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HORMONAL RECEPTOR STATUS IN FEMALE BREAST CANCER AND ITS RELATIONSHIP TO AGE AND TUMOR STAGES

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Abstract: Background: Breast cancer is the most common site specific cancer in women. Studies show that breast cancer in younger women is unique and needs a different treatment strategy from that might be used for older women with breast cancer .the prognosis and management of breast cancer is influenced by classic variables as the histological type, grade and stage, status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2/neu) status.

Objectives: To find the relationship between the age of female patients having invasive breast cancer with estrogen (ER), progesterone (PR) receptors status, HER-2/neu expression and stage of tumor.

Patients and methods: All mastectomies female patients due to invasive breast cancer presented to breast clinic and ward in AL-Hussein teaching hospital in Al-Samawa city from January 2020 to December 2022 were included in this study prospectively. Data collected including the type of cancer, stage of cancer , hormone receptors(ER, PR), HER-2/new expression, all analysis was done in AL- Hussein teaching hospital laboratory using the same methods, eliminating the problem of inter laboratory differences. Data was analyzed using SPSS 20 study, p value <0.05 regarded as significant.

Results: There is inverted significant relation between the hormone receptors status estrogen receptor (ER), progesterone receptor (PR) and the age of the patients (p- value 0.017 and 0.033 respectively).HER-2/neu overexpression were more in patients younger than 40 years old (p- value 0.0043). Patients younger than 40 years old are likely to have tumor with higher stages (p- value 0.035) compared with older female patients.

Conclusions: The younger women in our study had tumors that were distinctly different from older women. Younger women had tumors that were more likely to be of higher stage, ER negative, PR negative and positive HER-2/neu..

Key words: Breast cancer; estrogen receptor; progesterone receptor; HER-2/neu; age.

Introduction:

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20 to 59 years [1-2]. It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer-related deaths in women [2]. Breast cancer was the leading cause of cancer-related mortality in women until 1987, when it was surpassed by lung cancer [2]. Increased exposure to ER is associated with an increased risk for developing breast cancer, whereas reducing exposure is thought to be protective [3,4]. Correspondingly, factors that increase the number of menstrual cycles, such as early menarche, null parity, and late menopause, are associated with increased risk. Moderate levels of exercise and a longer lactation period, factors that decrease the total number of menstrual cycles, are protective [4]. The average lifetime risk of breast cancer for newborn U.S. females is 12 % [5]. The longer a woman lives without cancer, the lower her risk of developing breast cancer. Thus, a woman aged 50 years has an 11% lifetime risk of developing breast cancer, and a woman aged 70 years has a 7% lifetime risk of developing breast cancer. Because risk factors for breast cancer interact, evaluating the risk conferred by combinations of risk factors is difficult [5].

Several important medical decisions may be affected by a woman's underlying risk of developing breast cancer [6]. These decisions include when to use postmenopausal hormone replacement therapy, at what age to begin mammography screening, when to use tamoxifen to prevent breast cancer, and when to perform prophylactic mastectomy to prevent breast cancer[7].

Prognosis and management of breast cancer are influenced by the classic variables such as histologic type and grade, tumor size, lymph node status, status of hormonal receptors—estrogen receptor (ER) and progesterone receptor(PR)— of the tumor, and, more recently, HER-2 status[8].

HER-2/*neu* is a member of the epidermal growth factor receptor family of growth factor receptors in which ligand binding results in receptor homodimerization and tyrosine phosphorylation by tyrosine kinase domains within the receptor. Tyrosine phosphorylation is followed by signal transduction, which results in changes in cell behavior. When overexpressed in breast cancer, HER-2/*neu* promotes enhanced growth and proliferation, and increases invasive and metastatic capabilities. Clinical studies have shown that patients with HER2/*neu*–overexpressing breast cancer have poorly differentiated tumors with high proliferation rates, positive lymph nodes, decreased hormone receptor expression, and an increased risk of recurrence and death due to breast cancer [9-

10).

Routine testing of the primary tumor specimen for HER-2/*neu* expression should be performed on all invasive breast cancers. This can be done with immunohistochemical (IHC) analysis to evaluate for overexpression of the cellsurface receptor at the protein level or by using fluorescent in situ hybridization(FISH) to evaluate for gene amplification. IHC is scored on a qualitative scale from 0 to 3+, based on interpretation of staining intensity, with 0 and 1+ classified as negative, 2+ as borderline, and 3+ as positive, FISH is scored on a quantitative scale with less than 2 copies of the HER2 gene classified as negative[11,12]. Patients whose tumors overexpress HER-2/*neu* are candidates for anti–HER-2/*neu* therapy, trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody directed against HER-2/*neu*. Randomized clinical trials have demonstrated that single-agent trastuzumab therapy is an active and well-tolerated option for first-line treatment of women with HER2/*neu*–overexpressing metastatic breast cancer. More recently, adjuvant trials demonstrated that trastuzumab also was highly effective in the treatment of women with early-stage breast cancer when used in combination with chemotherapy. Patients who received trastuzumab in combination with chemotherapy had a 52% reduction in the risk of breast cancer recurrence compared with those who received chemotherapy alone [13].

Hormones play an important role in the development and progression of breast cancer. Estrogens, estrogen metabolites, and other steroid hormones such as progesterone all have been shown to have an effect. Breast cancer risk is related to estrogen exposure over time. In postmenopausal women, hormone replacement therapy consisting of estrogen plus progesterone increases the risk of breast cancer by 26% compared to placebo [14].

Patients with hormone receptor–positive tumors survive two to three times longer after a diagnosis of metastatic disease than do patients with hormone receptor–negative tumors. Patients with tumors negative for both ER receptors and PR receptors are not considered candidates for hormonal therapy. Tumors positive for ER or PR receptors have a higher response rate to endocrine therapy than tumors that do not express ER or PR receptors. Tumors positive for both receptors have a response rate of >50%, tumors negative for both receptors have a response rate of <10%, and tumors positive for one receptor but not the other have an intermediate response rate of 33% [15].

ER and PR receptor status can be measured in archived tissue using immunohistochemical techniques. Hormone receptor status also can be measured in specimens obtained with fine-needle aspiration biopsy or core-needle biopsy, and this can help guide treatment planning. Testing for ER and PR receptors should be performed on all primary invasive breast cancer specimens. The tumor hormone receptor status should be ascertained for both premenopausal and postmenopausal patients to identify patients who are most likely to benefit from endocrine therapy [15].

Patients and methods:-

All female patients presented with invasive breast cancer visiting the breast clinic and wards in AL-Hussein teaching hospital in Al-Samawa city included prospectively in this study from January 2020 to December 2022. Her clinical information with details of her operation and the histopathological finding (histological type, tumor stage, axillary lymph node number, hormonal (ER and PR) receptors status and HER-2/neu expression) recorded.

All patients operated upon by modified radical mastectomy with axillary lymph node clearance. Specimens were routinely processed and fixed overnight in 10% buffered formalin. Four to five micrometer thick formalin fixed, paraffin embedded tumor sections were stained with Haematoxylin and Eosin. Tumor characteristics were classified by TNM staging system and bloom –richardson system for grading. ER and PR receptors status expression done with (IHC), ER and PR positive as >10% of tumor cells showing nuclear staining. HER-2/neu expression done with (IHC) analysis to evaluate for overexpression of the cellsurface receptor at the protein level, IHC is scored on a qualitative scale from 0 to 3+, based on interpretation of staining intensity, with 0 and 1+ classified as negative, 2+ as borderline, and 3+ as positive. All analysis was done in AL- Hussein teaching hospital laboratory using the same methods, eliminating the problem of inter laboratory differences.

We dichotomized the patients in 2 groups: younger than (group 1) and equal to or older than 40 years old (group 2) (<40 years and ≥40 years of age). Younger women were grouped together as they represent a special high-risk population for whom routine screening is not recommended.

In this study we correlate the age of the patients with: histological type of tumor, stage of tumor, grade of tumor, hormonal (ER, PR) receptors status expression and with HER-2/neu expression.

Chi-square tests were used to compare the distribution of patients demographics, tumor characteristics between group 1 and group 2.P-values (<0.05) were considered to be statistically significant. All analyses were conducted using SPSS 20.0 ™ statistical software.

RESULTS

The total NO. of patients collected was 172 patients during the period of study ,The youngest age was 28 year and the oldest age was 86 year. The distribution of patients by age classification was as follows: Forty three (25%) younger than 40 year old (group 1), mean age 33.5(range 28 to39 years) while 129(75%) were 40 year and older age (group 2), mean age 63 year (range 40 to 86 years).

Relationship between histopathological type of cancer and age of patient, the most common histological type was invasive ductal carcinoma: involving 40 females (93%) in group 1 and 120 females (93%) in group 2, invasive lobular carcinoma: involving 3 female (7%) in group 1 and 8 female (6.2%) in group 2, and one female with medullary carcinoma (0.8%) in group 2,ther is no significant difference between them (P- value o.834) as shown in table (1).

Table (1):- Relationship between histopathological type of cancer and age of patient.

		% of total patients	Histopathology			Total	P- value
			Ductal carcinoma	Lobular carcinoma	Medullary carcinoma		
Age	Group 1	25%	40 93.0%	3 7.0%	0 0%	43 100.0%	0.834
	Group 2	75%	120 93.0%	8 6.2%	1 0.8%	129 100.0%	
Total		100%	160 93.0%	11 6.4%	1 0.6%	172 100.0%	

The relationship between the stage of cancer and age of patients, group 1 are more likely to presented with higher stage (stage III=53.6% for group 1 vs. =27.2% for group 2), whereas group 2 are more likely to present at an earlier stage (stage II=61.3% vs. 37.2% for group1), the relation is significant (P- value

0.035), as shown in table (2).

Table (2):- Relationship between tumors staging and age of patient.

				Staging					Total
		stage I	stage IIA	stage IIB	stage IIIA	stage IIIB	stage IIIC	Stage IV	
Age	Group 1	4 9.3%	9 20.9 %	7 16.3 %	14 32.6 %	6 14.0 %	3 7.0%	0	43 100%
	Group 2	15 11.6 %	46 35.7 %	33 25.6 %	26 20.2 %	5 3.9%	4 3.1%	0	129 100%
Total		19 11.0 %	55 32.0 %	40 23.3 %	40 23.3 %	11 6.4%	7 4.1%	0	172 100%
P- value				0.035					

The relationship between grade of the tumor and age of patients, group 1 are more likely to presented with grade 3 (39.5%) vs. (18.6%) for group 2, whereas group 2 are more likely to present with grade 1 (42% for group 2 vs. 23.2%for group1), this relation is significant (P- value 0.0103), as shown in table

(3).

Table (3):- Relationship between tumors grade and age of patient.

			grade		Total
		1	2	3	
age	Group 1	10 23.2%	16 37.2%	17 39.5%	43 100.0%
	Group 2	55 42%	50 38.7%	24 18.6%	129 100.0%
Total		65 37.7%	66 38.3%	41 23.8%	172 100.0%
P- value			0.0103		

Relationship between size of cancer and age of patients, group 1 mostly presented with larger size >5 cm (30.3% for group 1 vs. 14.8% for group 2), whereas group 2 are more likely to present with smaller size<5cm (86.3% for group 2 vs. 69.7%for group1), the relation is significant (P- value **0.001**) as shown in table 4.

Table (4):- Relationship between size of tumor and age of patient.

			Size			Total
		T1 (<2cm)	**T2 (2-5cm)**	**T3 (>5 cm)**	**T4 (any size with direct extension to chest wall or skin)**	
age	**Group 1**	**9 20.9%**	**21 48.8%**	**6 14.0%**	**7 16.3%**	**43 100.0%**
	Group 2	**22 17.1%**	**88 68.2%**	**17 13.2%**	**2 1.6%**	**129 100.0%**
Total		**31 18.0%**	**109 63.4%**	**23 13.4%**	**9 5.2%**	**172 100.0%**
P- value			**0.001**			

Relationship between NO. of involved axillary lymph node and age of patient, there is no significant difference between axillary lymph node NO. and age of patients(P- value o.147) , but group 1 had cancer that were more likely to have more axillary lymph node number (N0=30.2% were N1,N2 and N3 =69.8%) compared with group 2 (N0=48.1% were N1,N2and N3= 52%) as shown in Table (5) .

Table (5):- Relationship between NO. of involved axillary lymph node and age of patient.

			axillary lymph node			Total
		N0	N1 (1-3)	N2 (4-9)	N3 (>=10)	
age	Group 1	13 30.2%	14 32.6%	13 30.2%	3 7.0%	43 100.0%
	group 2	62 48.1%	38 29.5%	25 19.4%	4 3.1%	129 100.0%
Total		75 43.6%	52 30.2%	38 22.1%	7 4.1%	172 100.0%
P- value			0.147			

The relationship between ER hormone receptors and age of patients, 30 patients (69.8%) and 13 (30.2%) out of 43patients in Group 1 have negative and positive estrogen hormone receptor compared with 63 patients (48.8%) and 66(51.2%) out of 129 patients in Group2 respectively. there is significant association between ER hormone receptors and age (P- value o.o17) as shown in Table 6.

Table (6):- Relationship between ER hormone receptor and age of patients.

		ER hormone receptor		Total
		Positive	Negative	
age	Group 1	13 30.2%	30 69.8%	43 100.0%
	Group 2	66 51.2%	63 48.8%	129 100.0%
Total		76 44.2%	96 55.8%	172 100.0%
P- value		0.017		

The relationship between PR hormone receptors and age of patients, 26 patients (60.5%) and 17 (30.2%) out of 43patients in Group 1 have negative and positive PR hormone receptor compared with 55 patients (40.3%) and 77(59.7%) out of 129 patients in Group2 respectively. there is significant association between PR hormone receptors and age (P- value 0.033) as shown in Table 7.

Table (7):- Relationship between PR hormone receptor and age of patients.

		PR hormone receptor		Total
		positive	negative	
age	Group 1	17 39.5%	26 60.5%	43 100.0%
	Group 2	77 59.7%	52 40.3%	129 100.0%
Total		94 54.7%	78 45.3%	172 100.0%
P- value		0.033		

The relationship between HER-2/neu and age of patient, 23 patients (53.5%) and 20 (46.5%) out of 43patients in Group 1 have positive and negative HER2/neu hormone receptors respectively compared with 38 patients (29.5%) and 91(70.5%) out of 129 patients in Group2. there is significant association between HER-2/neu hormone receptors and age (P- value 0.0043) as shown in Table 8.

Table (8):- Relationship between HER-2/neu and age of patient.

		HER-2/neu		Total
		positive	negative	
Age	Group 1	23 53.5%	20 46.5%	43 100.0%
	Group 2	38 29.5%	91 70.5%	129 100.0%
	Total	61 35.5%	111 64.5%	172 100.0%
	P- value	0.0043		

Discussion

Breast cancer in patients under 40 years of age is uncommon; however, it has generated considerable Interest because of the associated unfavorable outcome reported in several studies [16, 17]. Given the lack of routine screening programs for women younger than40 years, it is not surprising those women in this age group are more likely to present with a palpable mass and that their tumors tends to be larger and are more likely to have nodal involvement, than tumors detected by screening [18,19].

Studies from United States (Brinton LA 2008)[20] , China(Ava Kwong 2008)[21], Hong Kong(2004) [22] , Iran (Ali pourzand2011)[23] estimated that 8%, 12.1%, 17.6%, 17% of breast carcinomas are presented in women younger than 40 years old respectively , while in our study it is 25%. The full reason for the peak of onset of breast cancer at the age of 40 is still unclear, although the Asian population has a lower incidence of breast cancer, the cause of this high percentage compared to the United States may be due to genetic and environmental factors [22, 23].

Invasive ductal carcinoma was common in both age groups(93%) a finding is similar to that found by Ali pourzand(2011)[23],AndresCK,Broadwater et al (2008)[24],JenniferL Gnerlich(2012)[25].

In agreement with a study *Elrasheid A H Kheirelseid(2011)* [26], invasive Lobular carcinoma in our study is slightly more common in younger age group than older age group (7% vs. 6.2%) .Another published studies estimated that invasive Lobular carcinoma were more in older age group as in AndresCK,Broadwater etal (2008)[24],JenniferL Gnerlich(2012)[25].

However, in contrast, the NO. of medullary carcinoma is so small that no significance can be drawn from these findings.

The younger women in our study, like other previously published studies *Jennifer L Gnerlich(2012)*[25] , *Winchester (1996)* [27] were likely to be diagnosed at more advanced stages of disease (stage III) 53.6% for group 1 vs.27.2% for group 2 ,higher grade (grade 3) 39.5% for group 1 vs.18.6% group 2 , larger tumor size (>5cm) 30.3% for group 1 vs. 14.8% for group 2.

In our study, lymph node metastases found to be more in group (1) (N1, N2, N3) was 69.8% vs. 52% for group (2), but p- value was not significant and this result is similar to study: CJ Fisher, MK Egan (1997) [28].

In relation to hormone receptor status, many published studies show that tumors in young women have lower ER , PR positivity and higher HER/2neu expression , *Jennifer L Gnerlich(2012)[25] show:28% and 30.1% of tumors in women less than 40 years of age were ER and PR negative vs. 14.2% and 20.4% in women over 40 respectively. Elrasheid Kheirelseid1etal(2011)[26] show: 42% ,29.7% of tumors in women less than 40 years of age were ER ,PR negative and 30.6% were HER2/neu positive vs. 25.5% ,27.5% ER ,PR positive and 18.6% were HER2/neu negative in women over 40,respectively* . Carey K. Anders, *etal (2008)[24]show: ER positivity* in young women *(positive vs. negative) 71% vs. 80%, respectively; (P-value 0.027), higher IHC expression of HER-2/neu (positive vs. negative) 52% vs. 24%, respectively.*

In our study younger women group revealed higher frequency of ER, PR negativity and HER2/neu overexpression (*69.8% , 60.5% and53.5% of tumors in group(1) were ER , PR negative and* HER2/neu overexpression *vs. 48.8%,40.3% and 29.5% in group(2) respectively*). These findings strongly support accumulating evidence that breast cancer in young patients is biologically more aggressive and associated with unfavorable prognostic markers in relation to their older counterparts.

Conclusion

- Breast cancer in younger age groups is more aggressive than in older age groups.
- The younger women in our study had tumors that were distinctly different from older women and were characterized by unfavorable biological parameters.
- Younger women had tumors that were more likely to be higher stage, ER negative, PR negative and positive HER-2/neu. All of these characteristics are associated with a more aggressive tumors and poorer prognosis.

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