Online Journal of Health and Allied Sciences
Peer Reviewed, Open Access, Free Online Journal
Published Quarterly : Mangalore, South India : ISSN 0972-5997
Volume 8, Issue 3; Jul-Sep 2009

Original Article:

Reproductive Risk Factors for Breast Cancer: A Case Control Study

Meshram II, Ex-Lecturer,
Hiwarkar PA, Associate Professor,
Kulkarni PN, Ex-Professor,
Department of Preventive and Social Medicine, Indira Gandhi Medical College, Nagpur

Address For Correspondence:
Indrapal Ishwarji Meshram,
Senior research officer, Division of community studies,
National Institute of Nutrition, Indian Council of Medical Research,
Jamai- Osmania (PO), Taranaka, Hyderabad- 500007
E-mail: indrapal.m@rediffmail.com

Citation: Meshram II, Hiwarkar PA, Kulkarni PN. Reproductive risk factors for breast cancer: A case control study *Online J Health Allied Scs.* 2009;8(3):5
URL: http://www.ojhas.org/issue31/2009-3-5.htm
Open Access Archives: http://cogprints.org/view/subjects/OJHAS.html and http://openmed.nic.in/view/subjects/ojhas.html

Submitted: Apr 29, 2009; Accepted: Sep 9, 2009; Published: Oct 15, 2009

Abstract:
Background: Breast cancer is second most important cancer among Indian women. Although risk factors are not much prevalent as in western countries, incidence rate is increasing in India. The study was undertaken to study various risk factors associated with breast cancer. **Methods:** A hospital based group matched case control study was undertaken to identify risk factors. The study consisted of 105 hospitalized cases confirmed on histopathology and 210 group matched controls selected from urban field practice area, Sadar, without any malignancy. Bivariate analyses included odds ratio (OR), 95% confidence interval (CI) for odds ratio. **Results:** Earlier age at menarche ≤ 12 years of age, late age at first full term delivery, nulliparity, Lack of breast-feeding were found to be significantly associated with the risk of breast cancer in both pre menopausal & post menopausal women while age at menopause at or after 50 years was significantly associated with the risk in post menopausal women. **Conclusions:** Study suggests that the changes in menstrual and reproductive patterns among women i.e. early age at menarche and late age at first childbirth and some environmental factors in Central India may have contributed to the increase in breast cancer risk, particularly among younger women.
Key Words: Breast cancer, breast-feeding, menarche, parity

Introduction:

Urbanization, industrialization, changes in life style, population growth and ageing all have contributed for epidemiological transition in the country. The absolute number of new cancer cases is increasing rapidly, due to growth in the size of the population and increase in the proportion of elderly persons as a result of improved life expectancy following control of communicable diseases.

The burden of breast cancer is increasing in both developed and developing countries, and in many of the regions of the world, it is now the most frequently occurring malignant disease in women and comprises 18% of all female cancer. Worldwide, breast cancer is the fifth most common cause of cancer death (after lung cancer, stomach cancer, liver cancer, and colon cancer).(1) In 2005, breast cancer caused 502,000 deaths (7% of cancer deaths; almost 1% of all deaths) worldwide. Among women worldwide, breast cancer is the most common cause of cancer death.(1)

In the United States, breast cancer is the third most common cause of cancer death (after lung cancer and colon cancer). In 2007, breast cancer is expected to cause 40,910 deaths (7% of cancer deaths; almost 2% of all deaths) in the U.S. (2). Women in the U.S. have a 1 in 8 lifetime chance of developing invasive breast cancer and a 1 in 33 chance of breast cancer causing their death.(3)

Breast Cancer is the most common malignancy affecting women worldwide. The peak occurrence of breast cancer in developed countries is above the age of 50 years, as compared to India, where it occurs in a younger age group, about a decade earlier then their western counterparts.(4)

Age standardized incidence rates vary between 9–32 per 100,000 women. An increasing trend in the incidence rates of the breast cancer has been reported from the various registries of National Cancer Registry Project.(5) Breast Cancer constitutes 18.5 percent of the total new cancer cases in Indian women today.

The study was carried out to study various risk factors and their association with the disease.

Materials and Methods:

The present case control study was carried out at Indira Gandhi Govt. Medical college Hospital, Nagpur over a period of one year. Cases diagnosed on histopathology as breast cancer for the first time, and were admitted in surgery department were selected for the study. Only incident cases (new) were included in the study. Wards were visited twice weekly and any new case diagnosed on histopathology were included in the study after explaining the objectives of the study to the subject. For each case, two age matched (group matched) controls were selected from the community of urban field practice area, Sadar, by adopting stratified random sampling procedure. Controls free from any malignancies were selected for the study.

Ten hypothesized risk factors, namely, age at menarche, age at first full term delivery, parity, breast feeding, age at menopause, history of Benign Breast Disease, use of oral contra-

ceptive, duration of reproductive life, obesity, family H/o breast cancer were tested for significance.

Data was collected on pre-designed proforma. Detail information on socio-demographic, menstrual and reproductive history; age at menopause and use of exogenous estrogen for a postmenopausal woman was obtained. Menopausal status was decided by asking the subjects whether she had no menstrual periods (menses) for 12 months and has no other medical reason for her menses to stop. The natural age for menopausal onset is between 45 to 55 years with a mean age of 51 years, worldwide.(6) Mean age of menopause in India is 44.3 years. (7)

Anthropometrical measurements such as height and weight were recorded for all the subjects.

Necessary ethical clearance was obtained from Institutional Ethical Review Committee before start of the study and oral informed consent was obtained from the subjects.

Statistical Analyses: Data was analysed by using SPSS (Version 11.0). Mean, standard deviation, odds ratio with 95% confidence level was applied. Bivariate analysis was carried out using reproductive risk factors and breast cancer

Results:

Out of total 105 cases studied, about 83% belong to Hindu, 14% Muslim and only 2% were Christians. About 43% cases were illiterate compared to 30% illiterate controls. The most common type was infiltrative duct carcinoma (96%). Most of the cases were in stage II (45%), and stage III (35%). Per capita income was similar for both cases and controls.

Mean age of cases was 48.4 years (SD 11.28) and that of controls 48.8 years (SD 11.28). The age of cases ranges from 20-70 years. Maximum numbers of cases were in 40-49 years age group (38%). Nearly 20% of cases were below 40 years while 21% of cases were above 60 years of age [Table I].

Table I: Distribution of study subjects according to socio-demographic variable and menopausal status.

Particulars	Cases	Controls
Age (yrs)	n (%)	n (%)
<40	20 (19.1)	40 (19.1)
40-49	40 (38.1)	80 (38.1)
50-59	23 (21.9)	46 (21.9)
≥60	22 (20.9)	44 (20.9)
Education of women		
Illiterate	45 (42.9)	64 (30.5)
<10 years	55 (52.4)	136 (64.8)
≥10years	5 (4.8)	10 (4.8)
Religion		
Hindu	88 (83.8)	177 (84.3)
Muslim	15 (14.3)	29 (13.8)
Christian	2 (1.9)	4 (1.9)
Menopausal status		
Pre-menopause	48 (45.7)	81 (38.6)
Post menopause	57 (54.3)	129 (61.4)

Women who had menarche at early ages (≤12 years) were at increased risk compared with women who had menarche between 13-15 years of age (O.R.= 4.99, CI =2.26-10.99, p<*0.001*). Menarche after 15 years of age was associated with reduced risk of breast cancer (O.R.= 0.33, CI =0.12- 0.87) [Table II]. There was no difference in the dietary intake as most of the cases were from rural areas and belongs to lower and middle class.

Table II: Bi-variate analyses for risk factors of breast cancer

Risk factors		Cases (%)	Controls (%)	O.R.	95% C. I.	p value
Age at menarche (years)	≤12	23 (21.9)	10 (4.8)	4.99	2.26- 10.99	<0.001*
	13-15	77 (73.3)	167 (79.5)	1•		
	≥16	5 (4.8)	33 (15.7)	0.33	0.12- 0.87	
Age at first full term delivery (years)	≤20	31 (35.2)	116 (57.1)	1•		<0.01*
	21- 25	48 (54.5)	74 (36.5)	2.43	1.42- 4.16	
	>25	9 (10.3)	13 (6.4)	2.59	1.01- 6.55	
Parity	Nulliparous	17 (14.2)	7 (3.3)	5.6	2.22- 13.9	<0.001*
	Parous	88 (83.8)	203 (96.7)	1•		
Total duration of breast feeding (years)	Absent	18 (17.1)	7 (3.3)	1.71	0.54- 5.35	<0.001*
	< 2	18 (17.1)	12 (5.7)	1•		
	2-4	26 (24.8)	53 (25.3)	0.32	0.13- 0.77	
	5-6	30 (28.6)	89 (42.4)	0.22	0.09- 0.52	
	≥7	13 (12.4)	49 (23.3)	0.17	0.06- 0.45	
Age at menopause (years)	< 45	14 (24.6)	69 (53.5)	0.28	0.14- 0.57	<0.001*
	45- 49	26 (45.6)	53 (41.1)	1•		
	≥50	17 (29.8)	7 (5.4)	7.41	2.86- 19.15	
H/o BBD	Yes	14 (13.3)	5 (2.4)	6.31	2.21- 18.04	<0.001*
	No	91 (86.7)	205 (97.6)	1•		
Use of oral contraceptive	Yes	5 (4.8)	2 (1.0)	5.2	0.99- 27.27	0.08
	No	100(95.2)	208 (99.0)	1•		
Body mass index	<25	82 (78.1)	156 (74.3)	1•		0.54
	≥25	23 (21.9)	54 (25.7)	0.81	0.46-1.14	

• Reference group; * Significant

Age at first child birth was observed an important risk factor. The risk was more for women who had first child after 25 years compare to women having first child at or before 20 years of age. (O.R.=2.59, CI = 1.01- 6.55, , *p<0.001*). [Table II]

Risk of breast cancer was five times higher in nulliparous than parous women (O.R.=5.6, CI = 2.22-13.9, p*<0.001*) [Table II]. The risk was 4.5 and 9.4 times more among nullparous and those having only one child (O.R. for parity 0 Vs parity 2=4.05, CI = 1.36-12.03, *p<0.001*, O.R. for parity 1 Vs parity 2=9.44, CI = 2.37-37.68).

Lack of or less duration of breast feeding was associated with the risk of breast cancer. Mothers who do not breast-fed in their lifetime were at higher risk than those who had breast-fed their children. (O.R.= 1.71, CI = 0.54-5.35, *P<0.001*). Total duration of breast-feeding is also important. As the total duration of breast-feeding increases, risk of breast cancer decreases. [Table II]

Menopause (≥50 years of age) was observed to be associated with increased risk. The risk was 7.9 times more among women who had menopause at or after 50 years of age compared to women who had menopause before 45 years. (O.R.=7.91, CI=2.86-19.15). The effect of artificial menopause cannot be ascertained because of fewer numbers of cases. [Table II]

The risk was more among mothers with past history of benign Breast Disease (O.R.=14.81, CI= 2.21- 18.04, p *<0.001*) [Table II].

No association was observed between overweight (BMI ≥25), use of oral contraceptive and breast cancer. [Table II]

Discussion:

Breast cancer incidence rates are increasing worldwide. In India, it is the most common cancer among women in many regions and has overtaken cervix cancer. The continuing rise in breast cancer incidence has created an urgent need to develop strategies for prevention.

Age is an important risk factor. The breast cancer risk increases as the age advances. In the present study, maximum numbers of cases were observed in 40-49 years (38%) followed by 50 –59 years (22%) age group with average age of 48.4 years. Average age of the patients seen in the six hospital based cancer registries during the period 1994–98 was found to range from 44.2 years in Dibrugarh and 49.6 years in Bangalore and Chennai registries.(8) Other studies also reported similar findings.(9,10) The average age of occurrence of breast cancer amongst US white females has been reported to be 61.0 years.(11) The average age of occurrence of the breast cancer in India reveals that the disease occurs a decade earlier, as compared to western countries. The reason for early age of occurrence amongst Indian women needs to be further studied.

Although breast cancer can be detected at earlier stages by simple breast examination, maximum (>90%) cases were diagnosed in advance stages i.e. stage II, III and stage IV. This shows lack of awareness among the women.

Earlier age at menarche i.e. at or before 12 years was observed important risk factor.

Gao YT et al (2003) in their case control study observed higher risk for women who had menarche before 13 years of age. (12)

The effect of age at menarche on breast cancer risk may be mediated simply by the prolonged exposure of breast epithelium to estrogen produced by regular ovulatory cycle.(13) In addition, some studies have demonstrated that women with early menarche have higher estrogen levels than women with later menarche for several years after menarche.(14)

The women who had first full term delivery after 25 years of age was found to be at higher risk than women who had first child before 20 years of age.

Rao DN et al (1994) observed relative risk of 5.4 times for women delivering first child after 30 years compared to 15 years of first delivery.(15)

The ultimate mechanism through which early pregnancy protects the breast from cancer development remains largely unknown. Several hypotheses have been proposed to account for the hormone-driven protective effects of parity. Recent experiments demonstrate the important role of the *p53* tumor suppressor gene in the hormone-induced protection.(16)

Nulliparous women were at higher risk than parous women. The risk decreases as the parity increases. A case-control study carried out in Madras, India showed that single women compared to married women had 4–5 fold higher risk for development of breast cancer in the age group of 40–54 years and 55 and above.(17) High incidence of breast cancer among Parsi women was partly due to more unmarried women, late age at marriage and first childbirth, less children and consanguinity of marriage.(18) Some study suggests that parity may affect not only estrogen levels but also long term secretion of prolactin.(19)

Breast-feeding is a common practice In India. The risk was found to be more among nulliparous because of lack of breast-feeding practices. Several authors found protective effects of breast- feeding on breast cancer risk.(20,21,22)

The protective effect of breast-feeding on breast cancer risk is explained as breast-feeding maintains normal endocrine balance via modulation of ovarian or pituitary activity.

It was observed that the risk was more for women who had menopause after 50 years compared to women who had menopause before 45 years of age.

Negri Eva et al also observed similar findings.(23)

The explanation given is that in women with late age at menopause, higher risk may be related to their higher lifetime exposure to estrogen and progesterone.(24)

Proliferative benign breast diseases (cystic type) in the past were observed to be associated with increased risk of breast cancer.

Dixon J. M. et al (1999) in their study observed that women with palpable breast cyst are at increased risk of breast cancer at young age.(25)

Hartmann LC et el (2005) observed that the relative risk associated with atypia was 4.24, as compared with a relative risk of 1.88 for proliferative changes without atypia and of 1.27 for non-proliferative lesions.(26) This may be due to increasing use of mammography has increased the frequency of breast biopsies, most of which yield benign findings.

Other authors also observed similar findings in their studies. (27,28)

Apart from these factors, some environmental factors may have influence, direct or indirect, on breast cancer, particularly among younger women that needs further studies.

Conclusion:

Breast cancer occurs decades earlier in Indian women compared to western women and is a leading cause of mortality among women in developing countries such as India, as most of them are diagnosed in late stages because of ignorance about detection of breast cancer in initial stages simply by self-breast examination. So raising awareness about the procedure and screening for high risk women so that it can be diagnosed in the initial stages and thus reduces mortality.

Limitations of the Study:

Because of case control nature of the study, certain bias arises in the study. Important is recall bias, which was minimized by including only incident cases. Medical records were checked to confirm past history of benign breast diseases. Radiation exposure and environmental exposure could not be ascertained because of lack of facility. Selection bias was minimized by selecting controls from similar socioeconomic group.

Acknowledgement:

The authors duly acknowledge the contribution and help of Surgery and Pathology Department, Indira Gandhi Govt. Medical College Nagpur. Authors are also thankful to Ms. Patil, social worker, Department of Community Medicine, for her cooperation during survey in the community.

Source of Funding:

Nil

References:

1. World Health Organization. Facts sheet No. 297: Cancer 2006.
2. Cancer. Facts & Figures American Cancer Society 2007. Available at www.cancer.org/downloads/STT/CAFF2007
3. What Are the Key Statistics for Breast Cancer? 2006. American Cancer Society.
4. Reliance Life launch portal for Breast Cancer Genomics. Available at www.moneycontrol.com/india/news/pressnews/reliance-life-launch-portal–for-breast-cancer-genomics.
5. Siddiqi M, Sen U, Mondal SS, Patel DD, Yeole BB, Jussawala DJ et al. Cancer statistics from non-ICMR registries: Population based registries, CRAB (Cancer registry Abstract). *Newsletter of the National Cancer Registry Project of India* 2001. page 47-59.
6. Premature menopause risks rising: Available at www.indiatogether.org/2007
7. Indian women reaching menopause at 30. Available at www.timesofindia.indiatimes.com/articleshow/1363050.cms
8. National Cancer registry Program: Ten year consolidated report of the Hospital Based Cancer Registries, 1984–1993: An assessment of the burden and care of cancer patients**.** Indian Council of Medical Research. New Delhi; 2001.
9. Gupta P, Sharma RG, Verma M. Review of breast cancer cases in Jaipur region. *J Ind. Med Assoc* 2002;100:282-284.
10. Goel AK, Seenu V, Shukla NK, Raina V. Breast cancer presentation at a regional cancer center. *Natl. Med. J. Ind.* 1995;8:6-9.
11. Parkin DM, Whelan SL, Ferlay J, Storm H. Cancer Incidence in Five Continents. Vol. VIII. International Agency for research on Cancer [IARC] 2002, Lyon, France, IARC Scientific Publication No. 155**.**
12. Gao YT, Shu XO, Dai Q, Potter JD, Brinton LA, Wen W et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. *J. Natl. Cancer Inst.* 2003;95(6):478-83.
13. Mac Mahon B, Trichopolous D, Brown J. Anderson AP, Aoki K, Cole P et al. Age at menarche, Probability of ovulation and breast cancer risk. *Int. J. Cancer*1982;29:13-16.
14. Mac Mahon B, Trichopolous D, Brown J. Anderson AP, Cole P, DeWaard F et al. Age at menarche, urine estrogen and breast cancer risk. *Int. J. Cancer*1982;30:427-31.
15. Rao DN, Ganesh B, Desai PB. Role of reproductive factors in breast cancer in low risk area: case control study. *Brit. J. Cancer* 1994;70:129-132.
16. Medina D. The Protective Effect of Pregnancy. *Clinical Cancer Research* 2004;10:380-84.
17. Gajalakshmi CK, Shanta V. Risk factors for female breast cancer. A hospital based case-control study in Madras, India. Acta Oncol. 1991;30:569-574.
18. Jussawalla DJ, Jain DK. Breast cancer and religion in Greater Bombay women: An epidemiological study of 2130 women over a 9-year period. *Br. J Cancer* 1977;36**:**634-638.
19. Mussey VC, Collins DC, Mussey PI, Martinosaltzman D, Preedy JR. Long term effects of a first pregnancy on the secretion of prolactin. *New Eng. J. Med*1987;316:229-234.
20. Byers T, Graham S, Rzepka T, Marshal J. Lactation and breast cancer, evidence for negative association in pre-menopausal women. *Amer. J. Epid.* 1985;121:664-74.
21. Mc Tiernan A, Thomas DB. Evidence for a protective effect of lactation on risk of breast cancer in young women, results from case-control study. *Amer. J. Epid.*1986;124:353-358.
22. New-comb PA, Egan KM, Titus-Ernstoff L, Trentham-Dietz A, Greenberg ER, Baron JA et al. Lactation in relation to post menopausal breast cancer. *Amer. J. Epid.*1999;150:174-82.
23. Negri Eva, Vecchia L, Bruzzi P, Dardanoni G, Decarli A, Palli D et al. Risk factors for breast cancer: Pooled results from three Italian case control studies. *Amer. J. Epid.* 1988;128:1207-15.
24. Breast Cancer Risk Factors. Available at www.ucsfhealth.org/adult/medical_services/cancer/breast/risk.html
25. Dixon JM, Mc Donald C, Elten RA, Miller WR. Risk of breast cancer in women with palpable breast cyst, A prospective study. *The Lancet* 1999;353:1742-45.
26. Hartmann LC, Sellars TA, Frost MH, Lingle WH, Degnim AC, Ghosh K et el. Benign breast disease and the risk of breast cancer. *N. Eng. J. Med.* 2005;353(30):297-99
27. Levi F, Randimrison L, Van-Cong TE, Vecchia CL. Incidence of breast cancer in women with fibroadenoma. *Int. J. Cancer* 1994;57:681-83.
28. Palli D, Turco MR, Simencini R, Bianchi S. Benign breast disease and breast cancer, A case control study in a cohort in Italy. *Int J. Cancer* 1991;47:703-6.