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Original Article
Hormone Receptors
Pak Armed Forces Med J 2021; 71 (Suppl-1): S118-22

ASSOCIATION OF HORMONE RECEPTORS WITH RISK FACTORS AMONG BREAST CANCER PATIENTS

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ABSTRACT

Objective: To compare the risk factors with estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status of breast cancer patients.
Study Design: Cross sectional comparative study.
Place and Duration of Study: This study was carried out in Multidisciplinary Lab-1 of Army Medical College, National University of Medical Sciences, Rawalpindi, in collaboration with Department of Pathology of Army Medical College, NUMS Rawalpindi, from Jan 2019 to Jan 2020.
Methodology: A total of 50 individuals including radiologically diagnosed cases of breast cancer with different stages and 10 healthy controls without cancer. Patients with any co-morbidity were excluded. Participant's sample was collected and subjected to ER, PR and HER2 estimation. Other factors i.e. age, gender, marital status, breast feeding, menopause status, side of the breast affected were all taken into consideration.
Results: Patients characteristics showed that the mean age, marital and menopause status were linked with breast cancer. The data showed that hormone receptors i.e., ER (p=0.0001), PR (p=0.0002) and HER2 (p=0.0001) were positive among most of the cancer patients as compared to the healthy subjects without cancer. There were no association found between age and hormone receptors. Marital status, breast feeding, menopause and side of breasts involved also had no association with hormone receptors.
Conclusion: No significant association found between risk factors and hormone recpetors status of breast cancer patients in our population.

Keywords: Breast cancer, Estrogen receptor (ER), Risk factors, Human epidermal growth factor receptor 2 (HER2). Progesterone receptor (PR).

INTRODUCTION

Cancer is uncontrolled growth of cells. Genetic and Epigenetic modifications add to the initiation of cancer and it's progression[1]. There are two classes of cancers. One is benign and the other is referred as malignant. The benign tumors are not fatal but only in particular conditions like tumors of the brain. These brain tumors are very dangerous even if histologically they are benign. The tumors that belong to malignant type are precarious and they metastasize to other tissues of body[2]. Breast cancer is an extremely heterogeneous disease and it involves the milk carrying ducts, lobules and inner layer of mammary gland. Breast cancer is the fifth leading cause of cancer deaths. Breast tissue's malignancy is among the common tumours of the female. It accounts for 24.2% of all malignant cases of female cancers globally. Every one in four diagnosed cases of cancer in women are breast cancer. Breast cancer is the most common in 154 of the 185 countries which were included in GLOBOCA, 2018. The mortality rate of women due to Breast cancer according to Globocan 2018 is 15.0%[3]. Breast cancer is multifactorial and multistage disease. It's initiation andprogression involve risk factors along with genetic and epigenetic changes. The primary risk factors involve in its development are age, sex, obesity, high hormone level, exposure to estrogen in lifetime, iodine deficiency in diet, race and economic status. In the pathogenesis of it's development, viruses may also play role at any stage[4]. Risk factors for breast cancer development in southeast Asian Population

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Received: 21 Jun 2020; revised received: 15 Sep 2020; accepted: 24 Sep 2020

could be different from Europeans. Risk factors such as smoking, alcohol, obesity, nulliparity, early menarche, hormonal drug consumption are rare in Southeast Asian breast cancer patients[5]. There are receptors on the surface of breast cancer cells and in their nucleus and cytoplasm. Hormones such as estrogen and progesterone bind to their cognate receptors that leads to changes in cells. These receptors are estrogen receptors (ER), progesterone receptors (PR) and HER2 receptors[6]. Triple negative breast cancers lack all of these three receptors. They are more aggressive type and usually express receptors for other hormones such as prolactin or androgens[7]. In the precancerous and cancerous lesions estrogen can proliferate the cells by its hormonal activity. Moreover, important fraction of breast carcinoma is estrogen-receptor negative[8]. The role of ER as an oncogene is well-known but the value of PR as therapeutic target and biomarker is much divisive. Almost two-thirds of breast cancers are ER and PR positive. Postmenopausal women mostly develop ER ± PR ± cancers[9]. Risk factorsrelated with estrogen receptor (ER) and progesterone receptor (PR) positive breast tumors include mechanisms that are associated withendogenous hormone exposure while the cause of ER and PR negative breast cancers may be non-hormonal[10]. The purpose of this study is the determine the link between different clinical characteristics of patients with that of cancer stages.

METHODOLOGY

The research was cross sectional comparative study carried out in the department of Biochemistry and Molecular Biology Army Medical College Nums, Rawalpindi in collaboration with Pathology department of Army Medical College, from January 2019 to January 2020. Approval was taken from Ethical Review Committee of Army Medical college, Rawalpindi and National University of Medical Sciences, Islamabad. Sample size for our study was 50 females including 40 patients of different stages of breast cancer and 10 without cancer healthy subjects.The subjects were recruited in the study using convenient sampling technique. A structured questionnaire was filled out by all the included after taking the informed consent. The demographic and biological data was obtained from the Radio-logically diagnosed patients of breast cancer visiting Pathology department of Army Medical college, Rawalpindi. Data included age of patients along with their socioeconomic status, education, marital status, history of breast feeding, pre or postmenopausal status and their receptor status whether ER, PR or HER2 positive. Statistical analysis was done using SPSS 22. *p*-values were calculated and *p*-value of ≤0.05 was considered significant. For qualitative variable, frequencies and percentages were calculated. Chi square test and Fisher Exact Test were used where applicable.

RESULTS

A total of 40 patients were included in the study, Mean age was 45.70 ± 12.86 years range from 16 to 74 years. Patient's characteristics showed that the mean age of normal healthy participants without cancer was lower as compared to cancer patients. All the participants included in the study were female. Percentage of the married women was significantly higher in cancer patient's group as compared to without cancer healthy group. Breast feeding was not a significant factor between the two groups i.e, cancer patients and healthy subjects without cancer. Half of the cancer patients had pre-menopause and the other half had post-menopause phase. But 90% of the healthy without cancer women were of pre-menopause phase (table-I). The data showed that ER (p=0.0001), PR (p=0.0002) and HER2 (p=0.0001) were positive among most of the cancer patients as compared to the healthy subjects without cancer (table-II). There were no significant association found between age and ER, PR and HER2 receptors, as shown by their *p*-values 0.484, 1.00 and 1.00 respectively. Marital status, breast feeding, Menopause, side of breast involve had no association with ER, PR and HER2 receptors as shown by their *p*-values given in table-III.

DISCUSSION

Cancer is becoming the major cause of death worldwide. Its incidence is also increasing. Breast

cancer is one of primary reason of death among females worldwide. It is a heterogeneous disease as genetic and epigenetic modifications, risk factors and many subtypes and molecular markers contribute to its development[11]. All the subjects included in our study were females as Breast cancer is more prevalent in females as compared to males. According to Globocan 2018, the most frequently diagnosed cancer and leading cause of death in females all over the world is breast cancer. It accounts for almost 25% of all cancer cases and 15% of all cancer deaths among females[12].

Risk factors for breast cancer development are also important so as the genetic factors. Age is one of the significant demographic risk factor. Mean age of patients in our study was 45.70 ±

Table-I: General characteristics of the participants.

Characters		Healthy Subjects without Cancer, n (%)	Cancer Patients n (%)	*p*-value
Age		38.40 ± 13.62	45.70 ± 12.86	
Gender		Females	Females	1
Marital Status	Married	6 (60)	39 (97.5)	0.0041
	Un-Married	4 (40)	1 (2.5)	
Breast Feeding	Yes	6 (60)	28 (70)	0.71
	No	4 (40)	12 (30)	
Menopause	Pre	9 (90)	20 (50)	0.031
	post	1 (10)	20 (50)	

Table-II: Clinical parameters.

Hormone Receptors		Healthy Subjects without Cancer, n (%)	Cancer Patients n (%)	*p*-value
Endrogen Receptor (ER)	Positive	-	28 (70)	0.0001
	Negative	10	12 (30)	
Progesterone Receptor (PR)	Positive	-	26 (65)	0.0002
	Negative	10	14 (35)	
Human epidermal growth factor receptor 2 (HER2)	Positive	-	28 (70)	0.0001
	Negative	10	12 (30)	

Table-III: Association of ER, PR & HER2 receptor with different clinicopathologic parameters.

	Endrogen Receptor (ER)		*p*-value	Progesterone Receptor (PR)		*p*-value	Human Epidermal Growth Factor Receptor 2 (HER2)		*p*-value
	Positive	Negative		Positive	Negative		Positive	Negative	
Age									
≤45.70 (mean)	11 (39.3)	3 (25)	0.484	10 (35.7)	4 (33.3)	1.00	6 (37.5)	8 (33.3)	1.00
>45.70 (mean)	17 (60.7)	9 (75)		18 (64.3)	8 (66.7)		10 (62.5)	15 (66.7)	
Marital Status									
Married	26 (92.9)	12 (100)	0.637	27 (96.4)	11 (91.7)	0.249	15 (93.8)	23 (95.8)	0.338
Unmarried	1 (3.6)	-		1 (3.6)	-		-	1 (4.2)	
Divorce	1 (3.6)	-		-	1 (8.3)		1 (6.3)	-	
Breast Feeding									
Yes	18 (66.7)	10 (83.3)	0.445	19 (70.4)	9 (75)	0.718	12 (75)	16 (69.6)	0.406
No	5 (18.5)	1 (8.3)		4 (14.8)	2 (16.7)		3 (18.8)	3 (13)	
Menopause									
Pre	15 (53.6)	5 (41.7)	0.490	15 (53.6)	5 (41.7)	0.490	8 (50)	12 (50)	1.00
Post	13 (46.4)	7 (58.3)		13 (46.4)	7 (58.3)		8 (50)	12 (50)	
Side of Breast Involved									
Right	13 (46.4)	7 (58.3)	0.566	12 (42.9)	8 (66.7)	0.312	9 (56.3)	11 (45.8)	0.460
Left	13 (46.4)	5 (41.7)		14 (50)	4 (33.3)		7 (43.8)	11 (45.8)	
Both	2 (7.1)	-		2 (7.4)	-		-	2 (8.3)	

12.8 years range from 16 to 74 years. Overall risk increases in old age. All the deaths due to breast cancer in America, in the year 2016, were over the age of 40 and 60. So, it is recommended to do mammography screening after the age of 40[13]. Increase in incidence may be because of low immunity and prolonged exposure to carcinogens with increase in age[14].

History of breast feeding was positive for total of 70% patients. Many studies have revealed that there is decrease risk for breast cancer development in lactating women. In a metaanalysis of n=65 studies it was concluded that exclusive breastfeeding reduces the risk of development of breast cancer among parous women as compared with those who do not breastfeed exclusively and are multiparous[15]. In our study 50% of breast cancer patients were premenopausal and 50% were postmenopausal It has been suggested that in both premenopausal and postmenopausal women, younger women had more aggressive disease including higher stage, hormone receptor-negative disease and lymph node positivity[16]. There is inverse correlation between history of breast feeding and premenopausal status but there is no decrease in risk for developing the disease in postmenopausal with history of lactation[17].

Right side of breast was involved in 50% breast cancer patients as compared to left side. Left side was involved in 45% of cases whereas 5% of patients have bilateral disease. These findings are opposite as compared to report by Asif *et al*, Who reported that breast cancer is more prevalent in left breast rather than right breast, 47.7% in left and 41.5% in right[18].

Regarding ER,PR and HER2 status, 70% were ER positive and 70% were also PR positive while 40% were HER positive. ER and PR are very important in choice of treatment therapy. Positive for these receptors respond to endocrine therapy[19]. In our study *p*-value was calculated to find out association of ER,PR and HER2 positive patients with risk factors of Age, marital status, breast feeding, menopausal status and side of breast involved. We found no association as *p*-values were 0.05. Turkoz *et al*, also did not find any significant differences between risk factors including early menarche and late menopause, family history, history of smoking, blood group and molecular subtypes of breast cancer that are based upon the ER,PR and HER2 status[20].

CONCLUSION

Age, marital status and menopause phase along with other clinical factors i.e, hormone receptors (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor2 (HER2) were strongly correlated with breast cancer. No significant association found between risk factors and ER, PR and HER2 status of breast cancer patients in our population. Analyzing the relationship of risk factors of breast with possibility of development of different molecular subtypes of breast cancer not only helps to improve to know the etiology of disease but may also aid in improvement of prevention plans.

ACKNOWLEDGEMENTS

Authors are thankful to Dr. Raza Jaffer and Dr. Tariq Sarfaraz (Pathology department AMC NUMS) for their excellent support and guidance. We owe special gratitude to Army Medical College, Rawalpindi, for providing us the oppor-tunity and facilities to do our research. We are greatly thankful to National University of Medi-cal Sciences (NUMS) for funding this project.

Disclosure

We are highly obliged to National University of Medical Sciences, Islamabad for giving us funding for our project.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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