cancer in Iraqi Patients

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ABSTRACT

Background: The prognosis of breast cancer depends on several factors, lymph node status is the most important single prognostic factor, other factors include tumor stage, grade, lymphatic and vascular invasion and ER, PR and HER2/neu status. Age of the patient also had an effect the presentation and prognosis of the disease.

Objectives: To evaluate the effects of age on the presentation of breast cancer patients and to compare various age groups according to various prognostic factors, which include tumor grade, stage, lymph node status, histopathology type and hormonal receptors (estrogen and progesterone receptors) with HER2/neu receptor.

Methods: A retrospective study of 688 consecutive cases (687 females and one male), all of them were preoperatively diagnosed with breast cancer and treated with modified radical mastectomy and axillary dissection retrieved from Baghdad Teaching Hospital in Medical City Complex and Al-Rahibat private hospital, Baghdad, Iraq from January 2004 to December 2013. The patients were divided into three age groups: young age (<40 years), middle age (40-60 years) and old age (>60 years). The data were analyzed according to standardized tumor characteristics, which include grade following the recommendations of Scarff, Bloom and Richardson, stage (according to the American Joint Committee on Cancer (AJCC), lymph node status, histopathology type and hormonal receptors (estrogen and progesterone) and HER2/neu receptor status. The data then had been analyzed using SPSS program for statistical analysis and the results were presented in tables and figures.

Results: Middle age women (40-60 years) were most commonly affected (n=405, 58.9%). The most common grade of tumor was grade II among all age groups. Young patients (<40 years) with breast cancer were more likely to be of higher stage (54.3% with stage III) and of higher lymph node status, N2 (26.1%) and N3 (28.3%). The invasive ductal carcinoma (IDC) was the most common type in all age groups. ER was positive in 545(79.2%) and negative in 143 (20.8%) patients. PR was positive in 532 out of 688 (77.3%) and negative in 156 (22.7%) cases and most negative ER and PR was found in the young age group. HER 2/neu was available only in 424 cases and it was positive in 119 (28.1%) and negative in 305 (71.9%) cases. By analyses there was significant statistical difference in the ER and PR among age groups as old age patients were more likely to be ER (p value 0.030) and PR (p value 0.008) positive. On the other hand, there was no significant association between age and (grade, histopathology and HER2/neu receptor).

Conclusion: Middle age women were at increased risk of developing carcinoma of breast and the most common type was invasive ductal carcinoma in all age groups of grade II. Young patients (<40 years) mostly they presented with advanced stages and higher node status with most negative ER and PR were found in young age patients (<40 years) indicating more aggressive disease in this age group.

Keywords: Breast cancer, Age, Tumor stage, Estrogen receptor, Progesterone receptor, Prognosis.

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Breast cancer is the second leading cause of cancer-related deaths, second to lung cancer, with approximately 40,000 deaths caused by breast cancer annually⁽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 latest Iraqi Cancer Registry⁽²⁾. This shows that the breast is the leading cancer site among the

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Iraqi population in general, surpassing even lung cancer⁽²⁾.

Estrogen and progesterone receptors (ER and PR) are proteins in or on certain cells that can attach to certain substances, such as hormones, that circulate in the blood. All invasive breast cancers should be tested for both of these hormone receptors either on the biopsy sample or when they are removed with surgery⁽³⁾. Patients whose tumors are ER positive and PR negative have a 30 to 40% chance of responding to hormonal treatment compared with those whose tumors are ER negative and PR positive. Those whose tumors are both ER and PR positive have about a 70% chance of responding to endocrine therapy of any type, while those with both ER- and PR-negative tumors have less than a 5% chance of endocrine response⁽⁴⁾.

Gene amplification, which usually results in over expression of the encoded transmembrane protein p185, occurs in one third of breast cancers. The two most common assay systems use fluorescence *in situ* hybridization (FISH) and immunohistochemistry. Amplification and over expression of Her-2/ neu (C-erbB-2) gene and protein has been seen in 10-34% of invasive breast cancers, it is associated with adverse prognosis in both node negative and node positive disease. Its chief application lies in its prediction of response to therapy with trastuzumab (Herceptin) and pertuzumab. The interpretation of the immunohistochemistry staining is done as follows: More than 10% of cells show weak staining of the cell membrane 1+. More than 10% of cells show moderate staining of the cell membrane 2+. More than 10% of cells show a continuous strong staining of the cell membrane 3+. It is recommended that all 2+ results need to be confirmed by the FISH technique⁽⁵⁾.

A number of tumor and host characteristics have been found useful in predicting the risk of recurrence and the chance of death from breast cancer following primary surgery. Traditional prognostic factors, i.e., those that predict the risk of recurrence or death from breast

cancer, include: Number of positive axillary nodes.(as most important single prognostic factor), tumor size, tumor grade (histologic or nuclear), lymphatic and vascular invasion, the ER and PR positivity. By contrast, the only well-established predictive factors, i.e., those that predict the chance of responding to therapy with a specific treatment, are ER and PR⁽⁶⁾.

Using the HER-2/*neu* oncogene as a prognostic factor for response to trastuzumab demonstrates that about 35% of women with HER-2-expressing tumors will respond to single-agent trastuzumab⁽⁷⁾. HER-2/*neu* overexpression has also been suggested to predict for differential response to aromatase inhibitors over tamoxifen⁽⁸⁾, and for differential response of anthracyclines vs non-anthracycline-containing regimens.

The aims of this study are to study the effects of the age on the prognosis of breast cancer and the characteristics of different age groups of breast cancer patients.

Methods

A retrospective study of 688 consecutive patients with invasive breast cancer were treated with modified radical mastectomy and axillary dissection (no breast conservation surgery) retrieved from Baghdad Teaching Hospital, Medical City Complex and Al-Rahibat private hospital in Baghdad of Iraq from January 2004 to December 2013.

Inclusion criteria: Patients who were diagnosed with breast cancer during this period by our surgical team were included in this study.

Exclusion criteria: Patients with recurrent breast cancer, those with medical comorbidities that made them unfit for general anesthesia and patients with lack of required data for the study.

The 688 cases were divided into three age groups: Group 1; <40 years old (young age), group 2; 40-60 years old (middle age), group 3; >60 years old (old age).

These groups were analyzed according to six tumor characteristics which include: Tumor grade (I,II,III and in situ), Tumor Stage (according to the American Joint Committee on cancer (AJCC), Lymph nodes status, Histopathological type, Hormonal receptors: ER and PR and Immunohistochemistry (human epidermal growth factor receptor 2) (HER-2/neu). These variables were compared to the age groups. HER-2/neu was included into the study from 2010 and on as it became available in our country, it was performed on 424 out of 688 cases.

Data of all cases were checked for any error or inconsistency then transferred into a computerized database program; Microsoft excel software was used. All variables were coded with a specific code for each variable and prepared for statistical analysis. SPSS (statistical package for social sciences) software for windows version 20, was used in statistical analysis. Descriptive statistics were presented as frequency (number of cases) with proportions (percentages), and as mean ± standard deviation. Chi square test and Fisher's Exact Test were used to compare frequencies and proportions. In all statistical tests and procedures, level of significance P value was set at ≤ 0.05 considered as significant difference or association. Finally, results were presented in tables and figures.

Results

The number of patients who were included in this study was 688. The female number was 687 (99.85%) and only one male (0.15%). They were divided into three age groups, namely; women under 40 years (referred to as 'young') (n=92, 13.4%), women from 40-60 years (n=405, 58.9%) as most common age group (middle age) and women > 60 years (referred as 'old' women) (n=191, 27.8%). and the mean age was (52.33+SD 11.86), with minimum age was 17 and the maximum was 85 years.

The most common grade of tumor was grade II (72.8%) among all age groups and as follows: Those who were young presented with grade I in only 7 (7.6%) cases out of 92, grade II was in 60 (65.2%) cases and 24 (26.1%) cases presented with grade III tumor and only one (1.1%) case was carcinoma in situ.

For the most common age group (middle age) grade I was present in 50 (12.3%) out of 405 patients, 270 (66.7%) with grade II, in 78 patients (19.3%) the result was grade III and in 7 cases (1.7%). The rest was carcinoma in situ.

In the old age group the grades was I in 18 patients (9.4%), II in 139 patients (72.8%) and III in 32 out of 191 cases (16.8%) while two cases were in situ (1%), (Table 1).

Table 1: Description of the grade of breast carcinoma cases according to the age groups.

		grade				Total
		I	II	III	In situ	
age <40	Count	7	60	24	1	92
	% within age	7.6%	65.2%	26.1%	1.1%	100.0%
40-60	Count	50	270	78	7	405
	% within age	12.3%	66.7%	19.3%	1.7%	100.0%
>60	Count	18	139	32	2	191
	% within age	9.4%	72.8%	16.8%	1.0%	100.0%
Total	Count	75	469	134	10	688
	% within age	10.9%	68.2%	19.5%	1.5%	100.0%

P =0.398 Pearson Chi-Square = 6.232 (df= 6)

In the young age group, one case (out of 92) came with stage 0 (1.1%), 20 with stage I (21.7%), 20 cases were staged as II (21.7%), 50 cases (54.3%) with stage III, and in only one case (1.1%) the stage was IV. In the middle age group, the 405 cases were divided between stages as follows: 7 in stage 0 (1.7%), 58 in stage I (14.3%), 172 cases with stage II (42.5%), 167 (41.2%) with stage III and only one case (2%) was with stage IV. The stage distribution in the old age group (159 cases) was as follows: 2 in stage 0 (1%), 23 cases (12%) in stage I, 92 (48.2%) were staged as II, 69 cases (36.1%) were staged as III, and 5 cases (2.6%) were stage IV disease, (Table 2).

In the young age group, 20 patients were N0 (21.7%), 22 were N1 (23.9%), 24 were N2 (26.1%) and 26 cases were N3 (28.3%). In the middle age group, the patients were distributed as 122 cases were N0 (30.1%), 148 cases were N1 (36.5%), 76 cases were N2 (18.8%) and in 59 cases with N3 (14.6%). In the old age group, 80 cases were N0 (41.9%), 47 were N1 (24.6%), 34

patients were N2 (17.8%) and 30 patients were N3 (15.7%), (Table 3).

In the 1st age group (young), the invasive ductal carcinoma (IDC) was the most common type and present in 84 (91.3%) out of 92 cases, 5 cases were lobular carcinoma (LC) (5.4%), one case (1.1%) came with mixed invasive ductal and lobular carcinoma, one(1.1%) was ductal carcinoma in situ and one case (1.1%) was Paget's disease. For the 2nd age group (middle age), IDC also was the commonest type 342 (84.5%) out of 405, 33 were LC (8.1%), 16 cases were mixed IDC and LC (4%), 7 (1.7%) were ductal carcinoma in situ, 5 cases (1.2%) were Paget's disease, one case was medullary carcinoma (MC) (subtype of IDC) (0.2%) and one case was invasive cribriform (Inv. crib) subtype (0.2%). The 3rd age group (old age) was distributed as: 164 (85.9%) out of 191 were IDC, 19 were LC (9.9%), 5 were mixed IDC and LC (2.6%), two were ductal carcinoma in situ (1%) and onecase (0.5%) was Paget's disease, (Table 4).

Table 2: Distribution of the stages of breast carcinoma cases according to the age groups.

		stage					Total
		0	I	II	III	IV	
age <40	Count	1	20	20	50	1	92
	% within age	1.1%	21.7%	21.7%	54.3%	1.1%	100.0%
40-60	Count	7	58	172	167	1	405
	% within age	1.7%	14.3%	42.5%	41.2%	.2%	100.0%
>60	Count	2	23	92	69	5	191
	% within age	1.0%	12.0%	48.2%	36.1%	2.6%	100.0%
Total	Count	10	101	284	286	7	688
	% within age	1.5%	14.7%	41.3%	41.6%	1.0%	100.0%

Pearson Chi-Square =27.583 (df= 8) P <0.001

Table 3: Distribution of the lymph node status of breast carcinoma cases according to the age groups.

			N status				Total
			N0	N1	N2	N3	
age <40	Count		20	22	24	26	92
	% within age		21.7%	23.9%	26.1%	28.3%	100.0%
40-60	Count		122	148	76	59	405
	% within age		30.1%	36.5%	18.8%	14.6%	100.0%
>60	Count		80	47	34	30	191
	% within age		41.9%	24.6%	17.8%	15.7%	100.0%
Total	Count		222	217	134	115	688
	% within age		32.3%	31.5%	19.5%	16.7%	100.0%

Pearson Chi-Square = 28.049 (df = 6) P= 0.001

Table 4: Distribution of the histopathological types of breast carcinoma cases according to the age groups.

			Histopathology							Total	
			IDC	IDC-MC	DCIS	Inv. crib. C	LC	MIXED IDC+LC	Paget		Phyllodes
age <40	Count		84	0	1	0	5	1	1	0	92
	% within age		91.3%	.0%	1.1%	.0%	5.4%	1.1%	1.1%	.0%	100.0%
40-60	Count		340	1	7	1	33	16	5	2	405
	% within age		84.0%	0.2%	1.7%	0.2%	8.1%	4.0%	1.2%	.5%0	100.0%
>60	Count		164	0	2	0	19	5	1	0	191
	% within age		85.9%	.0%	1.0%	.0%	9.9%	2.6%	0.5%	.0%	100.0%
Total	Count		588	1	10	1	57	22	7	2	688
	% within age		85.5%	0.1%	1.5%	0.1%	8.3%	3.2%	1.0%	0.3%	100.0%

Pearson Chi-Square = 8.186 (df = 14) P=0.879

In comparison of ER characteristics between the study age groups in current study found that 545 (79.2%) patients were positive ER and 143 (20.8%) were negative ER. In the young age group of patients, ER was positive in 66 (71.7%) out of 92 cases and negative in the remaining 26 (28.3%) cases. In the middle age group, ER was positive in 317 out of 405 cases (78.3%)

and negative in 88 cases (21.7%). In the old age group, the ER was positive in 162 out of 191 cases (84.8%) and negative in 29 cases (15.2%), (Figure 5).

Out of 688 cases, 532 were found to be PR positive (77.3%) and 156 cases (22.7%) were PR negative.

In the young age group of patients, PR was positive in 61 out of 92 patients (66.3%)

and negative in the remaining 31 patients (33.7%). In the middle age group, PR was positive in 313 out of 405 cases (77.3%), negative in 89 cases (22.7%). In the old age group, the PR was positive in 158 out of 191 cases (82.7%) and negative in 27 cases (17.3%), (Figure 6).

HER 2/neu was available in 424 cases out of 688, it was positive in 119 case

(28.1%), negative in 355 (71.9%). In the young age group of patients, HER2/neu was positive in 21 out of 52 cases (40.4%), negative in 31 cases (59.6%). In the middle age group, HER2/neu was positive in 68 out of 246 cases (27.6%), negative in 178 patients (72.4%). In the old age group, the HER2/neu was positive in 30 (23.8%) out of 126 cases, negative in 96 patients (76.2%), (Figure 7).

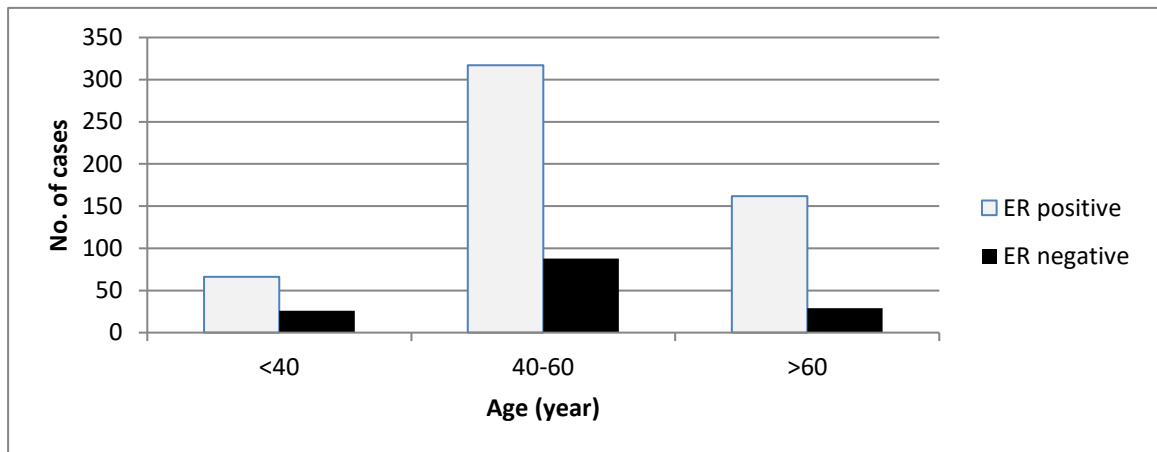


Figure 5: Distribution of the ER status of breast carcinoma cases according to the age groups.

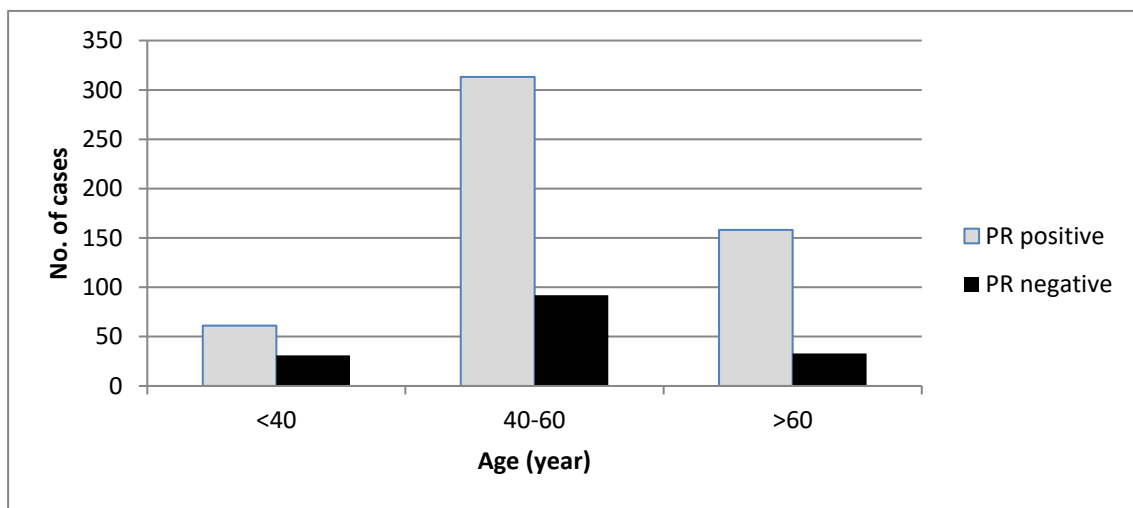


Figure 6: Distribution of the PR status of breast carcinoma cases according to the age groups.

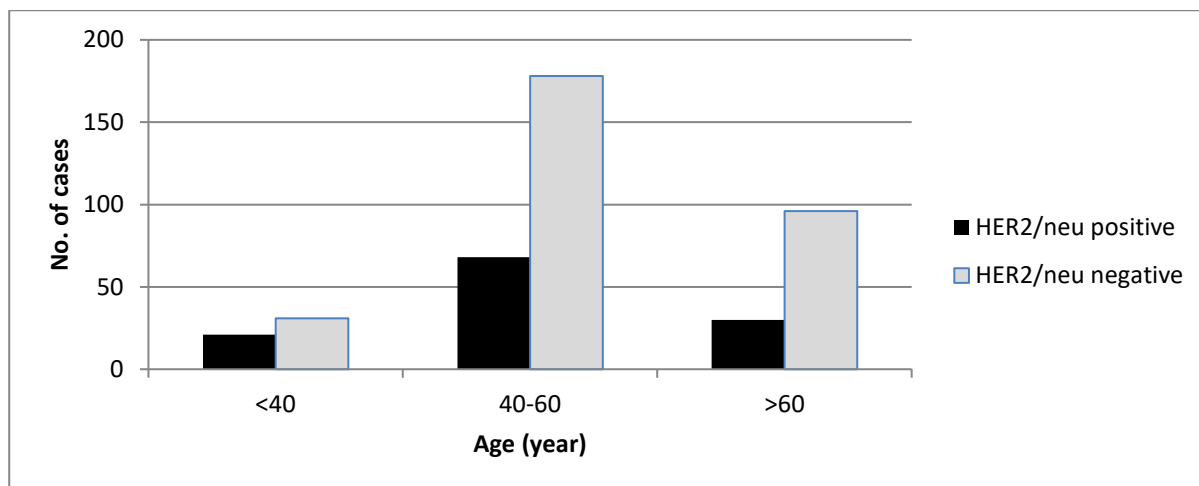


Figure 7: Distribution of the HER2/neu status of breast carcinoma cases according to the age groups.

Discussion

The risk of breast cancer increases with the age, in our study we found that 13.4% of patients were young (< 40 years) while in a similar study by Ali Pourzand et al (on 105 patients with unilateral breast cancer from August 2008 until March 2010 in Iran) it was 17.1%⁽⁹⁾. Aysha S AlZaman et al (on 109 patients with breast cancer between 2010 through 2013 in Manama, Bahrain) found that 43% were young⁽¹⁰⁾ while Bland KI et al (on 240,031 breast carcinoma patients in 10 years study) in united states found that 5-7% are young⁽¹¹⁾ however this difference may be because of age distribution among population and many genetic and environmental factors may play a role in this difference.

The most common age group of patients in the current study was the middle age (40-60) years (58.9%) which is comparable to a similar study by Aysha S AlZaman et al (about 57%)⁽¹⁰⁾ while Bland KI et al found that the most common age group was the old (>60 years) (about 50%)⁽¹¹⁾. We assume that this difference may be related to the mean age of population and increasing percentage of patients who live longer. Regarding tumor grade our study showed that grade II is the most common grade for the cases (72.8%) and this is similar to other study in UK by Diab SG et al⁽¹²⁾.

The association between grade of the tumor and age was not statistically significant in our study (P 0.398) while Avis N et al found that there was a significant association between young age and high grade tumors indicating worse prognosis in this age group⁽¹³⁾ and this may be explained by difference in tumor characteristics between different populations⁽¹⁴⁾.

Young patients mostly present with higher tumor stages (P <0.001) than older women indicating more aggressive tumors in the young patients which is supported by other studies by Ali Pourzand et al⁽⁹⁾, Aysha S AlZaman et al⁽¹⁰⁾, Bland KI et al⁽¹¹⁾ while a similar study in Egypt by Osama Hussein et al shows only a modest relation (not significant) between young age and higher stage⁽¹⁵⁾. This difference may be explained by difference in sample size and duration of the study as both are less in this study as compared to the current study.

In the current study, we found that young patients had higher lymph node status (P = 0.001) than older women had and this affects the tumor stage of patients making them at a higher stage in comparison with other age groups and this is similar to other studies by Ali Pourzand et al⁽⁹⁾, Aysha S AlZaman et al⁽¹⁰⁾ and Diab SG et al⁽¹²⁾. A study was done in Australia by Colleoni M, Rotmensz N et al⁽¹⁶⁾ and another one by Anders C, Hsu D et al⁽¹⁷⁾ did not show any

significant association between age of the patients and lymph node status and this may be due to the level of lymph node dissection and the number of lymph nodes obtained with the specimen.

The most histopathological type in all age groups was invasive ductal carcinoma and we did not find any significant difference in the histopathological type regarding the age group. This finding is supported by Ali Pourzand et al⁽⁹⁾ and Aysha S. AlZaman et al⁽¹⁰⁾ but in Diab SG et al in UK⁽¹²⁾.

There was a significant difference between the groups of patients with infiltrative ductal cancers and more percentage was found in those <40 years. In the current study, the most common histopathology type was invasive ductal carcinoma in young age group but it was non-significant statistically in comparison with other age groups ($P = 0.879$) and this may be due to sample size difference and different tumor characteristics between Iraq and UK.

We found that there is significant association between age group and hormonal receptor status (ER and PR) ($P = 0.03$ for the ER and $P = 0.008$ for the PR) and most negative ER and PR was found in those <40 years and as age increases. There is increase in the percentage of positive receptors and decrease in the percentage of negative receptors and this is another indicator of tumor aggressiveness in young people as their response to hormonal therapy will be less. This finding was also found in Aysha S AlZaman et al⁽¹⁰⁾ and Bland KI et al⁽¹¹⁾ while in Ali Pourzand et al⁽⁹⁾ and de la Rochefordiere A et al⁽¹⁸⁾ there was a significant association with PR only and non significant association with ER in the young age group was found. Regarding the HER2/neu difference among age groups, in the duration from 2004 -2010 the receptor checking was not available in Iraq and it was available only in 424 cases. There was no statistical significance between age group and HER2/neu status ($P 0.08$) which is supported by Raquel Prati et al⁽¹⁹⁾ while Aysha S AlZaman et al⁽¹⁰⁾

showed that most positive HER2/neu was found in the young age group and Ali Pourzand et al⁽⁹⁾ found that most positive HER2/neu was found in the old age group.

In conclusion; Breast cancer in younger age groups is more aggressive than that in older age groups as young people are more likely to present with higher stages, higher lymph node status and more negative ER and PR in comparison with middle and old age groups.

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