Original article

Reproductive risk factors and Breast cancer: a case control study from rural India

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Abstract:

Background: Breast cancer is the most common type of cancer in women and is influenced by reproductive factors perceived by women worldwide. *Aims:* To identify the reproductive risk factors of breast cancer in newly diagnosed cases and to find out the strength of association of the risk factors with the breast cancer. Material and Methods: A hospital based case-control study was conducted in Satara district, India during year 2009 to 2011 among newly diagnosed cases of breast cancer and matched controls. A total of 434 participants including 217 cases and 217 controls were enrolled by purposive sampling technique from selected hospitals of study area. The information was collected by employing pre-tested questionnaire by utilizing interview method. *Statistical Analysis used:* Descriptive statistics, Odds ratio and Chi-square test was used to find out strength of association and statistical significant difference. *Results:* Highest proportion [31.80%] breast cancer cases was in age group 40-49 years with lowest age of 25 years at diagnosis of the disease. A very high proportion of both cases [88.02%] and controls [67.28%] were Hindu by religion and were from rural residence. Maximum proportion of breast cancer cases were housewives [63.59%], literate [71.42%] and from upper economic class [56.68%]. The proportions of cases were higher as compared to the controls with respect to risk factors like unmarried status, nulliparity, history of abortion, post menopausal status, absence of breast feeding and the history of exposure to hormonal contraceptives. The risk of getting breast cancer as indicated by Odds ratio was 8 times higher in unmarried women, 2.8 times in nulliparous women, 2.4 times with post menopausal status, 10.4 times with absence of breast feeding, 1.5 times with exposure to hormonal contraceptives and 4.5 times with history of ovarian disease respectively. *Conclusion:* The reproductive risk factors such as unmarried status of women, nulliparity, menopause, absence of breast feeding, history of ovarian disease and use of contraceptives were strongly associated with breast cancer.

Keywords: breast cancer; reproductive risk factors; Odds ratio

Introduction:

Breast cancer is the most common type of cancer in women worldwide. It is reflected as an important public health problem for adult women residing in developing countries like India.[1] Breast cancer alone accounts for 16% of all female cancers [2,3] with 14% mortality, of which about half of the cases and 60% deaths are estimated to occur in economically developing countries.[4] It is estimated that by 2030 the global burden of breast cancer will increase to over 2 million new cases per year.[5]

The age incidence rate of breast cancer in urban Indian women has been 25 to 30 per 100,000 women per year. The average increase in breast cancer cases over a period of last 30 year in Mumbai was 11% per decade. Breast cancer is increasing both in young under the age 40 yrs [11%/ decade] and old women above the age of 40 yrs [16 %/ decade]. There are an estimated 100,000 to125, 000 new breast cancer cases detected in India every year and this number of breast cancer cases in India is estimated to double by 2025.[6]

The factors that contribute to the international variation in incidence rates of breast cancer largely stem from differences in reproductive and hormonal factors and the availability of early detection services. Reproductive factors which increase the risk of breast cancer include menopausal status of women,

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nulli-parity, use of postmenopausal hormone therapy, oral contraceptives, failure of breast feeding, late age at first birth etc.[7] Epidemiological studies have shown that the incidence of breast cancer has increased in developing countries; however there is limited data about the reproductive risk factors related to breast cancer in these countries.[8]

Satara is one of the district in the state of Maharashtra, India where 68% population resides in rural areas. Since last two to three decades, there is socio-demographic, economic and cultural transformation happens among women due to increase in educational level of women. This transformation has also brought about many lifestyle changes, such as increase in the habit of smoking, increase the marital age and first pregnancy, decrease the duration of breast

which will reduce the burden of the disease.

Materials and Methods:

The hospital based case- control study was conducted in Satara district of the state Maharashtra, India. The district is spread across 10,484 km^2 with a total population of 30.03 lac. The literacy rate of the district is 84.20% of which female literacy is 76.29%. The district has 11 blocks and 1707 villages with average density of population of the 287 per sq. km [census 2011].

The study was conducted in purposively selected public and private hospitals located in Satara district providing the diagnostic and therapeutic cancer services were included to indentify and enroll the breast cancer cases. The study was conducted over the period of thirty six months [Jan 2009 - Dec 2011]. All

Table 1[A]: Demographic distribution of cases and controls

Variables	Group		Total No (%)	Test of Significance	p- value
	Case No (%)	Control No (%)			
Age(yrs): ≤ 30	7 (3.23)	7 (3.23)	14(3.22)	0.14	0.88
30 – 39	40 (18.43)	40 (18.43)	80(18.43)		
40 – 49	69 (31.80)	69 (31.80)	138(31.79)		
50 – 59	52 (23.96)	53 (24.42)	105(24.19)		
≥ 60	49 (22.58)	48 (22.12)	97(22.35)		
Religion: Hindu	191 (88.02)	191 (88.02)	382(88.01)	0.00	1. 000
Muslim	19 (8.76)	19 (8.76)	38(8.75)		
Christian	7 (3.23)	7 (3.23)	14(3.22)		
Residence: Rural	146 (67.28)	146 (67.28)	292(67.28)	0.00	1.00
Urban	71 (32.72)	71 (32.72)	142(32.71)		

feeding, decrease in fertility and changes in dietary habits. It is well known that breast cancer stood the rank second amongst the all cancerous conditions in Indian women.[8] But till date no one has studied the problem to identifying reproductive risk factors of breast cancer faced by women residing in rural area of Satara district.

The aim of this study was to assess the strength of association between identified reproductive risk factors and breast cancer among the women residing in Satara district, western Maharashtra, India. The results of this study can contribute to the better understanding of specific reproductive risk factors for breast cancer which will be helpful to formulate a public health policy for increasing the awareness among women

newly diagnosed cases of breast cancer and matched controls which were selected from hospitals as well as relatives with respect to number, age, religion and residence following 1:1 ratio. A sample size consists of total 434 women include 217 cases and 217 controls were enrolled by purposive sampling technique according to inclusion and exclusion criteria of study: *Inclusion Criteria:* All newly diagnosed cases of cancer breast within the period of one year of diagnosis, irrespective of stage of diagnosis of breast cancer, willingness to participate in study and residents of Satara district. *Exclusion Criteria:* Old cases of cancer breast i.e. diagnosed more than one year, not willing to participate and temporary migrants. A pre-tested structured questionnaire that include socio-

demographic, economic characteristics of the women, reproductive characteristics like age at menarche, number of children, menopausal status [artificial or physiological], hormonal contraceptive history and breast feeding etc. was utilized to collect the data from the cases and the controls through individual, personal interview method on schedule basis. The Patient's comfort was maintained and checklist was used to avoid duplication of cases and controls.

The data so collected was entered into Microsoft Excel 2007 and analyzed by using Statistical Packages for Social Sciences [SPSS] statistical software version 17. Descriptive statistics i.e. mean,

the age group ranging from 25 to 70 years with the mean age of 48.59 and 48.43 years for the cases and the controls respectively. With respect to age, religion and residence, maximum 31.80 %, 88.02% and 67.28% of both cases and controls were in age group of 40-49 yrs, Hindu by religion and residing in rural area respectively. No statistically significant difference with respect to age, religion and residence between the cases and the controls, reflecting successful matching. [Table 1[A]]

The proportions of the cases and the controls with respect to occupation shows that maximum number of subjects were housewives, 63.59% and 61.75%

Table 1(B): Demographic and economic distribution of cases and controls

Variables	Group		Total No (%)	Test of Significance	p- value
	Case No (%)	Control No (%)			
Occupation: House Wife	138 (63.59)	134 (61.75)	272(62.67)	7.756	0.100
Daily Wagers	36 (16.59)	48 (22.12)	84(19.35)		
Self Employed	35 (16.13)	23 (10.60)	58(13.36)		
Civil Servant	5 (2.30)	3 (1.38)	8(1.84)		
Private Sector employee	3 (1.38)	9 (4.15)	12(2.76)		
Education: Illiterate	62 (28.57)	66 (30.41)	128(29.49)	16.33	0.002*
Primary	68 (31.34)	39 (17.97)	107(24.65)		
Secondary	73 (33.64)	95 (43.78)	168(38.70)		
Higher Secondary	6 (2.76)	14 (6.45)	20(4.60)		
Degree/Diploma	8 (3.69)	3 (1.38)	11(2.53)		
Income: Lowe class	94 (43.32)	110 (50.69)	218(50.23)	2.3	0.12
Upper class	123 (56.68)	107 (49.31)	216(49.76)		

[* = p value < 0.05 at 95% confidence interval]

standard deviation, and frequency percentages were calculated. Exposure rate of various risk factors in both cases and controls was found out for existence of association between the risk factors and the breast cancer. The strength of association was found out by using Odd's ratio at 95% confidence interval. The association between the risk factor and the breast cancer was analyzed by using chi-square test. Statistical significance was considered when *p value* was less than *0.05 at 95%* confidence interval.

Results:

In all, 217 women with breast cancer and 217 from the control group were interviewed. They were in

with apparent differences in occupational groups. Maximum cases as well controls, 71.42% and 69.58% were literate i.e. able to read and write in own language and showed statistically significant difference with respect to educational level [p< 0.05]. The proportion of cases was higher in the Upper socio- economic class 56.68% as compared to the controls 49.30%.[Table 1[B]].

The proportion of ever married and unmarried women was higher in cases [86.18% and 3.69%] as compared to controls [83.87% and 0.46%] and the risk of getting breast cancer was 8 times higher in unmarried women as compared to the ever married women. The

Table 2: Association of Reproductive risk factors with breast cancer

Reproductive risk factor	Group		Total No (%)	Odd's	CI	χ Statistic	P-value
	Case No (%)	Control No (%)					
Marital Status Unmarried	8 (3.69)	1 (0.46)	9(2.07)	8.2	1-66.7	10.17	0.01*
Married	187(86.18)	182(83.87)	369(85.02)				
Divorced	6 (2.76)	4 (1.84)	10(2.30)				
Widowed	16 (7.37)	30 (13.82)	46(10.59)				
Parity: Nulli-parous	11 (5.07)	5 (1.84)	16(3.68)	2.8	0.9-9.3	0.20	0.956
1 – 2	116 (53.46)	119 (54.84)	235(54.14)				
> 2	90 (41.94)	93 (42.86)	183(42.16)				
Abortions: 1	36 (16.59)	30 (13.82)	66(15.20)	1.6	1-2.7	9.628	0.022*
2	10 (4.61)	1 (0.46)	11(2.53)				
5	1 (0.46)	0 (0.00)	1(0.23)				
Nill	170 (78.34)	186 (85.71)	356(82.02)				
Menopause status: Post Menopause	124 (57.14)	78 (35.94)	202(46.54)	2.37	1.6-3.4	19.596	0.001*
No Menopause	93 (42.86)	139 (64.06)	232(53.45)				
Breast Feeding: No	56 (25.81)	7 (3.23)	63(14.51)	10.43	4.6-23.5	44.58	0.001*
Yes	161 (74.19)	210 (96.77)	371(85.48)				
OC Pills & Hormones Yes	69(31.79)	48(22.11)	117(26.95)	1.64	1-2.5	4.68	0.03*
No	148(68.20)	169(77.88)	317(73.04)				
Oophorectomy: Yes	36 (16.59)	9 (4.14)	45(10.36)	4.5	2.1-9.8	16.7	0.001*
No	181 (83.41)	208 (95.85)	389(89.63)				
Menarche Age: < 13 yrs	172(79.26)	151(69.58)	323(74.42)	0.59	0.3-0.9	4.8	0.02*
> 13 yrs	45(20.73)	66(30.41)	111(25.57)				

proportion of nulli-parous women was higher in the cases [5.07%] as compared to the controls [1.84%] and the risk of getting breast cancer in nulli-parous women was 2.8 times higher as compared to parous

women. The proportion of women giving history of abortion was higher in the cases [21.65%] as compared to the controls [14.28%] and the strength of association between abortion and breast cancer as indicated by the odd's ratio was 1.6. The proportion of women with menopause was higher in cases [57.14%] as compared to the controls [35.94%] and the risk of getting breast cancer was 2.4 times higher in women with menopause as compared to non-menopausal women. The proportion of women not breast feeding their babies was significantly higher in cases [25.88%] as compared to the controls [3.22%] and the strength of association between non breast feeding and breast cancer as indicated by odd's ratio of 10.4. The history of ever use of oral contraceptive [OC] pills and hormonal injections of Depot-medroxy progesterone acetate [DMPA] were significantly higher among cases [31.79%] as compared to the controls [22.11%] and the risk of getting breast cancer with the use of female sex hormones in the form of both OC pills and DMPA was 1.5 times higher in cases as compared to the controls. A history of oophorectomy before diagnosis of breast cancer was obtained from 36 breast cancer cases and 9 controls with an odd's ratio of 4.5 indicating a positive relationship between history of oophorectomy i.e. ovary disease and breast cancer. The proportion of women with history of age at menarche by recall method less than 13 yrs was higher in cases, 79.26% as compared to controls, 69.58% and vise versa with age at menarche more than 13 yrs and the difference was statically significant [p <0.05] [Table 2].

After multivariate logistic regression analysis, it was observed that reproductive risk factors such as nulli-parity, women with unmarried status, menopause, absence of breast feeding, history of oophorectomy, exposure to OC pills and DMPA were strongly associated with occurrence of breast cancer *[p <0.05]*. However, age at menarche and history of abortion though showing statistical association by univariate analysis were nullified during the multivariate analysis [Table 3].

Discussion:

The present study has revealed, lowest age at incidence of breast cancer to be 25 years as observed from a rural area of Western Maharashtra. The proportion of breast cancer cases has been maximum [74.19%] in the age group 30-60 years. Pakseresht S et al (2009),[9] have shown that the age incidence of breast cancer is maximum in the age group of 30-60 yrs with minimum age incidence has been 25 yrs. Similar findings also have been observed by Kamat R(2013).[10] The majority of breast cancer cases, 67.28% have been from rural area as compared to the urban area. However study conducted by Pakseresht S et al(2009) from urban area of Delhi[9] have shown maximum breast cancer cases to be from urban area and difference could be related to the placement of hospital and the population catered by it. The present study is conducted in Satara district where approximately 80 % population is residing in the rural area and the district is known to be from sugar belt of western Maharashtra.

In this study, majority of breast cancer cases, 88% are from Hindu religion and proportion of Muslim and Christians has been 8.7% and 3.2% respectively. The big gap in proportion of breast cancer cases with respect to religion could be due to the difference in the religion wise distributions in the populations groups in the India. Similar findings also have been reported by Badve RA (1990)[11] as 82.4%, 7.3% and 2.7% respectively for the Hindues, Muslims and Christiens and shows apparent difference when compared with our study and this difference could be due to time period of both the studies.

The majority of breast cancer cases [63.89%] in our study are housewives and similar findings are also observed by Pakseresht S et al (2009).[9] The proportion of illiterate to literate breast cancer cases are 28.57% and 71.43% respectively and this

Table 3: Multivariate logistic regression for reproductive risk factor and Breast cancer

Study variables	B	S.E.	Wald	Df	Sig.	Exp(B)
Nulli-parity	3.828	1.453	9.332	1	.009	45.957
Unmarried status	2.614	.689	13.690	1	.007	31.138
Menopause	-1.297	.310	17.508	1	.000	.273
No breastfeeding	3.614	1.053	11.780	1	.001	37.104
Oophorectomy	2.316	.686	11.400	1	.001	10.138
OC pills & DMPA	1.201	0.413	10.17	1	.001	1.13
Constant	2.275	1.428	2.538	1	.111	9.724

difference could be due to increase in women's literacy rate [82.9%] in Satara district. However, studies conducted by Parameshwari P (2013) [12] have shown maximum, 60% breast cancer cases among illiterate population from South Kerala. Even though in Kerala women have high literacy rate i.e. > 90% , majority of breast cancer cases were illiterate and difference in study results could be due to behavior of majority of literate Kerala women who prefer residence in abroad or in metros, however illiterate resides in local area.

In our study, the rate of occurrence of breast cancer cases is higher among women from upper economic class. A study is conducted in rural area but modern agriculture, cash crop of sugar cane associated with higher economic status, increased literacy and sound economic status could be responsible for high incidence of breast cancer among upper economic class rural population. Similar findings have been observed by Kelsey JL(1979) [13] from developed country. The behavioral aspects of upper economic class may be related to occurrence of breast cancer like having less number of children, late marriage etc. In the present study, out of 217 breast cancer cases 3.68% women having breast cancer have not been married and risk of getting breast cancer has been 8 times higher in these women as compared to married ones. Similar findings have also been noted by Parameshwari P (2013) [12] and Pakseresht S et al (2009).[9] The present study reveals, nearly 5.6% breast cancer cases are nulliparous and risk of getting breast cancer is 2 times higher in nulliparous women as compared to parous women. The parous women who have experience in pregnancy and breast feeding might have a protective effect on incidence of breast cancer. It could be due to the differentiation of mammary tissue during pregnancy [14] and a permanent reduction in prolactin production. Prolactin increases cell proliferation and decreases apoptosis in the breast. An increased risk of breast cancer in nulliparous women could be due to hormonal changes i.e. high levels of estrogen and progesterone. Similar findings are also noted by Mandana et al (2002)[15] and Rosner B(1994). [16]

Among breast cancer cases, the rate of abortion is 21.65% and indicates a risk for breast cancer with odd's ratio of 1.6 with confidence interval of 1 to 2.7. Similar finding has also been reported by Ozmen V (2009). [17] However several other studies have contradictory results about association of abortion and breast cancer and actual patho-physiology has not yet been fully understood. [18]

The risk of developing of breast cancer is 2.5 times higher in women with menopausal status as compared to non menopausal status. The menopause increases the risk of breast cancer by maximizing cumulative ovarian hormone exposure which is responsible for initiation of cancer process. [14] The risk of developing breast cancer is 10.5 times higher in women who have not made an attempt of breast feeding as compared to breast feeding women and it indicates the absence of breast feeding to be a risk factor for breast cancer. Similar findings also have been reported by Pakseresht S et al(2009)[9] and Parameshwari P(2013). [12] Breast feeding is thought to reduce breast cancer risk by reducing the total number of ovulatory menstrual cycles and have effect on ovarian hormones.[19]

Our study shows the risk of getting breast cancer is 1.6 times higher in women with use of OC pills and DMPA as contraceptive hormones as compared to non users. Studies conducted by Ozmen V (2009) [17] , Lodha R (2011)[20] have also observed similar findings. Similar findings have also been reported by Ozmen V (2009). [17] However a study conducted by Hulka BS (2001) [21] and Heiss G(2008) [22] have observed that hormone replacement is a risk factor for breast cancer and difference has been mainly due to use of estrogen alone or in combination with progesterone which enhances the breast cancer effect as compared to progesterone alone.[14] The ethinyl estradiol and progestin and these hormones would provide higher levels of estrogen and progestin during an oral contraceptive cycle than normal ovulatory cycle and which might be responsible for breast cancer.

The strength of association between history of ovarian disease or oophorectomy and breast cancer is 4.5 times higher in cases as compared to controls with significant statistical association [$p < 0.05$]. A similar finding also has been reported by Adam (2001) as of odd's ratio of 1.48 with confidence interval of 0.79-2.54. [23] Women with BRCA1 or BRCA2 gene mutations have a significantly increased risk of developing breast cancer and ovarian cancer. After oophorectomy women have been kept on hormone therapy which could further increase the risk of developing breast cancer as stated by Boyd S (1900). [24]

Conclusion:

Our study revealed that, maximum breast cancer cases were in age group 40-49 yrs.

The reproductive risk factors such as marital status of women, nulli-parity, post menopausal status, absence of breast feeding, history of ovarian disease and use of contraceptives were strongly associated with

breast cancer; however weak association was seen with factors such as age at menarche and history of abortion.

Ethical Consideration: Institutional ethics committee clearance, permissions from health institutions and informed consent from each study subject was obtained before actual data collection.

Conflict of interest: None declared.

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