Original Research Article

A study on epidemiology of HER2/NEU positive breast cancer of patients presented in a tertiary care teaching hospital, Kolkata, West Bengal

Soumya Banerjee[1], Sukanti Bhattacharyya[2], Shib Sankar Roy Chowdhury[3*], Nirmal Kumar Bhattacharyya[4], Sukumar Maity[5]

[1]Post Graduate Trainee, Department of General Surgery, Medical College & Hospital, Kolkata 88, College St, College Square, Kolkata, West Bengal 700073, India

[2]Assistant Professor, Department of Physiology, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India

[3]Associate Professor, Department of General Surgery, Medical College & Hospital, Kolkata 88, College St, College Square, Kolkata, West Bengal 700073, India

[4]Associate Professor, Department of Pathology, Medical College & Hospital, Kolkata 88, College St, College Square, Kolkata, West Bengal 700073, India

[5]Professor & Head, Department of General Surgery, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal 721645, India

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Abstract

Background: Breast cancer is the second most common cancer now, after lung cancer, when ranked by cancer occurrence in both sexes. The aim of this study was to determine the correlation between various modifiable and non modifiable risk factors among women with HER2/neu positive breast cancer attending at Medical College and Hospital, Kolkata. **Materials & Methods:** A cross sectional analytical epidemiological study in Out Patient Department & Emergency Department of General Surgery, Medical College& Hospital, Kolkata. Period of study was between January 2018 to June 2019. All the adult breast cancer patients attending Department of General Surgery, Medical College & Hospital, Kolkata were included in the study and that came out to be 25 HER2 neu positive and 35 HER2 neu negative patients. All together 60 patients were included. **Results:** We have found 60 patients among them 25 patients were ***HER2/neu*** positive and 35 patients were ***HER2/neu*** negative i.e. 42% of patients in our study found to be ***HER2/neu*** positive. Among these patients the patient with minimum age was 38 years old, and the maximum aged patient was 65 years old.The average age was 57.33 years. The average age of ***HER2/neu*** positive group was 57.77 years and the ***HER2/neu*** negative group was 56.48 years. About 35% of these patients had history of OCP intake. Among ***HER2/neu*** positive patients 57.1% & ***HER2/neu*** negative 42.9% had history of OCP intake. Most of the patients in this study are in pre-obese (BMI 25-29.99) class as per BMI. About 18 ***HER2/neu*** positive patients and 26 ***HER2/neu*** negative patients are within this group. Five (14.28%) patient in ***HER2/neu*** negative group and 3 (12%) in ***HER2/neu*** positive group has positive family history of breast cancer. In our study we have found that menarche of minimum age of 9 years and maximum age at 15 years. Maximum no. of patients found their menarche at the age of 12 years. **Conclusion:** From our study and analysis we could not establish any obvious significant difference between epidemiological distributions of breast cancer patients in respect to ***HER2/neu*** status. Hence this can be concluded from our study that there is no different epidemiological pattern of breast cancer in respect to ***HER2/neu*** status.

Keywords: Breast cancer, HER2/NEU positive**,** risk factors, epidemiology, West Bengal

***Correspondence**
Dr. Shib Sankar Roy Chowdhury
Associate Professor, Department of General Surgery,
Medical College & Hospital, Kolkata 88, College St, College Square, Kolkata, West Bengal 700073, India.
E-mail: shibsankarroychowdhury2020@gmail.com

Introduction

Breast cancer is a complex disease encompassing multiple tumor entities, each characterized by distinct morphology, behavior and clinical implications. It is one of the most common malignancies in women. The tumour is highly heterogeneous, with a wide range of biological, pathological and clinical characteristics. Of these characteristics, hormone receptors and HER2/neu status has a great influence on the clinical outcome [1].
It is the second most common cancer now, after lung cancer, when ranked by cancer occurrence in both sexes. About 55% of the global burden is currently experienced in developed countries, but incidence rates are rapidly rising in developing countries [2, 3]. For decades together, cervical cancer was the most common cancer in women in India, and more deaths in women in India were attributed to cervical cancer than any other cancer [4]. However, over the last 10 years or so, breast cancer has been rising steadily, and for the first time in 2012, breast cancer was the most common cancer in women in India, a way ahead of cervical cancer [5]. Estrogens have a crucial role in the proliferation and progression of breast cancer. Estrogen is the major steroid mitogen for the luminal epithelial cell population (the usual target for neoplastic transformation) [6]. The role of hormone receptors as prognostic and therapeutic tools has widespread acceptance in the management of breast cancer. The expression of estrogen receptor (ER), in particular, is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormonal therapy. The association between HER2/neu gene (C-erbB2) amplification and poor prognosis was first determined in 1987 by Salmon *et al*[6], whose results showed that amplification of the HER2/neu gene was strongly correlated with time to relapse(disease free survival) and overall survival. Not only the identification of HER2/neu status is important for determining the prognosis of breast cancer patients, but it is also important for selecting those with metastasis for therapy with trastuzumab (herceptin) [7, 8].The aim of this study was to determine the correlation between various modifiable and non modifiable risk factors among women with HER2/neu positive breast cancer attending at Medical College and Hospital, Kolkata.

Materials & methods

A cross sectional analytical epidemiological study in Out Patient Department & Emergency Department of General Surgery, Medical College& Hospital, Kolkata. Period of study was between January 2018 to June 2019. All the adult breast cancer patients attending Department of General Surgery, Medical College & Hospital, Kolkata were included in the study and that came out to be 25 HER2 neu positive and 35 HER2 neu negative patients. All together 60 patients were included.

Inclusion Criteria

1. Adult (≥18 years) female breast cancer patients attended in OPD & Emergency of Medical college and Hospital, Kolkata within the period of data collection.
2. Patients who had given informed consent

Exclusion Criteria

Unconscious, terminally ill patients and those who were unable to communicate with the researchers excluded. After obtaining necessary permission and approval from Institutional Ethics Committee, the patients will be approached at out-patient department and Emergency ward, General Surgery department, Medical college and Hospital, Kolkata.. They were explained about the purpose of the study and informed consent was obtained. They were interviewed using pre-designed questionnaire. Anthropometric measurements like height, weight and calculation of BMI and clinical examination, general survey and systemic examination. Presences of pallor, pulse, blood pressure, height, weight were recorded as baseline measures in all the cases. Along with these the IHC & HPE reports are also used as abasic requirement to diagnose the Her 2 neu status of the breast carcinoma.For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. Data had been summarized as mean and standard deviation for numerical variables, count and percentages for categorical variables. As per necessity Chi square test, Independent t test, Mann-Whitney U test were been done.

Results

From January 2018 to June 2019, an institution based cross sectional, observational and analytical study was carried out in the Department of General Surgery and Department of Pathology to find out the sociodemographic characteristics and disease profile of both HER2 neu positive and HER2 neu negative breast cancer patients taking a sample size of 60 female patients visiting General Surgery OPD of MCH, Kolkata.

HER 2 neu Distribution-In this study we found all together 60 patients of breast cancer patients. Among them 25 patients were HER 2 neu positive and others were HER 2 neu negative i.e. there were 42% of patients HER 2 neu positive [Table 1].

Table 1: Patient with distribution according to *HER2/neu* status [n=60]

Characteristics	Number (Percentage)
HER2/neu positive	25 (41.67%)
HER2/neu Negative	35 (58.33%)
Total no. of CA breast patient	60 (100%)

In this study we have patients of ages ranging from 38 years to 65 years age. The overall mean age was 57.33 years and the mode and median both is 58 years [Table 2]. Mean age of ***HER2/neu*** positive and negative breast cancer patients were found to be 57.77 (4.41) and 56.48 (6.38) years respectively, the differences were not found to be statistically significant (p=0.358).

Table 2: Distribution of breast cancer patients according to *HER2/neu* status and age (n=60)

Categories	Age in years Mean (SD)	P value (Using Independent t test)
HER2/neu Positive	57.77 (4.41)	0.358
HER2/neu Negative	56.48 (6.38)	

Table 3: Age wise distribution

Age (Yrs)	HER2/neu Positive	HER2/neu Negative	Total No. of CA breast
<30	0	0	0
30 - 39	0	1	1
40-49	3	1	4
50-59	14	21	35
≥60	8	12	20

Role of OCP intake is very much crucial in Breast cancer patients. In our study we have around 21 (35%) of patients who had h/o OCP intake. The number of ***HER2/neu*** positive patients who has history of OCP intake is 12 and the number of ***HER2/neu*** negative patients who have taken OCP is 9.Using Chi square test we have found the null hypothesis is true. So the differences were not found to be statistically significant (p=0.074) [Table 4].

Table 4: Association of *HER2/neu* status and oral contraceptive use among study participants (n=60)

Categories	*HER2/neu* Positive (%)	*HER2/neu* Negative (%)	P value (Chi-square test)
Used oral contraceptives	12 (57.1)	9 (42.9)	0.074
Did not use oral contraceptives	13 (33.3)	26 (66.7)	

Body mass index (BMI) is a simple index of weight for height that is commonly used to classify underweight overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (Kg/m^2). In this present study the p value is 0.122, hence the relation between her 2 neu status and BMI is statistically insignificant. From the table 5 we can see that maximum (72% for ***HER2/neu*** positive & 74.3% for ***HER2/neu*** negative) patients are in pre-obese group [Table 5].

Table 5: Distribution of body mass index with *HER2/neu* positivity in breast cancer cases

BMI	*HER2/neu* positive [n=25]	*HER2/neu* negative [n=35]
Under weight (<18.5)	2 (8%)	0
Normal (18.5-24.99)	3 (12%)	7 (20%)
Pre-obese (25-29.99)	18 (72%)	26 (74.3%)
Obese class I (30-34.99)	2 (8%)	0
Obese class II (35-39.99)	0	2 (5.7%)
Obese class III (≥40)	0	0

Table 6: Distribution of study participants according to Her2Nue Status and family history of breast cancer (n=60)

Category	*HER2/neu* positive [n=25]	*HER2/neu* negative [n=35]	*P value*
Positive family history	3 (12)	5 (14.28)	0.79
No family history	22 (88)	30 (85.72)	

Proportion of study participants with positive family history among ***HER2/neu*** positive and negative patients were found to be 62.5% and 57.7% respectively. The differences were not found to be statistically significant (p=0.79) [Table 6/Fig. 1].

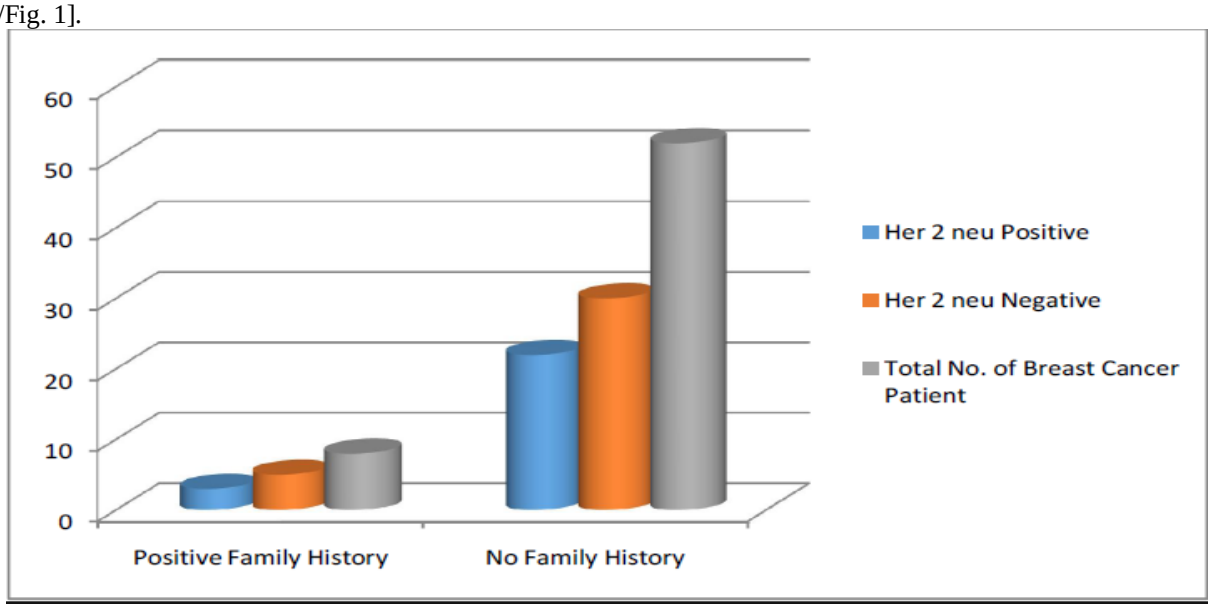

Fig 1: Chart comparing between *HER2/neu* positive and negative patient in respect to family h/o breast cancer

In our study we have found that menarche of minimum age of 9 years and maximum age at 15 years .Maximum no. of patients found their menarche at the age of 12 years [Table 7].

Table 7: Distribution of age of menarche in patients of breast cancer

Year of menarchae	*HER2/neu* positive [n=25]	*HER2/neu* negative [n=35]	CA Breast
9	*1*	*0*	1
10	*4*	*2*	6
11	*4*	*4*	8
12	*5*	*12*	17
13	*6*	*10*	16
14	*3*	*6*	9
15	*2*	*1*	3

In our study we have found maximum patients became mother for first time within the period of 20 to 29 years of their age. The mode & median value of age of first pregnancy was 20 years. The mean age was 20.62 years. The maximum value of age was 28 and the minimum age was 16 [Table 8].

Table 8: The pattern of age of first child birth among patients of breast cancer

Age in yrs	*HER2/neu* positive [n=25]	*HER2/neu* negative [n=35]	CA Breast
<20	*11*	*11*	22
20-29	*14*	*24*	38
≥30	*0*	*0*	0

As there is various hormonal changes occurs during the period of pregnancy. So the no. of completed full term pregnancy is important in case of breast cancer. In our study we found lady with maximum h/o full term pregnancy upto 7 in numbers. Maximum no. of lady had h/o 3 to 5 child [Table 9].

Table 9: Association of *HER2/neu* status and total number of child birth among study participants (n=60)

Categories	Total number of child birth Median (IQR)	P value (Using Mann-Whitney U test)
HER2/neu positive [n=25]	3 (2.5-4)	0.24
HER2/neu negative [n=35]	4 (3-5)	

As the P value of above test is 0.24 so it signifies that the Null hypothesis is valid so there is no significant association between ***HER2/neu*** status and total no. of child birth [Table 9].As there is obvious hormonal changes occurs during any pregnancy, and due to abortion the serial changes suddenly stops, so there become abrupt alteration of hormones. Maximum no. of h/o abortion is 3 in ***HER2/neu*** positive patients and in Her 2 neu negative patients maximum no. of abortion is 2. ***HER2/neu*** negative 7 patients & Her 2 neu positive 8 patients had no h/o abortion [Table 10].

Table 10: Association of *HER2/neu* status and history of abortion among study participants (n=60)

Category	*HER2/neu* positive [n=25]	*HER2/neu* negative [n=35]
Had h/o Abortion	8	7
Had no h/o Abortion	17	28

Table 11: Association of *HER2/neu* Status and total number of abortion among study participants (n=60)

Categories	Total number of child birth Median (IQR)	P value (Using Mann-Whitney U test)
HER2/neu positive [n=25]	1 (0-1.5)	0.51
HER2/neu negative [n=35]	1 (1-2)	

After using Mann-Whitney U test we get the p value 0.51. Hence the differences between ***HER2/neu*** positive and negative patients were not statistically significant [Table 11/Fig. 2].

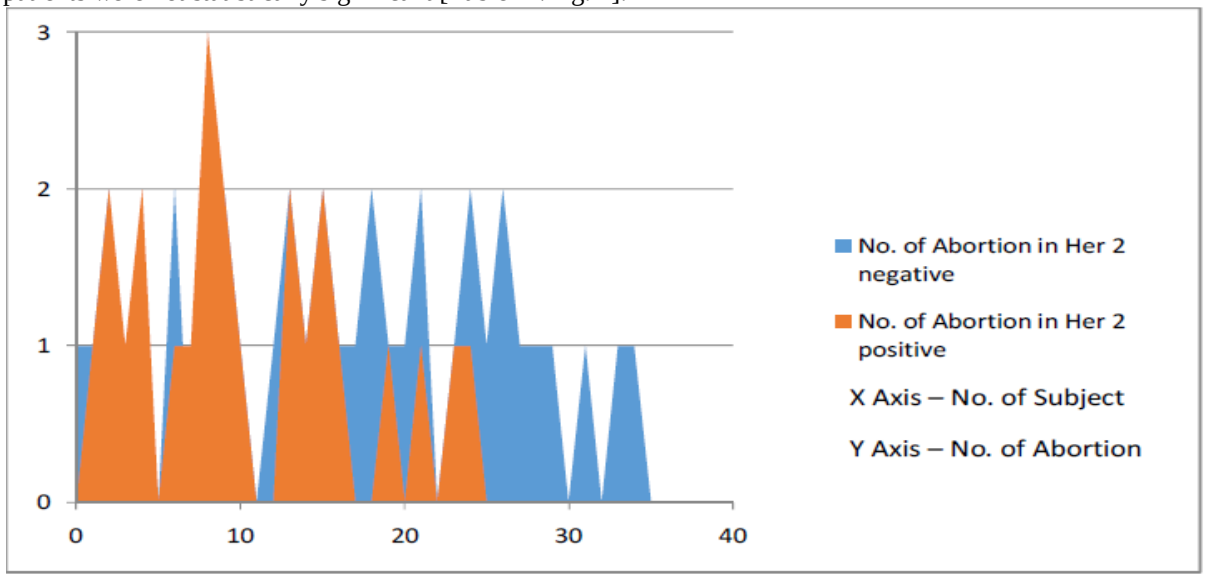

Fig 2: Graph showing the distribution of h/o abortion in breast cancer patients

Age of menopause is also important as this is the period till which hormonal changes occur in female body in regular interval. In our study we have found that maximum number of patient's menopause occurred between 46 to 50 years of age [Table 12].

Table 12: Distribution of age of menopause

Age of menopause	*HER2/neu* positive [n=25]	*HER2/neu* negative [n=35]	CA Breast
40-45	*0*	*6*	6
46-50	*15*	*20*	35
51-55	*8*	*8*	16
>55	*0*	*0*	0

Discussion

Breast cancer, is an important health problem in India. In the last decade, there is increase of knowledge and fast development of breast cancer management, which resulted in decrease of mortality rates. All women are at risk for developing breast cancer. The older a women is, the greater her chances of developing breast cancer. Approximately 77% of breast cancer cases occur in women over 50 years of age. Most important factor in reducing death from breast cancer is early detection. Early detection and treatment is a key to preventing breast cancer from spreading. ER-positive cancers continue to increase with age whereas the incidence of ER-negative cancers and ***HER2/neu*** positive cancers remains relatively constant. The number of ER-positive cancers detected in older women has risen as a result of mammographic screening (which preferentially detects ER-positive cancers) and menopausal hormone therapy (which is associated with an increase in these cancers). As a result, ER-negative and ***HER2/neu*** positive cancers comprise almost half of cancers in young women but fewer than 20% of cancers in older women [9, 10].In our study, which is a cross sectional observational study, we have taken 60 patients. Among them we found 25 patients are ***HER2/neu*** positive and 35 patients are ***HER2/neu*** negative. A distinct age-specific incidence pattern is observed for breast cancer, it is characterized by a rapid increase in incidence rate before menopause (up to age 50 years) and the rate of increase in incidence rates is much lower thereafter. This pattern may be due to the diminishing levels of circulating estrogens after menopause [11].In our study maximum patients (35 within 60) are found at the age of 5th decade. However there is no significant difference found between patients of ***HER2/neu*** positive or negative status H/o OCP Intake There are multiple types of hormonal contraception available by prescription, including OCPs, injectable contraceptives, hormonal intrauterine devices (IUDs), implants, vaginal rings, and transdermal contraceptive patches. OCPs are the most common type of hormonal contraception used, though their availability and frequency of use vary considerably worldwide. Rates of use are generally higher in developed countries, for example, in the United States approximately 82% of women have ever used OCPs and in 2002 approximately 11.6 million women of reproductive age were currently using OCPs [12]. A multitude of case–control studies, cohort studies, and pooled analyses have assessed the relationship between OCP use and risk of breast cancer among pre and post menopausal women, including recent studies that have focused on timing of use, specific durations of use, and hormonal content. Overall, the evidence supports that recent use of OCPs is associated with a modest increased risk of breast cancer among premenopausal women and that this relationship is strongest among very young women. In our study, the number of ***HER2/neu*** positive patients who has history of OCP intake is 12 and the number of ***HER2/neu*** negative patients who have taken OCP is 9.Using Chi square test we have found the null hypothesis is true. So the differences were not found to be statistically significant (p=0.074). BMI The physiological manifestation of energy balance in humans can be measured by indices of nutritional status or body fatness such as BMI, weight change, waist–hip ratio (WHR), and height. BMI is measured as weight in kilograms (kg) divided by the square of height in meters (m^2). Although an imperfect measure, BMI is highly correlated with percentage of body fat [13, 14]. The relationship between BMI and breast cancer risk has been extensively studied [14, 15]. Evidence for an association between BMI and breast cancer risk differs by menopausal status in that high BMI may be associated with a lower risk of premenopausal breast cancer, but is strongly associated with a higher risk of postmenopausal breast cancer [16, 17]. In our study the p value is 0.122, hence the relation between ***HER2/neu*** status and BMI is statistically insignificant.

Family History

The accumulation of epidemiologic evidence has clarified that the increased risk of breast cancer conferred by a positive family history varies with the degree of kinship, the number of affected relatives, and the onset ages in relatives and/or the women under study [18, 19]. In our study proportion of study participants with positive family history among ***HER2/neu*** positive and negative patients were found to be 62.5% and 57.7% respectively. The differences were not found to be statistically significant (p=0.79).

Age of Menarche and Menopause

Perhaps the most compelling evidence regarding the influence of endogenous hormones on breast cancer risk is found in the levelling off in the age-specific incidence curve of breast cancer after menopause when ovarian production of steroid hormones ceases. The ages at menarche and menopause, milestone events that determine the period over which women are exposed to endogenous ovarian hormones, have repeatedly been shown to be related to the risk of breast cancer [20-23]. However we could not found any statistical significant difference for ***HER2/neu*** status in respect to menarche & Menopause Age of first child birth. In a 1970 landmark study, MacMahon and colleagues concluded

that the observed protective effect of parity at least in part can be attributed to an earlier age at first birth in women with many children [24]. It is now estimated that for each additional year of age at first birth, the risk of premenopausal breast cancer increases by 5%, and increases by 3% for breast cancers diagnosed after menopause [25]. Compared to nulliparous women, women with a first full-term pregnancy before age 20 years have about half the risk of breast cancer [26]. Women with an older age at first birth (≥35 years) have the same risk of breast cancer as nulliparous women. In our study we have found maximum patients became mother for first time within the period of 20 to 29 years of their age. The mode & median value of age of first pregnancy is 20 years. The mean age was 20.62 years. The maximum value of age was 28 and the minimum age was 16. It has long been recognized that parity reduces the risk of breast cancer [26]. In our study as the P value of above test is 0.24 so it signifies that the null hypothesis is valid so there is no significant association between ***HER2/neu*** status and total no. of child birth.

Total Number of Abortion

The question whether an incomplete pregnancy affects future breast cancer risk has been under much debate. Based on findings from animal studies, it has been hypothesized that an increase in breast cancer risk may follow if the hormonal surge occurring during the first trimester is not followed by the protective components of breast tissue maturation and terminal differentiation of lobular structures during the second and third trimester [27]. Findings from early case-control studies indicated that induced abortions were associated with an increased risk of breast cancer [28]. In our study after using Mann-Whitney U test we get the p value 0.51. Hence the differences between ***HER2/neu*** positive and negative patients are not statistically significant.

Conclusion

A cross sectional analytical epidemiological study was designed during January 2018 to June 2019. The place of study was at Medical College Hospital, Kolkata. We have found 60 patients among them 25 patients were ***HER2/neu*** positive and 35 patients were ***HER2/neu*** negative i.e. 42% of patients in our study found to be ***HER2/neu*** positive. Among these patients the patient with minimum age was 38 years old, and the maximum aged patient was 65 years old.The average age was 57.33 years. The average age of ***HER2/neu*** positive group was 57.77 years and the ***HER2/neu*** negative group was 56.48 years. About 35% of these patients had history of OCP intake. Among ***HER2/neu*** positive patients 57.1% & ***HER2/neu*** negative 42.9% had history of OCP intake. Most of the patients in this study are in pre-obese (BMI 25-29.99) class as per BMI. About 18 ***HER2/neu*** positive patients and 26 ***HER2/neu*** negative patients are within this group. Five (14.28%) patient in ***HER2/neu*** negative group and 3 (12%) in ***HER2/neu*** positive group has positive family history of breast cancer. In our study we have found that menarche of minimum age of 9 years and maximum age at 15 years. Maximum no. of patients found their menarche at the age of 12 years. We have found maximum patients became mother for first time within the period of 20 to 29 years of their age. The mode & median value of age of first pregnancy is 20 years. The mean age was 20.62 years. The maximum value of age was 28 and the minimum age was 16. In our study we found lady with maximum h/o full term pregnancy upto 7 in no. Maximum no. of lady had h/o 3 to 5 child. Maximum no. of h/o abortion is 3 in ***HER2/neu*** positive patients and in ***HER2/neu*** negative patients' maximum no. of abortion is 2. ***HER2/neu*** negative 7 patients & ***HER2/neu*** positive 8 patients had no h/o abortion. In our study we have found that maximum number of patient's menopause occurred between 46 to 50 years of age. From our study and analysis we could not establish any obvious significant difference between epidemiological distributions of breast cancer patients in respect to ***HER2/neu*** status. Hence this can be concluded from our study that there is no different epidemiological pattern of breast cancer in respect to ***HER2/neu*** status.

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