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Article

Association of reproductive risk factors and comorbidities among molecular subtypes of Breast cancer in a Tertiary care Hospital

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The reasons for the recently observed increase in the incidence of breast cancer in the Indian population are not clearly understood, but thought to be largely explained by westernization of lifestyles and changes in reproductive behavior, which characterize exposure to hormones. Our aim is to review the reproductive risk factors and comorbidities and evaluate the association between molecular subtypes of breast cancer. A hospital-based analytical case-control study was conducted among the breast cancer cases with controls in a multispecialty teaching hospital for a period of one year. Totally, 130 subjects were recruited and an interview was conducted using a structured questionnaire to obtain demographic and risk factor data, including tissue marker status (ER, PR and HER-2) obtained from case files. Data were analyzed with SPSS-20 version. Results: The highest age group reported in this study was 51- 60 years which has a 3.8 times increased risk compared to other age and the age group of 31- 40 have a decrease risk of 0.33. In this study, the percentage of post menopause (68%) and mothers not breastfeeding (10%) was higher in cases compared to controls and a noted increase in the risk of breast cancer with odds ratio (OR) of 2.745 (p= <0.0001) and 9.08 (p=0.01) respectively. Duration of breastfeeding showed significantly (p=<0.0001)) moderate positive correlation (r=0.549, 0.457, 0.418 and 0.636) for luminal A, luminal B, HER+, and triple negative respectively. This study found that all the reproductive risk factors do not have correlation with a molecular subtype of breast cancer except breastfeeding. Post menopause and breastfeeding were common factors associated with all people and could be modifiable to prevent the occurrence of breast cancer through lifestyle changes.

Keywords: Reproductive risk factors. Breast cancer. Comorbidity. Hormone receptors. Tissuemarkers.

INTRODUCTION

According to a three year report of the Population-Based Cancer Registries by Indian Council Medical Research (ICMR 2012-2014), the foremost cancer types among females were breast (30.7%) and the respective Crude Rate and Age-Adjusted Rate of breast cancer per 100,000 populations were 40.6 and 37.9, respectively, in Chennai (Shreshtha, 2017). This report indicates that the incidence of breast cancer increased in the past two years and now contributes to nearly one of the most diagnosed cancers in this state of Tamilnadu. It has become very important to evaluate and review the risk factors in Indian women to ensure the awareness about cancer and preventive measures. The rationale behind the increasing incidence of cancer would be understood only by determining the risk factors associated with breast cancer, apart from age and family history.

Numerous studies show that reproductive factors like null parity, age at first child, menarche at the early age, breastfeeding and post-menopausal stage, were

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more closely causal to the development of breast cancer (Lakshmi, 2013). Prominent differences on these risk factors exist between countries in the incidence of breast cancer. However, only few studies were reported in the region of Tamilnadu.

Assessments of risk factors in relation to breast cancer classified by tumor subtypes based on tissue marker status have been inconsistent. Thus, to accurately estimate breast cancer risk, breast cancer cases should be divided according to the tissue marker status of a tumor, because of increased exposure to hormones that increase the propensity of either positive ER or PR or HER-2 breast cancer occurrence (Sisti, 2016). In India, many of these studies did not classify breast cancer cases by tissue marker status. Our aim is to review the reproductive risk factors and comorbidities and evaluate the association with tissue marker status of breast cancer patients

MATERIAL AND METHODS

A hospital-based analytical case-control study was conducted among the breast cancer cases with age-matched controls in Coimbatore district in Tamilnadu, India. There were 130 subjects in each of the cases and control groups. The study was conducted at the department of medical oncology, PSG Hospitals, Coimbatore, Tamilnadu, India attached to the PSG institutes of medical sciences and research (PSGIMSR). The study was completed over the period of one year from January 2015 to December 2015. As per previous reports, post menopause was considered as a risk factor (Mohite, 2015) was used for the calculation sample size. Therefore, the required number of controls was 130 and, thereby, a total of 260 individuals were included in the study.

All type of histopathologically confirmed cases of breast cancer, irrespective of their degree, between the age group 30 to 70 years, were included in the study as cases and age matched individuals (± 2 years) were designated as controls. Patients, who were not willing to participate in this study or those cases who were seriously ill and male breast cancer patients were excluded from the study.

Cases were selected by convenience sampling that had a pathologically confirmed breast cancer condition and were admitted for either breast cancer surgery or attended a chemotherapy cycle in the medical oncology ward of the hospital on a daily basis.

Participants for the control group were women without history of breast cancer or any neoplastic disease and were recruited from other departments of the same hospital or female bystanders of patients during the same period from the hospital. The study was conducted with ethical approval from Institutional ethics committee of the study hospital. After informing the purpose of the study to each of the study participants, a written informed consent was also obtained.

All recruited subjects participated in face-to-face interviews with trained interviewers using a structured questionnaire to obtain demographic and reproductive risk factor data, including age, BMI, medical and medication history, breast complaints, history of breast examination (self-examination, biopsy, and mammogram), age at menarche, menopausal status, oral contraceptives use, no of children, age at first full term delivery, total period of breast feeding, previous exposure to radiation, family history, and history of abortion.

The data on tissue marker status (ER, PR, and HER2) was obtained from pathological reports, which are found attached to case files. Based on the tissue marker status, the distribution of each subtype was as follows: luminal A type (ER+/PR+ status and HER2+), luminal B type (ER+/PR+ status and HER2-), HER2-overexpression (ER-, PR-, and HER2+), and triple negative (ER-, PR-, and HER2). Each of these factors was separately evaluated for the possibility of risk (OR) and correlation with each subtype of breast cancer according to the tissue marker status.

The data was analyzed with a statistical package for social sciences software (SPSS-20). The data is summarized in the form of tables. Odds ratio and Chi-square test were used to evaluate the significant factors associated with breast cancer with 95% confidence interval. Univariate Analysis with Pearson Correlation Coefficient was used to assess the association of risk factor and tissue marker status of breast cancer patients. A statistically significant level was considered as less than 0.05 using two tailed method wherever applicable.

RESULTS

A total of 260 participants were studied: 130 were cases and 130 were controls. All study participants were between the age group of 30 – 70 years, which has been described in [Table I]. The mean age was 51.4 and 49.7 years for the cases and controls, respectively. The

maximum cases (45.38%) belonged to the 51-60 age group and the lowest age of a patient with carcinoma of breast was found to be 30 years. About 80% of cases did not have any family history of carcinoma, but 20% of breast cancer patients had some kind of cancer history in their family.

Most of the cases and controls were from urban and rural areas of Coimbatore district, with a few of them from other districts of Tamilnadu. Maximum cases, as well as controls, were literate but not educated; they could write and read in their own language. Univariate conditional logistic regression analysis was done to evaluate the factors significantly associated with breast cancer. The distribution of cases and controls according to the presence of risk factors is represented in [Table II].

TABLE I - Age wise Distribution of Study Participants

Age in years	Cases N=130	Percentage	Controls N=130	Percentage	Odds Ratio
31-40	14	10.77	41	31.53	0.328*
41-50	40	30.77	38	29.23	0.431*
51-60	59	45.38	24	18.46	3.819***
61-70	16	12.31	25	19.23	1.852

TABLE II - Association of reproductive risk factor and breast cancer risk by odds ratio

Risk factors	Cases n (%) n=130	Controls n (%) n=130	Odds Ratio	P value
Age at menarche < 12 years > 12 years	16 (12) 109 (84)	16(12) 106(83)	0.972	0.546
Menopause status Post Pre	88(67.69) 36(27.69)	57 (43.84) 64(49.23)	2.745	<0.0001**
Age at menopause > 45 yrs < 45 yrs	15(17.05) 72(55.38)	12 (21.05) 42 ((73.68)	1.371	0.302
Oral contraceptives Yes No	15(12) 108(83)	6(5) 117(90)	2.708	0.033*
Abortion Never Ever	98(75) 30(23)	92(71) 15(12)	0.533	0.047*
No of Abortions One 2 or more	20(67) 2(7)	14(99) 1(1)	0.714	0.644

(continuing)

TABLE II - Association of reproductive risk factor and breast cancer risk by odds ratio

Risk factors	Cases n (%) n=130	Controls n (%) n=130	Odds Ratio	P value
Age at first child				
< 25 years	111(85)	89(67)	1.559	0.148
>25 years	16(9)	20(13)		
Birth				
Nulliparous	4(3.07)	7(5.38)	0.506	0.220
parity	123(94.62)	109(83.84)		
Breast feeding				
No	9 (10)	1(6)	9.802	0.012*
Yes	110(85)	111(86)		
Duration of breast feeding				
< 12 months	63(57)	44(40)	2.041	0.006*
> 12 months	47(35)	67(47)		
No of children				
One	13(10)	18(14)	0.597	0.128
Two or more	110 (55)	91(46)		
Body Mass Index				
Normal	56(42)	46(32)	1.643	0.105
Over weight	36(28)	18(14)	2.667	0.122
Obese	16(12)	3(2)		

*P **value is significant at the 0.01 level (2-tailed). * P value is significant at the 0.05 level (2-tailed).*

The proportion of women with history of age at menarche (by recall method) of more than 12 years was slightly higher in cases (n=109,84%) as compared to controls (n=106,83%) in this study and less than 12 years was equal in both cases (n=16,12%) and controls (n=16,12%) and these were not statistically significant (OR=0.972, P=0.55)

The percentage of post menopause was higher (n=88, 67.69%) in cases as matched to controls (n=57, 43.84%) and the risk of getting breast cancer was 2.745 (p=<0.0001) times higher for post-menopausal women as compared to premenopausal women. There was a statistically significant mean age of menopause of cases and controls, with cases attaining menopause at an early age (46.47+5.85 years) as compared to controls (47.6+ 5.64 years).

Hormone Receptor Tablets (HRT) or uses of Oral Contraceptive Pills (OCP) also plays important role in developing breast cancer. In this study, out of 130 patients, 12% (n=15) had a history of OCP use and the rest 83% (n=108) had not used any OCP in the past. The odds risk ratio of breast cancer among women who had used any type of OCP, as compared with those never used OCP was 2.07. The proportion of women not breastfeeding was significantly higher in cases (n=9, 10%) as compared to controls (n=1, 6%), and the strength of association between breastfeeding and breast cancer is reflected by the odds ratio of 9.08 (p= 0.01). Approximately, 3.07% (n=4) of cases and 5.38% (n=7) of controls were nulliparous. The age at birth of first child was not related to a risk of breast cancer.

In this study, 28% (n=36) of breast cancer patients were overweight and 12% (n=16) of control were obese and this shows a positive association with breast cancer risk with an OR of 1.55 and 2.66, respectively. Nearly, 23% (n=30) and 12% (n=15) of the cases and controls,

respectively, had a past history of abortion and no association with the risk (OR =0.5) of breast cancer.

In the control group, 95(73%) had comorbidities - the common co morbidity was hypertension (n=31, 33%). Among the 50 breast cancer patients (cases) who had comorbidities, a majority (n=31, 64%) had diabetes mellitus, which specified that the risk of getting breast cancer was 6.265 times higher while compare to control group. The next most common comorbidity (n=27, 54%) was hypertension. The least reported case was Cerebrovascular Accident (n=2, 4%). Table III shows the odds ratio of comorbidities among breast cancer.

The tissue markers status among breast cancer patients is illustrated in [Figure 1]. Tissue marker (Hormone receptor status and HER overexpression) status was available for 109 (84%) of the cases. 70 (64.22%) of the cases were estrogen positive and 39(35.77%) were negative and this was statistically significant ($p<0.0001$). Progesterone positive and negative cases observed in the study were 56 (51.38%) and 53 (48.62%), respectively. In this study, HER was over expressed in 55(50.45%) and was not expressed in 54(49.55%) cases.

The molecular subtypes of breast cancer patients are represented in Figure 2. In this study, 26.92% (n=35) of breast cancer patients were Luminal A, Luminal B (n=34, 26.15%), HER2 positive (n=21, 16.15%), and Triple negative (n=16, 12.31%).

In this study, the age at menarche showed a weak positive correlation ($r=0.198$) and significance ($p<0.01$) with luminal A, whereas, it showed moderate negative correlation ($r=-0.521$) and significance ($p<0.0001$) with HER+. Menopause status showed positive correlation ($r=0.155$) and significance ($p<0.001$) with luminal A, indicating an increase of risk with the increase of post-menopausal status, while no correlation was seen with other tissue markers.

Abortions showed no correlation with an increase in the risk of breast cancer. However, the number of abortions (2 or more) showed a negative correlation ($r=-0.671$) and significance ($p<0.001$), which indicated an increase of tissue marker status with the decrease in the number of abortions. Correlation of the ER/PR and HER 2 status of breast tumors among cases is shown in Table IV.

TABLE III - Association of comorbidities among breast cancer by Odds Ratio

Co morbidity		Cases (%) N=59	Controls (%) N=95	Odds Ratio (OR)	P value
DM		31(64)	21(22)	6.265	<0.0001**
HTN		27(54)	31(33)	2.424	0.01*
CVA		2(4)	10(11)	0.354	0.149
CVD		5	7(7)	1.164	0.515
RESPIRATORY	8	(8)	10(11)	1.333	0.373
THYROID	9	(8)	12(13)	0.601	0.291
OTHERS	16	(16)	7(7)	2.395	0.093

P **Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

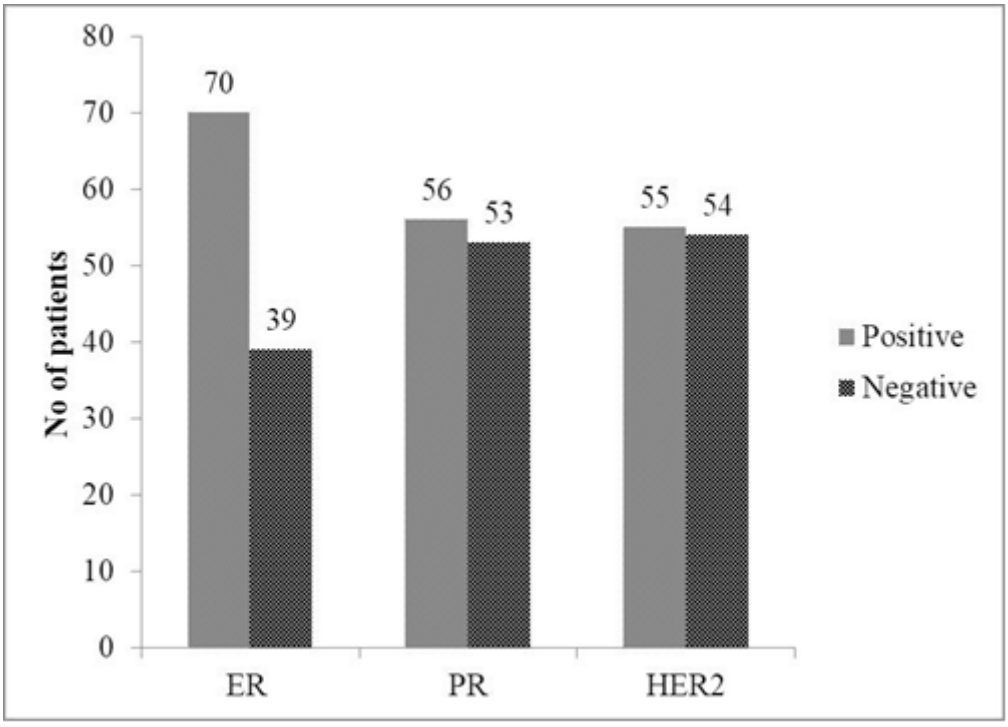

FIGURE 1 - Tissue Markers Status among Breast Cancer Patients
ER – estrogen receptor; PR- Progesterone Receptor; HER2 – Human Epidermal growth factor.

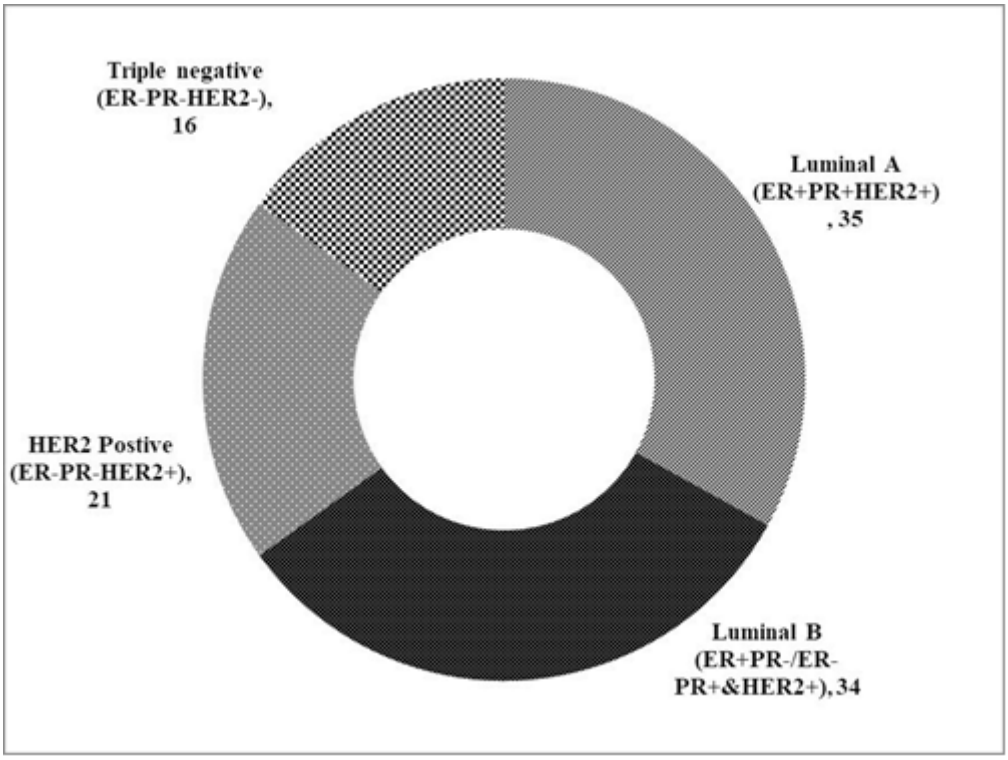

FIGURE 2 - Molecular Subtypes of Breast Cancer Patients
ER – estrogen receptor; PR- Progesterone Receptor; HER2 – Human Epidermal growth factor.

TABLE IV - Correlation of reproductive risk factor with molecular subtypes of breast cancer

Risk factors Categories	Luminal A			Luminal B			HER+			Triple negative		
	n	r	p	n	r	p	n	r	p	n	r	p
Age at menarche												
< 12 years	5	0.28	0.02	6	-0.06	0.48	17	-0.55	0.00**	2	0.12	0.20
> 12 years	31			16			5			17		
Menopause status												
Post menopause	22	0.16	0.08	15	0.05	0.57	18	-0.08	0.37	14	-0.03	0.74
Pre menopause	15			7			5			5		
Age at menopause												
<45yrs	7	-0.03	0.79	3	-0.02	0.89	0	0.15	0.2	3	-0.15	0.23
>45yrs	15			10			24			7		
Oral contraceptives												
Yes	9	-0.16	0.06	3	0.03	0.72	3	0.03	0.72	2	0.05	0.57
No	28			21			21			17		
History of abortion												
Yes	24	-0.16	0.06	20	0.11	0.19	20	0.152	0.08	18	0.07	0.42
No	13			3			2			4		
No of Abortions												
One	8	0.24	0.28	2	-0.67	0.001*	4	0.15	0.51	1	0.07	0.76
2 or more	0			2		*	0			0		
Age at first child												
<25yrs	24	-0.01	0.96	16	-0.09	0.38	20	0.04	0.73	15	0.06	0.57
>25yrs	7			2			2			3		
Parity												
Nulliparous	2	-0.03	0.75	0	0.11	0.24	1	0.001	0.99	3	-0.19	0.02*
Parous	44			24			21			16		

(continuing)

Breast feeding

TABLE IV - Correlation of reproductive risk factor with molecular subtypes of breast cancer

Risk factors Categories	Luminal A			Luminal B			HER+			Triple negative		
	n	r	p	n	r	p	n	r	p	n	r	p
Yes	2	0.02	0.81	0	-0.11	0.23	0	-0.11	0.24	2	0.13	0.15
No	24			24			21			15		
Duration of breast feeding												
<12 months	19	0.55	0.00**	17	0.46	0.00**	16	0.42	0.001*	8	0.64	0.00**
>12 months	15			7			5		*	7		
No of children												
One	4	0.004	0.97	2	0.14	0.2	0	0.101	0.35	3	-0.26	0.01**
Two or more	30			22			21			13		

n = Number of patients; r= Pearson co efficient; (-) indicate negative;
P **Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

In this study, the use of oral contraceptives indicated no significance to any of the tissue markers and partly showed negative correlation (r=- 0.194) and significance (p=0.027) with triple negative tissue marker. Breastfeeding showed no relation, whereas, duration of breastfeeding showed moderate positive correlation (r=0.549, 0.457, 0.418, and 0.636) for luminal A, luminal B, HER+, and triple negative, respectively. The significance of duration of breastfeeding to these tissue markers was seen (p<0.000, 0.000, 0.001, and 0.000) for luminal A, luminal B, HER+, and triple negative, respectively.

DISCUSSION

Totally, 260 (cases and controls) questionnaire forms were analyzed to assess the reproductive risk factor and 130 breast cancer patient's tissue marker status was correlated. A recent study reported that breast cancer incidence in India was approximately twice as high in urban women as compared to rural women because of urbanization factors. (Shreshtha, 2017).

The incidence is more above the age of 40 years, contributing to nearly 69% of the cancer patients reported in this study. Previous study reviews show that the occurrence of cancer is increased above the age of 40 years and the data from the registry shows that as age advances, the incidence of ancer also increases. As per the NCI statement, advancing age is the progressing key factor for many individual cancer types because of changes in the gene material (Ershler, 1997).

The results of our study show that the odds of BC were not associated with age at menarche, which was not in agreement to the earlier studies reported in Indian population. This is in accordance to a study by Aich *et al*., (2016), which also reported no significance in the age at menarche, but a higher chance of having breast cancer in late menopause (>50) years than earlier ones (OR=1.7). However, previous studies conducted in Northeast Brazil have revealed a positive association between early menarche and BC risk. According to the epidemiological studies, ovulatory menstrual cycles may have protective effect on BC. Many studies revealed conflicting trends regarding the association between

dysfunctional ovulatory cycles and BC risk (Augustin, 2017). Previous research data strongly support that the odds of developing breast cancer in postmenopausal women were more than pre-menopausal women (OR=1.2). This was similar to the result of this study that showed post-menopausal women to be at a higher risk (OR=2.745). Another recent report states that late age of menopause was an added risk factor due to prolonged duration of exposure to estrogen and progesterone (Thakur, *et al.*, 2017). The reason may be that many other elements like obesity; hormone therapy, and physical inactivity could influence the risk of getting breast cancer through hormonal systems during the postmenopausal period.

In pooled analysis, the relative risk of BC among women, who had the history of using oral contraceptives, compared with those women who had never used them, was 1.94. Our study found a relative risk of 2.07. Another study (Ursin *et al.*, 1998) revealed that when compared to those young women that never use OCP, those young women that used OCP for 12 or more years were associated with a small non-significant elevated BC risk. From these, it could be reasoned that the relation of oral contraceptives to BC poses small relative risk.

Unmarried (nulliparous) status is not that prevalent in Indian culture; the majority (97%) of women, who developed BC, was married in this study. Previous studies have suggested that nulliparous women have 8 times higher risk of getting BC compared to married women who have protective effect through pregnancy and breast feeding due to changes of mammary tissue, reduction of prolactin levels, and hormonal changes i.e. high levels of estrogen and progesterone (Russo *et al.*, 2005).

We did not find any statistically significant difference between case and control groups with respect to age at delivery of first child, however, this study results shows that an age of less than 25 years at first child delivery had the risk (OR = 1.78) compared to other age groups. These findings are similar to a study from Iran that concluded that younger age and number of pregnancies were risk factors for BC. (Mohammad *et al.*, 2011).

In this study, there was no increased risk of BC associated with the previous history of abortion, which is similar to the study done by Antony *et al.* (2018), which concluded that abortion did not emerge as a risk factor for the development of carcinoma of the breast. However, in studies by Balasubramanian *et al.* (2013), it was found that women who had a history of abortion have twice the risk than those did not have the history of abortion. Other studies indicate that induced abortion increased the risk of developing breast cancer because abortion leaves the breast epithelium in a proliferative state with an increased susceptibility to carcinogenesis (Kapil *et al.*, 2014). Our study findings are similar to the studies by Aich *et al.* (2016), which reported that chances of having breast cancer was higher among women who had not breastfed their children with OR of 1.4 and $p<0.01$, thereby, indicating breastfeeding as a protective factor. Breast feeding may slightly lower the risk of breast cancer, especially if continued for 1.5–2 years; probably by reducing the woman's total number of lifetime menstrual cycles. Various pathophysiological mechanisms such as decreased frequency and intensity of ovulation, thus maintaining the consistent lower level of estrogen; mobilization of endogenous carcinogens from the ductal and lobular epithelial cell environment; and facilitating the excretion of organ chlorides (xenoestrogens), are suggested as having the same carcinogenic potential as estrogen as explained by Helewa *et al.* (2002).

This study found that obesity had a high risk of developing breast cancer with an OR of 1.926, while underweight, normal, and overweight showed no significance. This finding was consistent with results of Mathew *et al.* (2008), which demonstrated that the risk of BC in obese women was higher than women with normal BMI because obesity can increase levels of circulating endogenous sex hormones, insulin, and insulin like growth factors that altogether increases risk. Some studies have found that higher BMI increases the risk of BC during menopause, but it decreases during premenopausal period (Bibi, 2017).

Comorbidities assessment in this study showed an OR of 6.265 for diabetes, indicating this as a high-risk factor and which agrees with a meta-analysis done by Boyle *et al.* (2012). The meta-analysis found a significant increased risk of breast cancer among women with diabetes. In another meta-analysis study by Shichong *et al.* (2011), the summary relative risk (SRR) for breast cancer in women with diabetes was 1.27 and they concluded that the risk of breast cancer in type 2 DM increased by 27%.

Several risk factors related to endogenous hormone exposure showed expected patterns of association with ER+PR+ but not with ER+PR- or ER-PR- breast cancers and Human epidermal growth

factor tissue marker-2 (HER 2). HER 2, one of a family of four membrane tyrosine kinases, was found to be amplified in a human breast cancer (Rulla 2012). Only a few of the risk factors like age at menarche, age at menopause, history of abortion, breast feeding, and BMI revealed significant correlation with molecular subtypes of breast cancer in this study. It may be due to the small sample size and lack of information about tissue marker status among breast cancer patients. Duration of breast feeding was the only one risk factor that shows a significantly positive correlation in this study to all sub types of breast cancer. This result differs from a previous study because the investigators stated they could not find any statistically significant association between breast cancer and ER tumors and concluded that no strong results were observed with respect to breast cancer sub groups. Similar studies by (Salma, 2014) hypothesized that the reproductive factor those are protective, also promote tumors that are non-hormone dependent and hence tumors that grow are more autonomous.

Similar to our study, previous studies observed that age at menarche were positively associated with hormone receptor positive tumor because of a rapid growth of breast tissue epithelium and especially the duration between puberty and first birth, that are more prone to damage from environmental carcinogens (Graham, 2004).

As reported by Lena *et al.* (2006), women who gained weight >30 kg during adulthood, had a 3 fold increased risk of ER+PR+ tumors (OR=2.7) but no risk of ER-PR-tumors (OR=1.0; p=0.064), which was similar to our study that BMI had the positive correlation with Luminal A i.e. ER+PR+HER+. Many study reports have not showed any differences between BMI of Luminal A, B, HER 2 over expression and triple negative breast cancer.

Previous history of abortions shows the weak negative correlation with Luminal B and this means that an increased amount of abortion has lesser exposure to the HER expression ER+PR-/ER-PR+. In contrast to our study, no distinct association was noted between the number of abortions and HR positive and HR negative tumor in a study done by Xiaoqing *et al.* (2007). The contrasting result of this study may be due to the inclusion of younger breast cancer patients, i.e. less than 35 years.

Parity was not related to any specific hormone receptor status as proposed previously by Salma *et al.* (2014) and consistent with another study, which could not find any statistically significant relation between the risk of triple negative tumors. In accordance with this study, nulliparous has not been associated with increased risk of breast cancer and as being more vulnerable to stimulating factors leading to more aggressive tumors.

The present study may conclude that the reproductive risk factors for breast cancer in our population deviated from previous studies, except for post menopause and breastfeeding. Apart from these factors, the study found that use of OCPs, age at first child (<25 years), and obesity are associated with a risk of breast cancer. Post menopause and breastfeeding were common to all people and could be modifiable to prevent the occurrence of breast cancer through lifestyle changes. This study also states that the women during postmenopausal period need to concentrate on many other elements like obesity, hormone therapy, and physical inactivity, which influence the risk of getting breast cancer.

The study also suggests creating awareness to the mother about the importance and duration period of breastfeeding to avoid breast cancer. Diabetes Mellitus, followed by hypertension, have strong association with increased risk of breast cancer, which insists the necessity of changing the current lifestyle scenario to reduce the incidence of breast cancer.

This study results confirm that the reproductive risk factors do not have correlation with the molecular subtype of breast cancer, except breastfeeding. However, the risk factors might have a role in breast cancer pathogenesis by way of hormones receptors (HR) and epidermal growth factor (HER2) and it has to show a correlation with molecular subtypes of breast cancer. Previous studies reports were inconsistent in this aspect and future studies need to address this problem with a larger population.

Moreover, this study confirms that addressing risk factors of breast cancer in multiple subpopulations are desperately warranted in an Indian context. In future, studies must analyze the risk factors among different subpopulations in India.

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