Original Article:
Breast Cancer Risk Factors According to Menopausal Status

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Abstract: BACKGROUND: Breast cancer is the most common cancer worldwide. The incidence and mortality rate is increasing in developing countries as compare to developed countries. The aim of this study was to evaluate the breast cancer risk factors in premenopausal and post-menopausal women. METHODOLOGY: In the present study, two hundred breast cancer patients and one hundred age matched controls were taken to study breast cancer risk factors. The odd Ratio (ORs) at 95% confidence interval (CIs) was computed to study significance of risk factor on menopausal status. RESULTS: The mean age for menopause was 46.52±4.72 for breast cancer cases and 45.9±4.29 for control group was observed. The marital status, parity, age at menarche at =13 years was found to be associated with breast cancer risk in premenopausal age group. Early age at first full term pregnancy, number of children more than three and lactation duration of more than one year were observed to be protective factors in both pre and postmenopausal age groups A history of spontaneous abortion had no significant effect on the risk of breast cancer diagnosed before or after menopause. The positive association of breast cancer was observed for Height, weight and body mass index (BMI) in postmenopausal women. CONCLUSION: In conclusion, present results suggest that changes in reproductive pattern, menstruation and anthropometric measurements contribute to the risk of breast cancer in both pre and post-menopausal women. Further genetic and hormonal relationship based studies have been suggested using a large cohort.
Key Words: Breast carcinoma, Risk factors, Menopause, Life style

Introduction:
Breast carcinoma is the second most common malignancy and leading cause of death in women worldwide.(1) Breast cancer is heterogeneous in its clinical, genetic and biochemical profile and greatly influenced by the hormonal factors. The incidence rate of breast cancer is much lower in Asian countries as compare to western countries. According to recent trends, it has been estimated that breast cancer incidence is increasing in all regions of the world with majority of rise seen in developing countries.(2) The age-standardized incidence rate for breast cancer in India is one-third that of Western countries.(3)

The geographical variations in incidence and mortality rates of breast cancer suggest the possible variations in breast cancer risk factors in different parts of the world. (4) The possible risk factors for breast cancer include the person's age, family history of breast cancer, reproductive history, menstrual cycle, anthropometric measurements (height, weight etc.) and pregnancy history.(5,6)

Some factors are related to personal behaviors, such as smoking, drinking alcohol, being overweight or obese, using oral contraceptives, breastfeeding, hormone therapy after menopause and diet etc. (7) Amongst these factors, reproductive history and menopausal status plays an important role in breast cancer. The etiological factors might be different according to menopausal status. The breast cancer risk factors among pre and post menopausal status is of considerable interest. (8) The present study aimed to evaluate breast cancer risk factors in premenopausal and post menopausal women.

Material and Methods
Study subjects and data collection: This study was conducted on two hundred breast cancer patients of premenopausal and postmenopausal age group from PGIMS, Rohtak. One hundred female of about same age group were selected as control group with no history of breast cancer or any other neoplastic disease. Breast carcinoma patients and controls were categorized in different age groups from less than 40 years to greater than 60 years. A well-structured questionnaire was used to get the information on different breast cancer risk factors. The questionnaire included marital status, age, pregnancy, abortion and cancer history, pedigree, lactation duration, taking birth controlling pills, smoking, alcohol consumption and anthropometric measurements like height, weight etc. Written informed consent was obtained from all participants.
Statistical analysis: The data was statistically analyzed using Medcalc software and SPSS 11.0 software. Mean, standard deviation, odds ratio with 95% confidence level was calculated to study risk factors.

Results

Out of two hundred breast cancer patients, 71% patients were found to be postmenopausal and 29% women were premenopausal. Sixty percent postmenopausal and 40% premenopausal women were observed in one hundred control groups. Mean age of premenopausal patients was 37.56±9.6 and of postmenopausal breast cancer patients was 54.5±6.8. The mean age of premenopausal age group controls was 36.9±6.8 and of postmenopausal age group was 54.7±7.8. The mean age for menopause was 46.52±4.72 for cases and 45.9±4.29 for control group. The mean age for the onset of breast cancer was observed 47.55±10.8.

Maximum number of cases (34%) were in 40-49 age group and only few cases (14%) were in age group <40 years. Maximum number of controls (37%) were in <40 years age group and only 17% were in >60 years age group. About 76% cases and 35% controls were found to be illiterate as most of the cases (66%) and controls (60%) were from rural background. About 5% breast cancer cases were found with family history of breast cancer (Table 1). Effect of family history on breast cancer was greater in first degree relatives. However, no consanguinity was observed in the present study.

Table 1: Distribution of cases and controls according to socio-demographical variables.

Characteristic	Cases (%) n=200	Controls (%) n=100
Age groups (years)		
<40	14	37
40-49	24	25
50-59	34	21
> 60	28	17
Education level		
No education	76	35
Less than high school	14	27
High school to intermediate	6	23
College	4	15
Place of residence		
Rural	66	60
Urban	34	40
Menopausal status		
Premenopausal	29	40
Postmenopausal	71	60
Family history		
Premenopausal	5	2
Postmenopausal	4	2

Reproductive risk factors: The association of reproductive risk factors for breast cancer according to menopausal status is shown in Table 2. The premenopausal women were associated with high risk of breast cancer with unmarried status and age at menarche below thirteen years. An inverse association was observed for null parity and postmenopausal breast cancer. Late age at first full term pregnancy was found significant in both subgroups (premenopausal and postmenopausal) ($p<0.05$).

Protective effect of increased number of births was observed for postmenopausal women. No association was observed for abortion history and age at first abortion in both subgroups. Breast feeding was noted to be more protective in premenopausal women. Protective effect of more than one year of lactation duration was found significant in both pre and postmenopausal women. The use of birth controlling pills was not found to be significantly associated with breast cancer risk (Table 2).

Table 2: Odds ratio analysis of reproductive variables among pre and postmenopausal women.

	Premenopausal women Cases/Controls(n=55)/(n=32) OR 95%CI			Postmenopausal women Cases/Controls(n=145)/(n=68) OR 95%CI		
Marital status						
Married	60/81			79/85		
Unmarried	40/19	0.3462*	0.1225 to 0.9781	21/15	0.6609	0.3023 to 1.4450
Age at menarche (years)						
≤13	45/25			30/35		
>13	55/75	2.5000*	0.9570 to 6.5305	70/65	0.7729	0.4192 to 1.4251
Parity						
Parous	79/100			78/83		
Nulliparous	21/0	0.0667*	0.0036 to 1.2274	22/17	0.7500	0.3327 to 1.6906
Age at first birth (years)						
≤25	35/50	0.5294	0.1736 to 1.6149	17/25	0.6000	0.2547 to 1.4134
26-29	19/31	0.5357	0.1486 to 1.9316	28/40	0.5870	0.2801 to 1.2303
>29	46/19	3.6000*	1.0384 to 12.4813	55/35	2.2794*	1.1062 to 4.6971
Number of births						
1	27/19	1.5474	0.4197 to 5.7045	34/25	1.5763	0.7191 to 3.4551
2	35/38	0.8471	0.2736 to 2.6224	47/31	1.9250	0.9207 to 4.0249
3+	38/43	0.8523	0.2812 to 2.5832	19/44	0.2994**	0.1377 to 0.6512
Abortion History						
Yes	57/35			33/25		
No	43/65	2.5758	0.8390 to 7.9076	67/75	1.5000	0.6830 to 3.2943
Age at first abortion (years)						
≤25	60/56	1.0565	0.3208 to 3.4800	50/67	0.8654	0.3480 to 2.1520
26-29	40/33	1.1837	0.2749 to 5.0970	40/33	1.4436	0.4479 to 4.6524
>29	0/11	0.1892	0.0075 to 4.7845	10/0	3.3649	0.1714 to 66.0639
Breast feeding						
Yes	38/77			72/79		
No	62/23	0.1875*	0.0561 to 0.6268	28/21	0.6842	0.2967 to 1.5777
Lactation duration (months)						
1-5	40/45	0.8718	0.3085 to 2.4636	39/26	1.7500	0.7272 to 4.2111
6-11	20/45	0.4318	0.1108 to 1.6824	46/32	1.8571	0.8017 to 4.3021
12+	40/10	2.6667*	1.0900 to 6.5237	15/42	0.2500**	0.0984 to 0.6349
Use of birth controlling pills						
Yes	16/6			14/10		
No	84/94	2.9348	0.5927 to 14.5325	86/90	1.3943	0.5592 to 3.4762
*p<0.05 **P<0.001; note: data are given a percentage						

Anthropometric measurements and lifestyle related factors: The positive association of breast cancer was observed for Height, weight and body mass index (BMI) in postmenopausal women. Obesity was clearly confined to post menopause and hence to the breast cancer risk. Cigarette or

tobacco smoke was not found to be associated with breast cancer risk as there were only few women who used to do smoke. No women in this study reported to have alcohol drinks (Table 3).

Table 3: Odds ratio analysis of anthropometric measurements and life style relates factors among pre and postmenopausal women						
	Premenopausal women Cases/Controls(n=55)/(n=32) OR 95%CI			Postmenopausal women Cases/Controls(n=145)/(n=68) OR 95%CI		
Height(Inches)						
<62	25/25	1.0244	0.3753 to 2.7962	17/21	0.8036	0.3877 to 1.6656
62-66	53/63	0.6692	0.2748 to 1.6300	52/37	1.8429*	1.0207 to 3.3273
>66	22/12	1.9535	0.5723 to 6.6675	31/42	0.6052	0.3336 to 1.0979
Weight (Kg)						
<55	33/44	0.6255	0.2550 to 1.5342	41/44	0.8690	0.4855 to 1.5554
55-65	45/31	1.8333	0.7330 to 4.5856	21/32	0.5686	0.2984 to 1.0835
>65	22/25	0.8372	0.3005 to 2.3324	38/24	1.9861*	1.0337 to 3.8162
BMI#						
<20	27/28	0.9583	0.3623 to 2.5347	29/28	1.0161	0.8308 to 1.2426
20-25	53/41	1.6302	0.6748 to 3.9381	21/37	0.7494*	0.5782 to 0.9714
26+	20/31	0.5500	0.2028 to 1.4916	50/35	1.2125*	1.0104 to 1.4551
Smoking						
Yes	22/13			15/12		
No	78/87	1.9535	0.5723 to 6.6675	85/88	1.2702	0.5318 to 3.0339
Alcohol consumption						
Yes	0/0			0/0		
No	100/100	0.5856	0.0113 to 30.2256	100/100	0.4708	0.0092 to 23.9787
*p<0.05 **P<0.001; # BMI calculated by using formula=weight (kg)/height (m2); note: data are given as percentage						

Discussion

Breast cancer incidence and mortality rates are increasing worldwide. There is a need to understand the risk factors of the disease to develop different strategies for prevention. Menopausal age is an important risk factor of breast cancer. The risk of the breast cancer increases with increase in age of person. In the present study, maximum numbers of cases were observed in 40-49 years (30%) followed by 50 –59 years (28%), >60 years (26%) and 16% cases belonged to <40 years age group similar to other studies. (9) The average age of occurrence of breast cancer was observed 47.55 ±10.8 in contrast to US female which were reported to have 61 years. (10)

The association of family history with breast cancer risk cannot be explained by characteristics like age at menopause, menarche, parity etc. Many studies have suggested that women with family history of disease are more likely to develop disease than those who have no family history at all.

(4,11) In the present study, 5% breast cancer cases were found with family history of breast cancer. Colditz et al. (2000) reported breast cancer risk increased in patients who had first degree relative with breast cancer history. (11) Although development of breast cancer is proved to be the result of combined effect of many factors like genetic, environmental etc. however, its actual mechanism is not yet clear.

In the present study positive association between reproductive variables and breast cancer risk was noted in both pre and postmenopausal women similar to many other studies. (6, 7, 11) The reproductive factors are mainly related with hormonal changes which affect breast tissue proliferation. (12) In the present study, significant association between single status and breast cancer risk was observed in premenopausal women similar to other studies. (6,9) The unmarried women were at higher risk for breast cancer development as compared to married women.

In the present study it has been noted that there is a high risk of breast cancer in premenopausal women having menarche before the age of thirteen consistent with other studies. (7,12) These studies also observed decrease in breast cancer risk by 9% for each additional year in age at menarche. The possible mechanism for this may be prolonged exposure of breast epithelium to estrogen produced by regular ovulatory cycle. In addition, some studies have also demonstrated that women with early menarche have higher estrogen levels than women with later menarche for several years after menarche.(13)

The risk of breast cancer was found to be significantly related with parity in premenopausal women. The negative association was observed between number of births and breast cancer risk in present study similar to other studies. (6,7) The protective effect of multiparity was greater in women diagnosed at postmenopausal stage similar to other studies. (12) The multiparity might cause a long-term protective effect against late breast cancers. Some authors proposed the hormone driven protective effects of parity. (14)

In the present study, it was observed that the women who had first full term delivery after 25 years of age were at higher risk of breast cancer than women who had first child before 25 years of age similar to other authors. (9) The effect of age at first full term delivery was similar in both pre and postmenopausal women. Some authors found relative risk of 5.4 times for women who had first full term pregnancy after 30 years. (7)

Some authors found inconclusive relationship between breast cancer and spontaneous abortion. (15) Spontaneous abortions result in the lack of differentiation of the breast cells that occurs at the end of full term pregnancy. The present study also evidenced no association between spontaneous abortions and breast cancer risk.

Breast-feeding is a common practice in India. The breast cancer risk was found to be more among nulliparous because of lack of breastfeeding practices. Many authors found protective effects of breast- feeding on breast cancer risk. (12,16) The protective effect of breast-feeding on breast cancer risk can be explained as breast-feeding maintains normal endocrine balance via modulation of ovarian or pituitary activity.

In the present study protective effect of lactation was found more in premenopausal women as compare to postmenopausal women consistent with other studies. (17) In this study it was reported that the risk of breast cancer was not significantly related to the use of oral contraceptive consistent with other results. (18) In contrast to the present study, some authors noted the risk was significantly increased among women who had stopped using oral contraceptives up to 10 years earlier of onset of breast cancer. (12)

Height has been associated with breast-cancer risk in many studies. (11,19) In the present study, the tall post-menopausal women were at high risk of breast cancer similar to other

studies. (17) It was proposed that the tall women have a greater mammary-gland mass, which could increase their risk of breast cancer. The association between weight gain and increased postmenopausal breast cancer has been shown in many studies. (20,21) In the present study, positive association between weight gain and postmenopausal breast cancer was found similar to other studies. (8,12)

The positive association between breast cancer risk and BMI has been observed in postmenopausal in the present study similar to others. (8) A slight negative association was also found in premenopausal women in some case-control studies. (8,12) It has been suggested that non ovulative cycles in obese premenopausal women may decreases the breast cancer risk. (22) In the present study no significant association was observed between smoking and breast cancer risk. In contrast Hirose et al. (1995) reported positive association of tobacco smoke with breast cancer risk. (17) They observed higher risk of breast cancer in young age smokers than those started at later age. The association was found significant for both pre and postmenopausal women. Several epidemiological studies have shown positive association between alcohol consumption and risk of breast cancer. (23) In the present study no breast cancer patient or women from control group was found to drink alcohol.

Conclusion

Breast cancer is a leading cause of mortality among women in both developed and developing countries. It is important to elucidate the risk factors for breast cancer in developing countries where incidence is at low level as compare to developed countries but is increasing rapidly. A majority of breast cancer cases are diagnosed in later stages because of ignorance of breast cancer detection in initial stages due to lack of awareness in developing countries. The present study focused on differences in breast cancer risk factors among pre menopausal and post menopausal women and provides evidence that breast cancer risk factors for premenopausal women are different from post menopausal women. Further studies should be aimed at genetic and hormonal relationship with menopausal status using a large cohort. These results could help in setting risk factors and helpful in raising awareness about screening for high risk women so as to diagnose the disease at initial stages and thus reduces mortality.

Conflict of interest: Nil

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