Reproductive Risk Factors for Female Breast Cancer: A Case – Control Study

BUTT Z.,[1] SHAHBAZ U.,[2] NASEEM T.,[3] ASHFAQ U.,[4]
KHAN U. A.,[5] KHAN M. R.,[6] HASHMIM A. T.,[7] BUKHARI M. H.[8]
Address for Correspondence: *Zeeshan Butt, Final Year MBBS, Department of Pathology, King Edward Medical University, Lahore*

Background: Breast cancer is the most common female cancer in Pakistan. Its incidence in Pakistan is 2.5 times higher than that in neighboring countries like Iran and India. Association of reproductive factors with breast cancer is unclear in our population.

Objectives: To find out the association of reproductive factors like parity, age at first live birth and lactation with breast cancer.

Design, Setting and Participants: It was a case-control study comprising 150 breast cancer patients and 300 control subjects. The study was done in Mayo Hospital Lahore between October, 2008 and April, 2009.

Methods: Both cases and controls were interviewed in wards after taking verbal consent. A short structured questionnaire was used to obtain information regarding basic demographic, menstrual and reproductive characteristics.

Results: Breast cancer patients and control subjects did not differ regarding age ($p = 0.9$), early menarche (OR for menarche at < 12 years vs. ≥ 12 = 1.6, 95% CI = 0.6 — 4.3), and late menopause (OR for menopause at ≥ 50 vs. < 50 = 1.0, 95% CI = 0.5 — 2.0). History of breast cancer in 1st degree relatives did not increase breast cancer risk (OR = 1.0, 95% CI = 0.5 — 2.1). Nulliparous women had significantly higher risk than parous women (OR = 4.7, 95% CI = 1.9 — 11.0). Women with younger age at first live birth (< 30 years) had less breast cancer risk as compared to women with ≥ 30 years of age at first live birth (OR = 0.2, 95% CI = 0.1 — 0.5). Breastfeeding had no effect on the risk of breast cancer in parous women.

Conclusion: Nulliparity and more age at first live birth was associated with increased breast cancer risk. Breastfeeding was not protective against breast cancer.

Keywords: breast cancer, nulliparity, lactation, risk factors.

Introduction

Breast cancer is the most common malignancy in Pakistani females.[1] where as in neighboring countries like India and Iran, breast cancer is the 2nd commonest female cancer.[2,3] Breast cancer incidence in Pakistan is about 2.5 times that in India and Iran. Pakistan has the highest breast cancer incidence rate in Asia except that in Israel. According to Karachi Cancer Registry, the first population-based cancer registry in Pakistan, the age-standardized incidence rate (ASR) for breast cancer in Karachi South (KS) for period 1995-1997 was 51.7/100,000 which accounted for one third of all female cancers.[1] This breast cancer incidence rate can be taken as an estimate of that in whole of Pakistan as the age, gender and religion distribution of population of Karachi South is similar to whole population of Pakistan.[4]

Every year approximately 1 million new cases of female breast cancer are diagnosed worldwide, most of which occurs in developed countries[5]. Breast cancer is the most common cancer in females accounting for 20% of all female cancers. Breast cancer is the leading cause of female cancer death. When combined for both genders, lung cancer contributes most to cancer-related mortality worldwide[6].

There is a wide variation in breast cancer incidence rates in different regions of the world. According to World Health Organization (WHO) estimates, breast cancer incidence is far more in America and Europe than in Asia[6]. South Asia has five times less ASR for female breast cancer than America and Canada. Breast cancer incidence is increasing in all regions of the world with majority of rise seen in developing countries due to progressive westernization of social, cultural and reproductive trends[7].

Reproductive and hormonal factors contribute most to development of breast cancer. Nulliparity, more age at first live birth and no breastfeeding are major reproductive risk factors for breast cancer in developed countries[8]. These factors are mainly responsible for the variation in breast cancer incidence seen in different regions of the world by virtue of their different prevalence in these regions. Risk of breast cancer increases in successive generations of people moving from low-risk areas to high-risk regions proving that changes in reproductive behaviour and lifestyle are more important than hereditary factors in the development of breast cancer[9].

The role of reproductive factors in the development of breast cancer in our population is different as compared to that seen in western population[10]. This is because parity, younger age at first live birth and lactation practices are part of our culture whereas these factors are far less prevalent in western women. We could identify only four case-control studies on risk factors for breast cancer in Pakistani women.[11-14] Not only their results are conflicting but they are also characterized by small sample sizes and errors in design of study and reporting of findings. Three of them had sample sizes of ≤ 300 and reported results simply in terms of p values instead of reporting odds ratios and their confidence intervals.[11-13] The largest of these studies, in terms of sample size, found that parity had no association with breast cancer and later age at menarche was a risk factor for breast cancer.[14] This is entirely opposite to well-established protective effect of parity and later age at menarche.

The objective of our study is to clarify the current controversies regarding association of reproductive factors with breast cancer in our population.

Materials and Methods

Design, Settings and Participants

This case-control study was conducted in Mayo Hospital, Lahore from November 2008 to April 2009. Cases comprised 150 confirmed female breast cancer patients who presented in the departments of Oncology and Surgery during the study period. Breast cancer patients were not eligible for participation in the study if their age was below 25 years or if time duration since diagnosis was more than 2 years.

The control population comprised 300 female patients, aged ≥ 25 years, having diagnoses other than breast cancer. Controls were sampled from different wards of the hospital through quota sampling. Patients with any cancer and gynecologic and obstetrical complications were not eligible as controls. We could not use random sampling for controls because there was no central electronic record of all the patients admitted in the hospital. Most of the patients in the hospital belonged to distant areas and taking interviews either at home or at telephone was not feasible. However, proportion of controls in each age-specific stratum was fixed in advance based on the expected age distribution of cases. The pre-determined age-specific quotas for sampling of controls were: 15%, 30%, 30%, and 25% for age groups 25-34 year, 35-44 year, 45-54 year, and ≥ 55 year respectively.

Data Collection

A structured questionnaire was prepared in English and in-person interviews were conducted in the wards, for both cases and controls. Verbal consent was taken from every patient. In addition to basic demographic details, participants were asked about their marital status, number of live births, age at first live birth and breastfeeding history. Information was also obtained regarding age at menarche, menopausal status, age at menopause and use of oral contraceptives. Information was collected up to the date of interview for controls and date of diagnosis of breast cancer for cases.

Data Analysis

For predictor variables other than reproductive ones, both unadjusted odds ratios (OR) and 95% confidence intervals (CI), and age-adjusted OR's and 95% CI's were calculated, using unconditional logistic regression, to assess their association with breast cancer. Early menarche was defined as menarche occurring at age < 12 years. Age at menopause was categorized as < 50 years and ≥ 50 years. We included following reproductive variables in our analysis: parity (nulliparous vs. parous), number of live births (1 – 2 live births vs. nulliparous, ≥ 3 live births vs. nulliparous), age at first live birth (< 30 years vs. ≥ 30 years, nulliparous vs. first live birth at ≥ 30 years), lactation for parous women only (never vs. ever), and duration of lactation (never breastfed vs. breastfed for < 3 months, never breastfed vs. breastfed for ≥ 3 months, never breastfed vs. nulliparous women). First unadjusted OR's and 95% CI's were calculated, using unconditional logistic regression, to assess association of reproductive factors with breast cancer. In the next stage adjustment was done for age, marital status, menopausal status and for variables, other than reproductive ones, who had $p < 0.25$. Age was entered as a continuous variable in the logistic regression model. All analyses were done using Statistical Package for Social Sciences (SPSS) version 16.

Results

Cases and controls did not differ regarding age, with mean ages 48.32 and 48.35 years respectively ($p = 0.982$). Table 1 shows the results of univariate logistic regression analysis for association of breast cancer and predictor variables other than reproductive ones. More cases than controls were unmarried but it was not statistically significant. Case and controls did not differ in age at menarche, menopausal status, and age at menopause. Family history of breast cancer in 1st degree relatives did not increase breast cancer risk. More controls had ever used oral contraceptives, with breast cancer odds ratio of 0.186 (95%CI= 0.066-0.540) for controls as compared with cases. Age-adjusted estimates for these variables were not different from the unadjusted ones (Table 1).

Table 2 presents comparison of cases and controls regarding reproductive risk factors. Nulliparous women had higher risk for breast cancer compared to parous women. OR for nulliparous women was 5.1 as compared to women with ≥ 3 children (95% CI = 2.149 – 12.212). Although nulliparous women had breast cancer OR of 2.23 compared to women with 1-2 children but it was not significant (95% CI = 0.70-7.13). Younger age at first live birth was associated with decreased breast cancer risk. Women with first live birth at < 30 years of age had breast cancer OR of 0.19 as compared to women with first live birth at ≥ 30 years. Among the parous women never breastfeeding, compared to ever breastfeeding, did not increase breast cancer risk. Longer duration of lactation (≥ 3 months) also were not protective (OR = 0.56, 95% CI = 0.203 – 1.530).

Discussion

We found that breast cancer patients and controls did not differ in age at menarche, menopausal status, and age at menopause. Many studies have shown that breast cancer risk is more for women whose menarche occur at an early age.[15,16] In one study early menarche (< 13 years) contributed to 44% of breast cancer cases in young and 26% of cases in older women.[17] However, there are contradictory findings in local and regional literature regarding ages at menarche and menopause and breast cancer risk. In a recent Iranian study, Mohouri et al[18] found that early menarche was a risk factor for breast cancer while age at menopause was similar in cases and contols. Two Indian case-control studies, Gajalakashmi et al[19] and Pakseresht S et al,[20] found no association between age at menarche and breast cancer risk. In the first and still the largest case-control study on female breast cancer done in Pakistan[14], Gilani GM showed that both early menarche and late menopause were protective. Various explanations have been put forward for this discrepancy. As suggested by Gilani GM, the estimates of the association of menstrual characteristics with breast cancer in our women are highly subjected to recall bias. This is because here most women are poor and illiterate and they do not remember exactly their ages at menarche and menopause.

Table 1: *Characteristics of cases and controls regarding risk factors other than reproductive ones.*

Variable	Case	Control	OR[1]	95% CI	OR[2]	95% CI
	N = 150	N = 300				
	n.	n.				
Marital status						
Single	5	3	3.4	0.8—14.5	3.5	0.8—15.4
Married	145	297				
Age at menarche						
< 12 years	7	9	1.6	0.6—4.3	1.6	0.6—4.3
≥ 12 years	143	291				
Menopausal status						
Premenopausal	64	111	1.3	0.8—1.9	1.6	0.9—2.8
Postmenopausal	86	189				
Age at menopause[3]						
≥ 50 years	17	36	1.0	0.5—2.0	1.0	0.5—2.0
< 50 years	69	153				
Family history						
Present	12	24	1.0	0.5—2.1	1.0	0.5—2.0
Absent	138	276				
Oral contraceptives use						
Ever	4	38	0.2	0.1—0.5	0.2	0.1—0.5
Never	146	262				

[1]Unadjusted Odds Ratio
[2]Odds Ratio adjusted for age
[3]For postmenopausal women only

We found that history of breast cancer in 1st degree relatives did not increase breast cancer risk. This is in contrast to most western literature and local literature that have shown increased risk for breast cancer if one had affected 1st degree relative.[21]

In our study nulliparous women had more risk of breast cancer as compared to parous women. Nulliparous women were at increased risk of breast cancer compared to parous women in many previous studies.[17,22] In parous women as the number of live births increased, the breast cancer risk further decreased. A study found that each live birth reduced life-time risk of breast cancer by 7%.[23] Previous local studies have produced inconsistent results regarding breast cancer and parity. Gilani GM[14] found that nulliparous women were not at increased risk for breast cancer compared to parous women. On the other hand Mahmood S et al[11] found increased breast cancer risk for parous women. This is entirely opposite to well-established protective effect of parity. Our women have more children than do western women, and this is one of the major causes of low incidence of breast cancer in our population as compared to western population.

Later age at first live birth was associated with increased risk for breast cancer. This has been found in most of western and local studies.[17,24,11,14] A review article concluded that compared to women with first live birth below 20 years of age, women with first live birth after age 30 years have two times more breast cancer risk.[5]

Reduction of breast cancer risk with ever breastfeeding was seen in many case-control and cohort studies.[25-27] Prolonged duration of lactation further reduced breast cancer risk. In a collaborative reanalysis of 53 studies, authors concluded that every 12 months of lactation reduces relative risk of breast cancer by 4.3%[28]. Breastfeeding practices are high in our country and most women breastfeed for longer durations. This has led some experts to say that breastfeeding has no relation with breast cancer in Pakistan[10]. We found that ever breastfeeding did not decrease breast cancer risk. Many local studies support our results. Parvez T et al[12] and Gilani GM[14] have reported that breastfeeding did not affect breast cancer risk. However, Faheem et al[13] and Mahmood S et al[11] showed that breast cancer risk was more for women with no history of breast cancer. Their results can be explained by the fact that their analysis for lactation and breast cancer risk was not restricted to parous women, instead they included all women. In Faheem et al[13] 12% of cases were unmarried compared to 3.3% of controls (p = 0.008). The proportion of married women who were nulliparous was not reported in their study. Since it is rare in our society that an unmarried woman has children, so more cases than controls in their study were nulliparous. And if the analysis for association of lactation and breast cancer is restricted to parous women only, it would have resulted in no association between lactation and breast cancer. Similar is the case with Mahmood S et al[11].

Table 2: *Characteristics of cases and controls regarding reproductive risk factors.*

Variables	Case N = 150 n.	Control N = 300 n.	OR[1]	95% CI	OR[2]	95% CI
Parity						
Nulliparous	17	8	4.7	1.9—11.0	4.6	1.6—13.5
Parous	133	292				
No. of live births						
Nulliparous	17	8	5.1	2.1—12.2	5.2	1.8—15.2
1 – 2	21	22	2.3	1.2—4.3	2.7	1.4—5.2
≥ 3	112	270	1.0	Reference	1.0	Reference
Age at 1st live birth						
Nulliparous	17	8	0.9	0.3—3.4	1.1	0.3—4.4
< 30 years	118	285	0.2	0.1—0.5	0.2	0.1—0.5
≥ 30 years	15	7	1.0	Reference	1.0	Reference
Lactation[3]						
Never	7	9	1.7	0.6—4.8	1.8	0.6—5.0
Ever	126	283				
Duration of lactation						
No lactation	7	9	1.0	Reference	1.0	Reference
< 3 months	6	6	1.3	0.3—5.8	1.4	0.3—6.4
≥ 3 months	120	277	0.5	0.2—1.5	0.5	0.2—1.5
Nulliparous	17	8	2.7	0.7—10.0	2.6	0.6—11.4

[1]Unadjusted Odds Ratio
[2]Odds Ratio adjusted for age, marital status, menopausal status, and use of oral contraceptives
[3]For parous women only

Our study had some limitations. First we could not explain our results regarding family history of breast cancer and breast cancer risk. Second, we think that our findings about age at menarche and menopause are subjected to recall bias.

Conclusion

Nulliparity and more age at first live birth are major reproductive risk factors for breast cancer in our population. The role of breastfeeding, ages at menarche and menopause needs clarification and further work.

References

1. Bhurgri Y, Bhurgri A, Hassan SH, et al: *Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry.* Int J Cancer 2000; 85 (3): 325-9.
2. Mousavi SM, Mohagheghi MA, Mousavi-Jerrahi A, et al: *Burden of breast cancer in Iran: a study of the Tehran population based cancer registry.* Asian Pac J Cancer Prev 2006; 7 (4): 571-4.
3. Chopra, R: *The Indian scene.* Journal of clinical oncology 2001; 19 (18): 106-111.
4. Bhurgri, Y: *Karachi Cancer Registry Data--implications for the National Cancer Control Program of Pakistan.* Asian Pac J Cancer Prev 2004; 5 (1): 77-82.
5. McPherson K, Steel CS, Dixon JM: *Breast cancer—epidemiology, risk factors, and genetics.* BMJ 2000; 321: 624-28.
6. Shibuya K, Mathers CD, Boschi-Pinto C, et al: *Global and regional estimates of cancer mortality and incidence by site: II. results for the global burden of disease 2000.* BMC Cancer 2002; 2: 37.
7. Bray F, McCarron P, Parkin D M: *The changing global patterns of female breast cancer incidence and mortality.* Breast Cancer Res 2004; 6: 229-239.
8. Kumar V, Abbas A K, Fausto N: *Robbins and Cotran Pathologic Basis of Disease*, New Delhi: Elsevier. 7th edition, 2004, pp 1131-35.
9. Tyczynski J, Tarkowski W, Parkin DM, et al: *Cancer mortality among polish migrants to Australia.* Eur J

Cancer 1994; 30A: 478-484.

10. Bhurgri Y, Bhurgri A, Nishter S, et al: *Pakistan - Country Profile of Cancer and Cancer Control.* JPMA, 2006; 56 (3): 124-130.
11. Mahmood S, Rana T F, Ahmad M: *Common deternin-ants of CA breast- A case control study in Lahore.* Annals of KEMU 2006; 12 (2): 227-228.
12. Parvez T, Anwar MS, Sheikh AM: *Study of risk factors for carcinoma breast in adult female general population in Lahore.* Journal of the College of Physicians and Surgeons, Pakistan 2001; 11 (5): 291-293.
13. Faheem M, Khurram M, Jafri IA, et al: *Risk factors for breast cancer in patients treated at NORI Hospital, Islamabad.* JPMA 2007; 57 (5): 242.
14. Gilani, GM: *Statistical aspects of epidemiology of breast cancer in Punjab, Pakistan*, in *Institute of Statistics*. 2003, University of the Punjab: Lahore. p. 231.
15. Iwasaki M, Otani T, Inoue M, et al: *Role and impact of menstrual and reproductive factors on breast cancer risk in Japan.* Eur J Cancer Prev 2007; 16 (2): 116-23.
16. Shantakumar S, Terry MB, Teitelbaum SL, et al: *Reproductive factors and breast cancer risk among older women.* Breast Cancer Res Treat 2007; 102 (3): 365-74.
17. Gao YT, Shu XO, Dai Q, et al: *Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study.* Int J Cancer 2000; 87 (2): 295-300.
18. Mahouri K, Dehghani-Zahedani M, Zare S: *Breast cancer risk factors in south of Islamic Republic of Iran: a case-control study.* East Mediterr Health J 2007; 13 (6): 1265-73.
19. Gajalakshmi CK, Shanta V: *Risk factors for female breast cancer. A hospital-based case-control study in Madras, India.* Acta Oncol 1991; 30 (5): 569-74.
20. Pakseresht S, Ingle GK, Bahadur AK, et al: *Risk factors with breast cancer among women in Delhi.* Indian Journal of Cancer 2009; 46 (2): 132.
21. *Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58, 209 women with breast cancer and 101, 986 women without the disease.* Lancet 2001; 358 (9291): 1389-99.
22. Lee E, Ma H, McKean-Cowdin R, et al: *Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and non-carriers: results from a population-based study.* Cancer Epidemiol Biomarkers Prev 2008; 17 (11): 3170-8.
23. Lambe M, Hsieh CC, Chan HW, et al: *Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden.* Breast Cancer Res Treat 1996; 38 (3): 305-11.
24. Li CI, Littman AJ, White E: *Relationship between age maximum height is attained, age at menarche, and age at first full-term birth and breast cancer risk.* Cancer Epidemiol Biomarkers Prev 2007; 16 (10): 2144-9.
25. Huo D, Adebamowo CA, OgundiranTO, et al: *Parity and breastfeeding are protective against breast cancer in Nigerian women.* Br J Cancer 2008; 98 (5): 992-6.
26. Tryggvadottir L, Tulinius H, Eyfjord JE, et al: *Breastfeeding and reduced risk of breast cancer in an Icelandic cohort study.* Am J Epidemiol 2001; 154 (1): 37-42.
27. Lee SY, Kim MT, Kim SW, et al: *Effect of lifetime lactation on breast cancer risk: a Korean women's cohort study.* Int J Cancer 2003; 105 (3): 390-3.
28. *Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease.* Lancet 2002; 360 (9328): 187-95.