RESEARCH ARTICLE

A Multicenter Matched Case Control Study of Breast Cancer Risk Factors among Women in Karachi, Pakistan

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Abstract

Background: Breast cancer (BC), the most common female cancer in Pakistan, is associated with a very high mortality. However, the roles of individual risk factors for BC among Pakistani women are still controversial. To assess potential risk factors for BC, a matched case-control study was conducted in two tertiary care hospitals of Karachi, Pakistan. Materials and Methods: The study population included 297 pathologically confirmed incident cases of BC patients diagnosed between January 2009 and December 2010. 586 controls without any history of BC were matched on hospital and ±5 years of ages. Results: Positive family history of BC (MOR=1.72; 95%CI: 1.10, 2.80 for first degree vs. none), single marital status (MOR=1.55; 95%CI: 1.10, 2.39 for single/divorced/widowed women vs. married women), older age at menopause (MOR=3.92; 95%CI: 2.52, 6.18 for menopausal women aged below 45 years, MOR=6.42; 95%CI: 3.47, 11.98 for menopausal women above 45 years of age compared with premenopausal women) conferred an increased risk of BC for women. Increasing parity decreased the risk of BC (MOR=0.90; 95%CI: 0.85, 0.97 for each live birth). Intake of Vitamin D supplements (MOR=0.30; 95%CI: 0.12, 0.81 for ≤3 years and MOR=0.27; 95%CI: 0.13, 0.56 for >3 years) was protective compared to non-users of Vitamin D. Conclusions: This study confirmed only few of the recognized risk factors in Pakistani women. The protective effect of Vitamin D is important from public health perspective and needs to be further explored through a randomized controlled trial.

Keywords: Breast cancer - risk factors - vitamin D - matched case control study - Pakistani women

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Introduction

Breast cancer is the commonest malignancy in women and comprises 18% of all female cancers. In Pakistan, BC is an enormous public health concern as its incidence is alarmingly high and mortality is the highest in any Asian population (Bhurgri et al., 2000; Bhurgri et al., 2007; Sohail and Alam, 2007). Affected women are typically young and often present with advanced disease (Usmani et al., 1996). The age-standardized rate (ASR) of breast cancer in Karachi, Pakistan was 69.1 per 100,000 averaged over the years 1998-2002, the highest recorded rate of breast cancer in Asia (Bhurgri et al., 2000). Advanced stage breast lump with local or loco-regional spread remains the commonest mode of presentation of carcinoma breast (Malik, 2002). The reasons for high rates of breast cancer in Pakistan are not known. However, the lifestyle is rapidly changing towards a western type of life, so it is of interest to study the pattern as well as the influence of breast cancer risk factors in our population. Overall, it is generally accepted that BC is a complex, heterogenous disease and is likely the result of interacting genetic and environmental factors. There is evidence for relationship between several lifestyle factors and breast cancer risk (Kruk, 2007). However, the results vary in different populations. The major influences on breast cancer appear to be certain reproductive factors and diet (McPherson et al., 2000). The former may not be entirely applicable to our population where high levels of fertility, early age at first pregnancy, multiple births and prolonged breast-feeding are the norm (Malik et al., 1992). One study was conducted in Punjab that analyzed some of the risk factors among Pakistani women but did not analyze the other important factors like physical activity and diet (Gilani and Kamal, 2004). Another study done in Lahore evaluated the difference between pre- and post-menopausal breast cancer regarding menstrual and reproductive risk factors(Zeeshan, 2012). Only a small proportion of all breast cancers can currently be explained by traditional risk factors, leaving most of the recent increase in incidence unsolved. The purpose of this study was to evaluate the relation between various risk factors and BC risk among all women of age between 18 years and 75 years in Karachi.

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Materials and Methods

This matched case control study was conducted between 2009 and 2010 in Karachi, which is the largest city of Pakistan, with a population of population of 2.5 crore. Two tertiary care hospitals in Karachi selected were Aga Khan University Hospital (AKUH), a private hospital and Jinnah Postgraduate Medical Center (JPMC), a public hospital.

Selection of cases and controls

All women of age between 18 years and 75 years in any of the above-mentioned hospitals were potential study subjects.

Case definition: All women with pathologically confirmed incident cases of primary breast cancer (*International Classification of Diseases* code 174 and code C50 from the Ninth Revision and Tenth Revision, respectively) diagnosed within 9-12 months of the interview were eligible as cases. Only women stable enough to be able to complete the interview were enrolled. Cases with breast cancer more than 1 year after diagnosis or with past history of any other cancer were excluded. For each case, 2 controls, individually matched to the hospital, and ±5 years of age were selected. The control group was composed of women attending outpatient services for general medical and surgical departments of the selected hospitals.

Sample size A total of 257 cases and 514 controls were required to achieve at least 80% power with the assumptions for the prevalence of the various risk factors amongst the control group in the range of 10-75%, a matched odds ratio of at least 2, a significance level of 5% and a case to control ratio of 1:2. This sample size was inflated for anticipated 10% non-response. Finally, we needed at least 282 cases and 564 controls.

Data Collection Prior to the interview, informed consent was obtained from all study participants. In-person interviews of cases and controls were conducted by trained doctors using a pre-tested structured questionnaire that included questions on diet, demographic factors, anthropometric measures, body mass index (continuous, kg/m^2), history of various medical conditions, family history of cancer, socioeconomic variables, time spent in household activities on a normal day, job history, tobacco habits, use of prescription and over-the-counter medications, use of nutritional supplements; number of exposure to dental and chest X-rays and other lifestyle factors including physical activity and dietary history. Reproductive variables were age at first live birth and parity, age at first pregnancy, number of pregnancies, variables representing exposures to endogenous hormones (age at menarche, age at menopause), number of pregnancies, and respective outcomes; duration of breast feeding; method of hormonal birth control, history of infertility; exogenous hormone use, gynecologic surgeries and mammography history. Anthropometric measurements were recorded from the medical records. For family history of breast cancer, we made comparisons of 1) women who reported first-degree relatives (mothers, sisters, and daughters) diagnosed with breast cancer with those who reported no family history and 2) women who reported second-degree relatives diagnosed with breast cancer (grandmothers and aunts), but no first degree relatives, with the same referent group. Socioeconomic status variable was created with the help of variables like home ownership, number of rooms, and number of people living in the house, and monthly income which were converted into tertiles. Factor analysis was used to identify the important variables for socio-economic factor. Histopathology reports, TNM staging and hormonal receptor status were obtained from medical records.

Statistical analysis

The data was analyzed using SPSS for Windows (version 18, SPSS Inc., Chicago, IL, USA). Conditional logistic regression used to identify the factors associated with breast cancer, and reported as crude matched odds ratio with 95% confidence interval in univariate analysis. Multi-collinearity among independent variables was assessed using Pearson correlation coefficient and Cramer's V for those variables whose p-value at univariate level was less than 0.25. None of these variables showed multi-collinearity i.e. correlation coefficient value of more than 0.8. In multivariable analysis, conditional multiple logistic regression was performed to identify risk factors of breast cancer while adjusting for other variables. To control for potential confounders of the variables of interest, we selected covariates considered to be risk factors according to previous breast cancer studies. Finally any variable with p-value >0.05, not a confounder or interacting with variables in the model was removed from the model to obtain a parsimonious and biologically meaningful model that best explains the phenomena of breast cancer. The results are reported as matched odds ratios (MOR) with 95% confidence intervals, that examined the association between breast cancer status and risk factors after adjustment for other relevant covariates including age at menarche, parity, age at first full-term pregnancy, miscarriage, breastfeeding, abortion, oral contraceptive use, and hormone replacement therapy.

Ethical consideration

The study was approved by the Ethical Review Board of AKUH and JPMC.

Results

A total of 297 cases and 586 controls were enrolled during the study period. The distribution of all the variables among cases and controls are reported in percentages for categorical variables including working status, exposure of smoking, medical histories of diabetes mellitus, hypertension, depression and asthma, first degree family history of hypertension among relatives, history of benign breast disease, family history of any type of cancer among relatives and outcome of first pregnancy. Mean (SD) is reported for quantitative variables including weight, height, BMI, total numbers of induced abortions, spontaneous abortions and ectopic pregnancies, duration of sleeping hours and life time breast feeding (in months) (Table 1). The mean age of cases was 46 years (SD 10.1).

Infiltrating Ductal Carcinoma (Invasive) was the most common histological type of breast carcinoma (81.1%) followed by ductal carcinoma in situ (4.1%), lobular carcinoma of breast (2.4%), and medullary carcinoma of breast (3.7%). 8.7% of breast cancers were classified as "others" (including mucinous adenocarcinoma, tubular adenocarcinoma, inflammatory breast cancer).

In univariate analysis, no significant differences were observed between cases and controls for age at menarche, age at first pregnancy, medical histories of diabetes, hypertension, thyroid, depression, asthma, family history of breast cancer or any other cancer, total stillbirths, BMI, socioeconomic status, usage of contraceptives or hormone replacement therapy. A significant increase in breast cancer was observed among single women (unmarried, divorced and widowed) compared to married women with higher education. Relative to the controls, cases on average were more likely to have a positive family history of breast cancer. In multivariable analysis, women having a family history of BC (MOR=1.72; 95%CI: 1.10, 2.80),

Table 1. Tumor Characteristics of Breast Cancer, Socio-demographic Characteristics and Potential Risk Factors of Cases and Controls in Two Tertiary Care Hospitals of Karachi (January 2009-December 2010)

Characteristics	Case (297) n (%)	Control (586) n (%)
Histopathology		
Invasive Ductal	240 (81.1)	
Invasive Lobular	7 (2.4)	
Invasive Medullary	11 (3.7)	
Carcinoma in situ	12 (4.1)	
Others	16 (5.4)	
Unknown/missing	11 (3.7)	
Hormone receptor status		
Non Triple Negative	203 (68.3)	
Triple Negative (TN)	42 (14.2)	
Unknown/missing	52 (17.5)	
Grading		
Grade I	18 (6.1)	
Grade II	140 (47.1)	
Grade III	79 (26.6)	
Unknown/missing	60 (20.2)	
Age at Menarche (years)		
≥12	264 (91.3)	527 (92.1)
<12	25 (8.7)	45 (7.9)
Working Status		
Yes	104 (35.0)	188 (32.1)
No	193 (65.0)	398 (67.9)
Medical History of Diabetes Mellitus		
No History	249 (84.1)	495 (85.2)
Borderline	5 (1.7)	7 (1.2)
Gestational diabetes	2 (0.7)	3 (0.5)
Type I/II diabetes	40 (13.5)	76 (13.1)
Medical History of Hypertension		
Yes	99 (33.6)	205 (35.0)
No	196 (66.4)	380 (65.0)
Medical History of Depression		
Yes	27 (9.2)	66 (11.3)
No	268 (90.8)	518 (88.7)
Medical History of Asthma		
Yes	15 (5.1)	40 (6.8)
No	281 (94.9)	545 (93.2)
First degree family History of Hypertension among relatives		
Yes	162 (55.5)	331 (58.2)
No	130 (44.5)	238 (41.8)
History of Benign Breast Disease		
Fibro Adenoma	5 (1.7)	47 (8.0)
Fibrocystic disease	1 (0.3)	24 (4.1)
Mastalgia	7 (2.4)	49 (8.4)
Abscess	3 (1.0)	17 (2.9)
Others	9 (3.0)	20 (3.4)
No disease	272 (91.6)	429 (73.2)
Family history of breast cancer among first degree relatives		
Yes	59 (10.1)	49 (16.5)
No	527 (89.9)	248 (83.5)
Family history of any other cancer among relatives		
None	222 (76.6)	458 (79.5)
Only first degree	36 (12.4)	70 (12.2)
Both first and second degree	32 (11.0)	48 (8.3)
Outcome of first pregnancy		
Live Birth	220 (74.10)	460 (78.50)
Still Birth/IUD	1 (0.30)	17 (2.90)
Spontaneous Abortion	29 (9.80)	49 (8.40)
Preterm	6 (2.00)	2 (0.30)
Never Pregnant	21 (7.10)	22 (3.80)
Never Married	20 (6.70)	36 (6.10)
Weight (in Kg.)*	67.37 (0.86)	68.15 (0.74)
Height (in cm)*	155.07 (0.45)	154.95 (0.34)
BMI (Kg/m^2)£	28 (24, 30)	28 (24, 30)
Duration of Sleeping hours*	6.3 (0.1)	6.3 (0.1)
Total months of breast feeding*	53.7 (54.0)	67.1 (57.7)
Lifetime use of oral contraceptives(in months)£		
	6 (2, 24)	2.8 (9, 33)
Vitamin D supplementation		
Nonuser	286 (96.30)	531 (90.60)
≤36months	6 (20.00)	24 (4.10)
>36months	5 (1.70)	31 (5.30)
Vitamin C supplementation		
Non user	269 (90.60)	515 (87.90)
≤36months	9 (3.00)	29 (4.90)
>36months	19 (6.40)	42 (7.20)
Vitamin E supplementation		
non user	292 (98.10)	570 (97.30)
≤36months	4 (1.30)	9 (1.50)
>36months	1 (0.30)	7 (1.20)
Multivitamin supplementation		
non user	208 (70.00)	405 (69.10)
≤36months	51 (17.20)	99 (16.90)
>36months	38 (12.80)	82 (14.00)
Whether exposed to smoking (Active or Passive)		
None	173 (58.20)	348 (59.40)
Only active smoker	5 (1.70)	8 (1.40)
Only Passive Smoker	109 (36.70)	217 (37.00)
Both	10 (3.40)	13 (2.20)
Physical activity (minutes /week)		
Vigorous activity	7.3 (2.29)	9.7 (2.81)
Moderate activity	393.4 (41.22)	433.0(37.08)
Walking	83.1 (8.41)	83.9 (6.09)
Sitting	1708.3 (63.82)	1797.7 (9.77)
Cooking	465.2 (23.85)	490.8(17.61)
Cleaning the house	204.2 (19.50)	178.4(13.03)
Laundry	165.5 (16.47)	150.9 (8.73)
Shopping	127.2 (13.23)	121.7 (8.77)

*Mean (SD), £Median (25 percentile, 75 percentile), BMI= body mass index, calculated by dividing weight in kilograms with height in meters squared

Table 2. Distribution of Crude and Adjusted Matched Odds Ratios (MOR) (95%CI) of Breast Cancer by Participants' Characteristics in Two Tertiary Care Hospitals of Karachi (January 2009-December 2010)

Characteristics	Crude MOR (95%CI)	Adjusted MOR (95%CI)	Characteristics	Crude MOR (95%CI)	Adjusted MOR (95%CI)
Levels of education			Relationship of Family History of Breast Cancer		
Illiterate	1		No family history	1	
Primary to Secondary	0.77(0.50, 1.19)		Mother	2.16(0.89, 5.23)	
Intermediate & above	1.33(0.91, 1.96)		Sister	2.55(1.22, 5.31)	
Marital Status			Other relatives	1.44(0.82, 2.53)	
Married	1	1	First degree family History of breast cancer		
Single/Widowed/Divorced	1.63(1.35, 2.36)	1.55(1.10, 2.39)	Did not have history	1	1
Ethnicity			Had history	1.84(1.2, 2.80)	1.72 (1.10, 2.80)
Urdu	1		First degree family History of any other cancer		
Sindhi	0.91(0.57, 1.46)		Yes	1.27(0.91, 1.76)	
Punjabi	0.61(0.39, 0.96)		No/Not Sure	1	
Pashto	0.58(0.28, 1.22)		Age of woman at first pregnancya	1.02(0.99, 1.06)	
Balochi	1.27(0.44, 3.65)		Total Pregnancies (Gravida)[a]	0.91(0.86, 0.96)	
Hindko	0.60(0.27, 1.31)		Parity	0.89(0.83, 0.94)	0.90(0.85, 0.97)
Memon/Gujrati	0.98(0.60, 1.60)		Total Stillbirthsa	0.70(0.39, 1.27)	
Other Languages	1.64(0.79, 3.41)		Total Duration of Breast Feedinga	0.99(0.99, .997)	
Outcome of first pregnancy			Total Duration of Contraceptive Use[a]	0.99(0.98, 1.002)	
Live Birth	1		Body Mass Index	0.98(0.94, 1.02)	
Still Birth/IUD	0.12(0.02, 0.93)		Multivitamin use		
Spontaneous Abortion	1.25(0.77, 2.02)		Non users	1	
Preterm	6.48(0.30, 32.30)		≤3years usage	1.02(0.68, 1.52)	
Nulliparous	1.58(0.99, 2.53)		>3years usage	0.88(0.57, 1.35)	
Menopausal Status			Vitamin D use		
Still Menstruating	1	1	Non users	1	1
Stopped at age ≤45 years	4.96(3.11,7.93)	3.92(2.52, 6.18)	≤3years usage	0.44(0.18, 1.12)	0.30 (0.12, 0.81)
Stopped at age >45 years	6.04(3.31, 11.02)	6.42(3.47, 11.98)	>3years usage	0.26(0.10,0.14)	0.27 (0.13, 0.56)
History of Benign Breast Disease			Vitamin C use		
Did not have any history	1		Non users	1	
Had history	0.21(0.13,0.34)		≤3years usage	0.59(0.27, 1.28)	
Medical History of Thyroid disease			>3years usage	0.82(0.43, 1.53)	
No	1		Vitamin E use		
Hypothyroidism	0.72(0.42, 1.26)		Non users	1	
Hyperthyroidism	0.53(0.21, 1.30)		≤3years usage	0.82(0.24, 2.81)	
			>3years usage	0.28(0.03, 2.32)	

*ORs adjusted for age at menarche and first live birth, breastfeeding duration, abortions, BMI, smoking and physical activity

single women compared to married women (MOR=1.55; 95%CI: 1.10, 2.39), menopausal women aged below 45 years (MOR=3.92; 95%CI: 2.52, 6.18) or above 45 years of age (MOR=6.42; 95%CI: 3.47, 11.98) compared to those who were still menstruating had higher risk of BC. Increasing parity decreased the risk of BC (MOR=0.90; 95%CI: 0.85, 0.97). Intake of Vitamin D supplements for <3years (MOR=0.30; 95%CI: 0.12, 0.81) or <3 years (MOR=0.27; 95%CI: 0.13, 0.56) was protective compared to non-users of Vitamin D.

Discussion

In this matched case control study, we confirmed the role of family history of breast cancer as risk factor for breast cancer among our women which is consistent with previous findings (Aghassi-Ippen et al., 2002; Ebrahimi et al., 2002; Norsa'adah et al., 2005; Hafize, 2011). However, younger age at diagnosis of the relative was not associated with increased risk of BC. A woman's risk of breast cancer is increased if she has a first degree relative who developed the disease before the age of 50, and the younger the relative when she developed breast cancer the greater the risk (Faheem, 2007). It strongly suggests genetic influences in BC development in our population. However, it is a proxy measure for both hereditary factors as well as common environmental or behavioral exposures that may underlie cancer risk.

Our observation of a positive association between age at menopause and breast cancer risk is also consistent with several previous reports (Ewertz and Duffy, 1988; Parsa and Parsa, 2009; Phipps et al., 2010). Late menopause after the age of 50 years leads to an increase in ovulatory cycles and subsequently higher endogenous estrogen levels over a woman's lifetime, with an increased vulnerability to environmental carcinogens, and thus increasing BC risk.

A high number of live births is recognized as protective against BC. Our study data provide evidence that, among parous women, a high number of births is associated with decreased BC. Our study showing the protective effect of parity is consistent with similar previous findings (Yuan et al., 1988; Egan et al., 1998). Several mechanisms have been proposed to explain the protective effect of pregnancy in the general population: decreased levels of estrogen and progesterone, increased levels of sex hormone-binding globulin, and pregnancy-induced differentiation of breast tissue (Lee et al., 2008).

Our study findings showed higher risk of BC among women with single marital status including unmarried, divorced and widowed status compared with married women. In similar studies, the risk of BC was higher for unmarried women compared with married women (Gajalakshmi and Shanta, 1991; Rao et al., 1994; Pakseresht et al., 2009). Being single in Pakistani society is

reported to be psychosocially stressful. Such psychosocial stress is usually chronic continuing indefinitely and may have significant effects on health (Fox, 1996; De, 1999). Adverse life events like divorce or death of spouse have also been reported as risk factors associated with BC in few other studies (Jasmin 1990; Fox, 1996; Ginsberg, 1996; Jacobs, 2000).

Vitamin D supplements usage for more than 36 months was protective [MOR (adjusted)=0.27; 95%CI: 0.13, 0.56]. This finding adds to the existing evidence on the protective role of Vitamin D supplementation in breast cancer risk. Measures of sunlight exposure and dietary vitamin D intake have been consistently associated with reduced risk of breast cancer (Lipkin and Newmark, 1999; Braverman, 2007; Welsh, 2007; Chen et al., 2009). However, the observed relationship in our study was based on the intake of Vitamin D supplements only and not on other Vitamin D variables like sun exposure or dietary sources of Vitamin D. Further research into the relationship between breast cancer and vitamin D and vitamin D–related lifestyle factors such as sun and milk consumption must be undertaken to create new opportunities in breast cancer prevention in which few potentially modifiable risk factors exist at present.

Cases and controls did not significantly differ with regard to having a first-degree relative with history of other cancers, breast feeding, previous radiation treatment, and age at menarche, use of hormone replacement therapy/ OCs/clomiphene. The findings of lack of association of nulliparity, age at first live birth, and age at menarche with breast cancer are consistent with other recent case control studies (Usmani, 1996; McPherson, 2000)

Our findings are based on a carefully designed multicenter hospital based matched case control study to assess both established and controversial breast cancer risk factors through a detailed questionnaire. Several limitations must be considered when interpreting the results from our study. First of all recall bias and inability to establish temporality between breast cancer and certain variables are inherent due to the case control study design. However, effort was made to minimize recall bias by using standardized questionnaire and the similar interviewing procedures for both cases and controls. Further, our study is less likely to be prone to both recall and survival bias because our case subjects were interviewed within 9-12 months of diagnosis.

This being a hospital based study; the results may not be applicable to the general population at large. We could not establish a relationship between certain factors like clomiphene use, and HRT because of the low prevalence of these exposures in our population.

In order to reduce breast cancer mortality effectively, we need to focus our efforts on prevention and early detection through approach to screening our high risk populations. This study confirms some of the risk factors of the western population but it fails to demonstrate many of the other recognized factors in Pakistani women.

This study confirms positive family history of breast cancer and late age at natural menopause as breast cancer risk factors. Therefore, it is recommended to women with these risk factors to perform breast cancer screening tests earlier.

Finally this study supports the beneficial effect of high parity and Vitamin D intake in decreasing BC risk after controlling for other confounders. Role of Vitamin D is of special public health significance because our population has low Vitamin D levels due to some genetic reasons. Therefore, diet or measures to increase Vitamin D especially in high risk population could play a preventive role. Furthermore, a randomized clinical trial aimed at clarifying this protective relationship for breast cancer risk could provide insights into the underlying cause of the BC in our population and preventive strategies.

In summary, our findings suggest that only few of the reproductive factors may play an important role in the development of breast cancer among our population compared to the Western populations. The discrepancies between our findings and other studies might be due to the different characteristics of Pakistani women that merit further investigation to further clarify the role of all the risk factors and obtain a deeper insight into the breast cancer epidemic in Karachi.

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