Breast Cancer Risk Factor Profile in Indian Women.

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***Abstract**: In India, the incidence of breast cancer is on the rise. However there is little data about the role of various known and/ or presumptive risk factors for breast cancer. This case-control study was conducted on 115 cases with diagnosed breast cancer and 127 controls. Socioeconomic, demographic, reproductive and other known risk factors were analyzed for their prevalence and odds ratio in the study population.*

Prevalence of risk factors determining endogenous or exogenous hormone exposure was low. However there was a statistically significant increased risk with reproductive risk factors such as : early menarche (<14 years vs >16 years, Odds ratio (O.R) 4.36, 95% confidence interval (CI) 108-10.1, p<0.001. chi square test), higher number of live births (<3vs >6, O.R 2.5 ; 95% CI, 1.0-5.7; p=0.026), higher number of abortions (>2 or nil, O.R 4.5; 95% CI, 2.2-9.0; p = <0.001) and duration of breast feeding 9<4vs => 10years, O.R 3.5 ; 95% CI 1.5-7.8; p = 0.006). Height (<145vs >161, O.R 3.0; CI 1.0-9.9; p=0.039), history of breast biopsy (0 vs > 1, O.R 4.6; CI 1.2-16.9; p= = 0.010) and higher mammographic density were found to be independent predictor of risk

(75% VS 0%, O.R 5.9). This study suggests that many known reproductive risk factors have an association with increased risk for breast cancer though their prevalence is low in our population. Breast therapy and mammographic density are independent predictors of risk and may become useful tools in breast cancer risk assessment.

***Keywords:** Breast cancer, Risk factors, Mammographic density, Indian women.*

INTRODUCTION

The risk factors for breast cancer in western populations have been extensively investigated, and it has been suggested that reproductive and life-style related factors are strongly associated with increased risk for breast cancer[1,2]. Various risk assessment models such as Gail, Clause, BRACPRO have been developed and validated in white women[3, 4]. They are used to recruit women for breast cancer screening protocols. However racial/ethnic differences exist in both prevalence as well as risks associated with particulars factors[5,6]. Many low or intermediate risk countries have studied risk factor profile of their populations and developed their own risk assessment protocols[7,8]. Not much data is available about the role of various risk factors for breast cancer in Indian women. A few earlier studies have reported the association of reproductive risk factors with increased risk for breast cancer[9-12]. In this study we examined the stratus of various known and presumptive risk factors for breast cancer and their relative risk in our population.

METHODS

This hospital based case control study was carried out during the period between April 2003 to March 2005 after approval from institutional review board; on 115 cases of histogically confirmed breast cancer; for the control females ≥ 35 years of age, without to the hospital with no complaints related to the breast or gynecological system, were included after an informed consent. Each control was examined in detail to exclude the presence of any breast lump and subjected to screening mammography to evaluate for in-situ lesions. Standardized structured questionnaire was used for the interview. The questionnaire was divided into sections comprising of demography, anthropometric measurements, reproductive history and established and potential risk factors for breast cancer. Mammographic density of the breasts of all controls and contra-lateral breast of breast cancer patients was measured by a qualified radiologist who was blinded to the identity of the subjects. Classification of densities using a six-category scale was done.[13] Demographic profile of cases and controls was compared. Prevalence of various risk factors in the study population was estimated and Chi square test was used to look for any significant difference in both the groups. Odds ratio for each risk factor were estimated with the help of univariate logistic regression analysis. Calculation of odds ratio for the risk factors assessed the relative value of each risk factor in the study population.

RESULTS

A total of 115 female patients with histologically confirmed breast cancer were compared with 123 controls. The maximum number of cases were in the age group of 35-44 years 939.1%), followed by 45-54 years (32.2%). Mean age of cases was 47.14 years and controls was 47.90 years. The most common histological type was infiltrating ductal carcinoma (92.1 %). Sixty eight present of cases presented at stage III or IV of breast cancer.

Socio-demographic data showed no difference in the literacy status between case and control group (58.5% of control and 49.6% of cases were illiterate). As regards religion72.9% of controls and 79.1% of cases were Hindus, 23.4% controls and 19.6% cases were Muslims and rest were Sikhs and Christians. Ninety six percent controls and 96.5% cases were married and over 85% in both groups were housewives. Awareness about breast cancer was recorded in 19.5% of controls and 16.5% of cases. Breast self examination was practiced by 4.8% of controls and 3.5% of cases.

Reproductive characterstics of the subjects (Table 1): mean age os menarchae in case group was 14.05 and control group was 14.85 years. Only 32.2% of cases and 14.6% of control subjects had early menarchae (<13years). Mean age at first live birth was 19.76 in study group and 18.69 in the control group. 67.8 % cases and 79.8% of control subjects had their first issue before the age of 20years. Mean number of live births in the study group were 3.63 and in control group were 4.26. Four control subjects and 3 cases were nulloparous. Majority in either group breast fed for 5-9 years. Mean value for the study group was 5.519 and control group was 7.159 years. As regards the difference between the age at first live birth and age at menarche (AGEFLB-AGEMEN) the mean was 6.2411 in the study group and 4.4958 years in control group. Study group also had

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a significantly higher number of abortions (Mean-1.12) compared to 0.52 in control group. Forty seven percent of cases were premenopausal and 35.7% were postmenopausal. Eight patients had undergo hysterectomy before menopause for benign indications.

Table 1: *Reproductive factors*

Reproductive factors	Cases		Controls		P value
	N	%	N	%	
Age at menarchae (Yrs)					
>=16	10	8.%	41	33.4	
14-15	68	59.1	64	54.0	<0.001(s)
<=13	37	32.2	18	14.6	
Age at the first live birth (Yrs)					
<=17	8	7.1	18	15.1	
18-21	83	74.1	88	74.0	(0.170 9NS)
>=22	21	18.8	13	10.9	
AGEFLB-AGMEN (yrs)					
0-3	17	15.2	52	43.7	
4-6	61	54.4	40	33.6	<0.001 9S)
>=7	34	30.4	27	22.7	
Number of live births					
>=6	18	15.8	25	20.3	
3-5	69	59.9	75	60.9	0.026 (S)
0-2	28	24.3	23	18.7	
Duration of breast feeding (yrs)					
=10					
5-9	14	12.2	30	24.4	
0-4	58	50.4	67	54.5	0.006 (S)
	43	37.4	26	21.1	
Number of abortions					
0	46	40.0	80	65.0	
1	30	26.1	28	22.8	<0.001 (S)
>=2	39	33.9	15	12.2	
Menopausal status					
Premenopausal	54	47	53	43.1	0.575
Postmenopausal	41	35.7	54	43.9	
Hysterectomy/Perimenopausal	20	17.3	16	13.0	

ANTHROPOMETRIC CHARACTERISTICS OF THE SUBJECTS

Mean height of the study group was 155.67 cm and control group was 154.01 cm (p = 0.039). There was no significant difference in the BMI of either group. Mean BMI of case group was 22.800 kg/m^2 and 22.368 kg/m^2 for the control group. BMI when considered separately for pre-menopausal and postmenopausal women was also not different.

Other known risk factors: History of breast cancer in the family was present in 3 patients but in none in the controls. None of the subjects in either group had history of ovarian or endometrial cancer in the family. Fourteen patients and six controls reported use of oral contraceptive pills (OCP) and one patient hormone replacement therapy 9HRT). Majority of subjects were pure vegetarian. None of the subjects in either group consumed alcohol. None had history of ionizing radiation. Three (2.4%) subjects in control group and twelve (10.4%) patients in the case group gave history of previous breast biopsy and the difference was significant.

Mammographic density patterns: (Table 2 & 3): There was no significant difference in distribution of subjects in the two groups according to the percent breast density seen on mammograms. We reanalyzed both the groups after dividing the study population in two age groups, based on the mean age at menopause for both the groups combined. The difference in mammographic density between the two groups was found to be significant in younger women (Subjects M=47 years of age)

Odds ratio for various risk factors: Table IV shows the results of univariate logistic regression analysis. We found that women who had menarche at 13 years years of age had 3.42 times risk compared to women who had menarhcae at 16 years and above. Women with first live birth at 22 years of age and later had 3.6 fold increase in risk of breast cancer as compared to a women with first live birth at 17 years and earlier. The risk of breast cancer rose to 3.8 times when the interval between age at first live birth and menarche was more than 7 years relative to an interval less than 0-3 years. Women with three live births had a 2.5 fold risk of breast cancer compared to women who gave birth to six or more children. Breast feeding of four or less years exposed women to 3.5 fold risk breast cancer compared to women who breast fed for ten or more years. Women with two or more abortions had a 4.5 fold risk of breast cancer as compared to women with no history of abortions. Women with height >=161 cm had a 3.1 times risk of breast cancer as compared to a woman with height <=145 cm. women who consumed non vegetarian food at least once a week were 2.8 timely more likely to develop breast cancer as compared to women who were pure vegetarians. Women with one or more previous breast biopsy had 4.7 times risk breast cancer compared to women with no breast biopsy. Women with breast density of 75% or more, the breast cancer risk rose to 5.9 fold as compared to women with breast density 0%.

Table 2*: Distribution according to mammographic density (%) for age group <=47 years*

Mammographic density (%)	Case group		Control group		Total
	N	%	N	%	N
0	1	2.0	10	14.7	11
0-<10	10	20.4	17	25.0	27
10-<25	8	16.3	10	14.7	18
25-<50	8	16.3	17	25.0	25
20-<75	13	26.5	9	13.2	22
>=75	9	18.4	5	7.3	14
Total	49	100	68	100	117

Chi square value 11.735, p value 0.039 (significant)

Table 3: distribution according to mammographic density (%) for age gropu >47 years

Mammographic density (%)	Case group		Control group		Total
	N	%	N	%	N
0	9	17.3	17	30.9	26
0-<10	18	34.6	16	29.1	34
10-<25	12	23.0	11	20.0	23
25-<50	8	15.4	5	9.1	13
50-<75	3	5.8	6	10.9	9
>=75	2	3.8	0	0	2
Total	55	100	52	100	107

Chi square value 6.236, p value 0.284

Table 4: *Results of univariate logistic regression analysis for all the factors combined*

Risk factors	Beta	Odd ratio	CI of odds ratio	Significance
Age at menarchae 9Yrs)				
=16	1.470	1.000	1.879-10.063	0.001 S
15	1.474	2.348	1.870-10.185	0.001 s
14	2.132	2.365	3.455-20.557	<0.001 s
<=13		3.428		
Age at the first live birth 9Yrs)		1.000		
1-17	0.425	1.530	0.543-4.311	0.421
18	0.742	2.100	0.789-5.591	0.138
19	0.855	2.352	0.850-6.507	0.009
20	1.121	3.068	0.982-9.591	0.054
21	1.291	3.635	1.231-10.731	0.019 S
>=21				
AGEFLB-AGMEN (Yrs)		1.000		
0-3	1.172	3.229	1.386-7.523	0.007 S
4	1.668	3.302	2.292-12.267	<0.001 S
5	1.945	3.492	2.463-19.848	<0.001 S
6	1.349	3.852	1.829-8.114	<0.001 S
>=7				
Number of live births				
>=6		1.000		
5	-0.445	0.641	0.257-1.599	0.340
4	0.113	1.120	0.502-2.500	0.782
3	0.904	2.469	1.069-5.702	0.034 S
0-2	0.525	1.691	0.745-3.836	0.209
Duration of breast feeding (Yrs)				
>=10		1.000		
5-9	0.618	1.855	0.898-3.831	0.095
0-4	1.265	3.544	1.593-7.885	0.002
Number of abortions				
0		1.000		0.053
1	0.622	1.863	0.993-3.498	<0.001 S
>=2	1.509	4.522	2.252-90.80	
Height (cm)				
<=145	0.020	1.000	0.371-2.804	0.968
146-150	-0.210	1.021	0.311-2.109	0.667
151-155		0.810	0.384-2.410	0.934

DISCUSSION

In contrast to a high prevalence of various reproductive factors in women in the west[1,2] we found a low prevalence in our study. Almost similar trend has been in other reports from India as well. In our study, only 32.2% patients and 14.6 % of cases had menarche below 13 years of age. The means age of menarche in our and other studies had been reported to be around 14 to 14.5 years[9, 10]. in our study the average age at first live birth was 19.76 years in cases and 18.69 in controls. First live birth before 20 years of age was seen in 67.8% of cases and 79.8 % of controls respectively. Other studies to report an average age at first live birth as 19.5-20.5 years [9-11]. Mean number of live births in our study were 3.63 and 4.26 in cases and controls respectively. Only four controls and 3 cases were nulliparous. An average parity of 3-5 has been reported in other studies as well.[10, 11] however the difference in number of live births in cases and control was statistically significant in our study as well as other studies. In our study majority in either group (i.e. 50.4% cases and 54.5% of controls) breast fed for 5-9 years. Other studies too report a high rate of breast feeding practice in Indian women[10-12]. Thus it can be seen that though some reproductive factors are significantly more prevalent in breast cancer patients compared to controls, but their overall prevalence is much lower in Indian women than women in the west. In our study only few patients underwent breast biopsy before the onset of illness. (2.4% in the control group and 10.4% in the case group). The difference was found to be statistically significant. Women with one or more biopsy had 4.7 times risk of breast cancer compared to women with no biopsy. However a large proportion of Indian women do not have access to hospitals with facilities for breast biopsy. Illiteracy and poverty further add to the problem. In our population a history of lumpiness instead of history of biopsy should be given some place in risk assessment.

Percent breast density is an expression of the mammary gland mass as a fraction of the total breast area, and thus presumably the total number of breast cells at risk for malignant transformation. There is a significant positive relationship between dense mammographic patterns and subsequent risk of breast cancer and the association has been particularly strong when the exposure is defined as % breast density[14]. In our study we found that the premenopausal women with breast density of 0%. Thus the highest category of percent density was found to exceed the Odds ration of most other risk factors in the study population. In a multiethnic case control study it was found that women with breast density of more than 50% had 3.6 times higher risk of breast cancer than women with less than 10% density, but the risk varied with ethnicity. Whereas the odds ratio was 5.3 for Caucasians and 4.2 for Native Hawaiians, it was only 3.2 for women of Japanese ancestry[15]. In other studies, it was seen that risk associated with dense patterns persisted for 8 years ad was greater in younger women than older women[16, 17]. Thus knowledge of a woman's breast density might be useful in determining the indication for screening.

Limitations of our study are that size of the study population is small and we were not able to do multivariate logistic regression analysis. However our study has identified mammographic density as an important risk factor which has not been investigated in Indian women in any other study so far. Benign breast biopsy and mammographic density need to be evaluated in larger studies for their potential role in risk assessment for breast cancer.

REFERENCES

1. ***Madigan M, Ziegler R, Benichon C et al.*** *proportion of breast cancer cases in the United States explained by well established risk factors. J natl cancer Inst 1995; 87:1681.*
2. ***Rockhill B, Weinberg CR, Newman B.*** *Population attributable fraction estimation for establish. Am J Epidemiol 1998; 147:826-33.*
3. ***Rockhill B, Spiegelman D, Byrne c, et al.*** *validation of gail et al model of breast cancer risk prediction and implication for chemoprevention. J natl cancer Inst 2001; 93:358-66.*
4. ***Berry Da, Ivarsen Es, Gudbjartsson DF, et al.*** *BRCAPRO validation, sensitivity of genetic testing of BRCA 1/BRCA 2 and prevalence of other breast cancer susceptibility genes. J Clin Oncol 2002; 20:2701-12.*
5. ***Chlebowski RT, Chen Z, Anderson GL.*** *Ethnicity and breast cancer: Factors influencing differences in Incidence and outcome, JNCI 2005; 97; 439-448.*
6. ***Hall IJ, Moorman PG, Millikan RC, Newman B.*** *Comparative analysis of breast cancer risk factors among African-American and white women. Am J Epidemiol 2005; 161: 40-51.*
7. ***Ng EH, Gao F, Ji CY, Ho GH, Soo KC.*** *Risk factors for breast carcinoma in Singaporean Chinese women: the role of central obesity. Cancer 1997; 80:725.31.*
8. ***Wu GH, Chen LS, Chang KJ et al.*** *Evolution of breast cancer screening in countries with intermediate and increasing incidence of breast cancer. J med screen 2006;13:23-7.*
9. ***Rao DN, Ganesh B, Desai PB.*** *Role of reproductive factors in breast cancer in a low risk area: a case control study. Br J cancer 1994; 70:129-32.*
10. ***Gajalakshmi CK, Shanta V, Swaminathan R, Sankaranarayan R, Black RJ.*** *A population – based survival study on female breast cancer in Madras, India. Br J cancer 1997; 75:771-5.*
11. ***Gupta P, Sharma RG, Verma M.*** *Review of breast cancer cases in Jaipur region. J Indian Med assoc. 2002; 100:282-3.*
12. ***Pakseresht S, Ingle GK, Bahadur AK, Ramteke VK. Singh MM, Garg S, Agarawal PN.*** *Risk Factors with breast cancer among women in Delhi. Indian J cancer. 2009; 46:132-8.*
13. ***Boyd NF, Jensen HM, Cooke G, Lee Han H.*** *Relationship between mammographic density and histologic risk factors for breast cancer. J Natl Cancer Inst 1992; 84:1170-79.*
14. ***Oza AM, Boyd NF.*** *Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol rev 1993; 15:196-208.*
15. ***Maskarinec G, Pagano I, Lurie G, Wilkens LR, Kolonel LN.*** *Mammographic density and breast cancer risk. Am J Epidemol 2005; 162:743-52.*
16. ***Boyd NF, Go H, Martin LJ, et al.*** *Mammographic density and the risk and detection of breast cancer. N Engl J med 2007; 356:227-36.*
17. ***Kelemen LE, Pankratz VS, Sellers TA, Brandt KR, Wang A, Janney C et al.*** *Age specific trends in mammographic density: The Minnesota breast cancer family study. Am J Epidemiol 2008; 167: 1027-36.*