RESEARCH ARTICLE

Demographic variation and risk factors regarding breast cancer among females in Southern Punjab, Pakistan

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Abstract

Objective: To explore epidemiology, clinical profiles and contribution of reproductive and non-reproductive risk factors in breast cancer development.

Methods: The case-control study was conducted from October 2017 to March 2018 at Quaid-i-Azam University, Islamabad, Pakistan, and comprised breast cancer patients and age-matched controls recruited from the Bahawalpur Institute of Nuclear Medicine and Oncology, and the Bahawal Victoria Hospital, Bahawalpur. Socio-demographic data, family history of cancer, reproductive health and lifestyle factors were recorded using a structured questionnaire. Data was analysed using SPSS 21 and Stata/IC 14.1.

Results: Of the 326 women, 163(50%) each were cases and controls. The mean age for both the groups was identical at 46.04±10.62 years. Positive family history and hypertension were significantly linked to increased breast cancer risk ($p<0.05$), while intense physical activity, increased anthropometric measurements and breastfeeding per child in months were inversely associated with the risk ($p<0.05$).

Conclusion: Established risk factors for breast cancer were reaffirmed.

Keywords: Breast cancer, Risk factors, South Punjab, Family history, Hypertension. (JPMA 71: 1749; 2021)

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Introduction

Globally, 1.7 million new breast cancer cases are diagnosed each year and 33% of them die of the disease.[1] Incidence rates are higher in Europe compared to Asia. The incidence rate of breast malignancy in Pakistani population is 2.5 times higher than India and Iran, accounting for 34.6% of female cancers.[2,3] Approximately 10% of all breast cancers have a hereditary background, while major contributors are non-genetic risk factors.[4] Various studies have reported contribution of non-genetic risk factors to breast malignancy from different populations, like Askhensi Jews, Australian, European and American populations,[4,5] but there are few such reports from Pakistan,[5-8] and none of them is based on the population in southern Punjab.

Studies regarding breast cancer risk factors include demographic findings, such as sub-ethnicity, family history of breast cancer, personal history of non-cancerous disease, alcohol consumption, body mass index (BMI) and hypertension (HTN).[9] Among reproductive factors, age at menarche (early menarche), age at first full-time pregnancy (FFTP), age at menopause (late menopause), parity, breastfeeding per child (duration ≥12 months/child), history of miscarriages, usage of oral contraceptive pills (OCPs) and hormone replacement therapy (HRT) were found to be linked to breast cancer.[9] Exposure to tobacco (smoking, hookah, naswar) has also been linked with breast malignancy.[2] Occupation-related risk factors, like night-shift working and physical activity, have been explored with mixed findings.[9,10]

Given the differences in social attributes, education, lifestyle and potential exposure to risk factors, breast cancer contributors in Pakistan may differ from those already reported for other populations. Relative mortality due to breast cancer is greatest in less-developed countries,[3] like Pakistan, which is attributed to detection at later stages due to lack of awareness and lack of access to early screening and treatment.[11,12] Therefore, characterisation of risk factors for breast cancer in local population can lead to improvement in diagnosis especially at early stage, management and efforts to avoid preventable behaviours and exposures. The current study was planned to investigate epidemiology, clinical aspects and risk factors associated with breast cancer in Pakistan's southern Punjab region.

Subjects and Methods

The case-control study was conducted from October 2017 to March 2018 at Quaid-i-Azam University (QAU), Islamabad, Pakistan, and comprised breast cancer patients and age-matched controls recruited from the Bahawalpur Institute of Nuclear Medicine and Oncology, and the Bahawal Victoria Hospital, Bahawalpur. After approval from the QAU ethics review committee, the sample size was calculated using Epitools software taking 5% margin

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of error, hazard ratio 2 and with power 80%.[13,14]

The sample was raised using non-probability consecutive sampling technique. Those included were histologically-confirmed breast cancer patients who visited the hospitals irrespective of age, family history, clinical presentation, histopathological type etc. Controls were healthy women with no history of breast or any other cancer, belonging to southern Punjab region who were individually matched to cases by age. They were recruited at the same time from among patients' attendants. Informed consent was obtained from both the cases and the controls.

Data was collected using a pre-designed questionnaire by a single investigator. The questionnaire was prepared in the light of published reports.[7,8] It was translated into the local language whenever required and backward into English to ensure uniformity and accuracy of data. The structured questionnaire included information on socio-demographic, menstrual and reproductive characteristics, family history of cancer in first- and second-degree relatives and several lifestyle factors, including night-shift working, smoking etc.

Height and weight were recorded for the calculation of body mass index (BMI) which was classified according to the World Health Organisation (WHO) cut-off values for Asian countries.[15] Physical activity was estimated in three subsets, including activity at work, activity of travelling, recreational activities as well as sedentary behaviour, and was recorded using the Global Physical Activity Questionnaire (GPAQ2).[16] At time of recruitment, menopausal status was determined as premenopausal if women had regular menstruation over the preceding 12 months, and postmenopausal if menstruation was absent in the last 12 months.

Data was analysed using SPSS 21 and Stata/IC 14.1. Qualitative variables were expressed as frequencies and percentages, while continuous variable were expressed as mean ± standard deviation (SD). Conditional logistic regression model was used to identify potential risk factors linked with breast cancer. Crude and adjusted odds ratio (ORs) obtained were used to estimate contribution of each factor. For all Ors, 95% confidence interval (CI) were calculated. Bivariable (unadjusted) and multivariable (adjusted) analyses were also conducted. $P<0.05$ was considered statistically significant.

Results

Of the 326 women, 163(50%) each were cases and

Table-1(a): Baseline characteristics.

Baseline Characteristics		Cases		Controls	
		Frequency	Percentage	Frequency	Percentage
Age in years	26-30	10	6.1	10	6.1
	31-35	19	11.7	19	11.7
	36-40	24	14.7	24	14.7
	41-45	38	23.3	38	23.3
	46-50	30	18.4	30	18.4
	51-55	14	8.6	14	8.6
	56-60	12	7.4	12	7.4
	61-65	7	4.3	7	4.3
	66-70	6	3.7	6	3.7
	71-75	2	1.2	2	1.2
	76-80	1	0.6	1	0.6
Socio-Economic Status	Poor	55	33.7	105	64.4
	Middle Class	98	60.1	56	34.4
	High	10	6.1	2	1.2
Profession	Student	0	0	1	.4
	Housewife	140	85.9	147	90.2
	Working	23	14.1	15	9.2
Education	Uneducated	76	46.6	120	52.1
	Primary	22	13.5	21	10.4
	Secondary	40	24.5	29	12.9
	Higher Education	25	15.3	56	24.5
Parity	Nulliparous	13	8.0	6	3.7
	1	8	4.9	14	8.6
	2	28	17.2	22	13.5
	3	27	16.6	34	20.9
	4	32	19.6	22	13.5

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Baseline Characteristics		Cases		Controls	
		Frequency	Percentage	Frequency	Percentage
	5	24	14.7	26	16.0
	6	15	9.2	17	10.4
	7	7	4.3	12	7.4
	8	8	4.9	6	3.7
	9+	1	0.6	4	2.4
Family History	Positive	61	37.4	21	12.9
	Negative	102	62.6	142	87.1
Personal History	Positive	10	6.1	10	6.1
	Negative	153	93.9	153	93.9
Intensity of Physical Activity	Light	90	55.2	88	54
	Moderate	56	34.4	40	24.5
	Vigorous	17	10.4	0.35	21.5

Table-1(b): Baseline characteristics.

Body mass index (BMI)	Underweight	1	0.6	16	9.8
	Normal	47	28.8	29	17.8
	Overweight	43	26.4	24	14.7
	Obese	72	44.2	94	57.7
Smoking	Yes	9	5.5	3	1.8
	No	154	94.5	160	98.2
Naswar	Yes	14	8.6	4	2.5
	No	149	91.4	159	97.5
Hookah	Yes	7	4.3	3	1.8
	No	156	95.7	160	98.2
Oral Contraceptive Pills	Yes	41	25.2	33	20.2
	No	122	74.8	130	79.8
Hormonal Replacement Therapy	Yes	30	57.7	31	63.3
	No	22	42.3	19	36.7
Age at first full term pregnancy	Nulliparous	13	8	6	3.7
	≤20	44	27.0	66	40.5
	21-29	95	58.3	78	47.9
	≥30	11	6.70	13	7.90
Age at menarche	11	20	12.3	25	15.3
	12	111	68.0	107	65.7
	13	19	11.7	23	14.1
	14+	13	8	8	4.9
Ethnicity	Saraiki	71	43.6	71	43.6
	Punjabi	70	42.9	71	43.6
	Muhajir	22	13.5	21	12.8
Menopausal Status	Premenopausal	111	68.1	114	69.9
	Postmenopausal	52	31.9	49	30.1
Breastfeeding per child (months)	Never fed	19	11.7	11	6.7
	≤6.5	68	41.7	28	17.2
	6.51-12.50	72	44.2	70	42.9
	12.51-18.50	3	1.8	31	19.0
	≥18.51	1	.6	23	14.1
Miscarriages	0	91	55.8	118	72.4
	1	35	21.5	25	15.3
	2	28	17.32	13	8.0
	3+	9	5.5	7	4.3
Night shift working	Yes	2	1.2	3	1.8
	No	161	98.8	160	98.2
Hypertension	Yes	63	38.7	13	8
	No	100	61.3	150	92

Table-2: Continuous variables.

Characteristics	Cases	Controls
Mean age (years)	46.04±10.62	46.04±10.62
Mean age at menarche	12.15±0.75	12.08±0.69
Mean age at menopause	48.60±3.63	49.31±3.03
Mean BMI (kg/m^2)	26.26±13.59	26.62±5.92
Mean age at first full term pregnancy**	20.71±7.2	25.52±6.49
Mean period in years for Breastfeeding per child***	7.41±3.20	12.16±5.53
Mean number of live births	3.7±2.19	4±2.1

*Among postmenopausal women. **Among parous women. ***Among breast-feeding women.
SD: Standard deviation.

Table-3: Clinical characteristics of breast cancer cases (n=163).

Clinical Characteristics		Frequency (n)	Percentage (%)
Clinical presentation	Unilateral breast lump	129	79.1
	Bilateral breast lump	7	4.3
	Breast lump and Nipple Discharge	16	9.8
	Fungating tumour	5	3.1
	Recurrence	6	3.7
Type of carcinoma	Invasive ductal Carcinoma	142	87.1
	Invasive lobular carcinoma	16	9.8
	Colloid Carcinoma	1	0.6
	Medullary Carcinoma	2	1.2
	Paget's Disease	2	1.2
Oestrogen receptor status	Positive	58	35.6
	Negative	49	30.1
	Unknown	56	34.4
Progesterone receptor status	Positive	51	31.3
	Negative	56	34.4
	Unknown	56	34.4
Her-2-neu status	Positive	14	8.6
	Negative	82	50.3
	Unknown	63	38.7
	Equivocal	4	2.5
Site of breast affected	Right	65	39.9
	Left	92	56.4
	Bilateral	6	3.7
Size of breast lump	0-2cm	1	0.6
	3-5cm	43	26.4
	6-8cm	92	56.4
	9-11cm	22	13.5
	Fungating tumour	5	3.1
Metastasis to lymph nodes	Axillary	121	74.2
	Axillary-Supraclavicular	23	14.1
	Axillary-Opposite Axillary	2	1.2
	No lymph Nodes Involved	14	8.6
	Not Examined	3	1.8
Stage of tumour	Stage Unidentified	68	41.73
	Stage I	0	0
	Stage II	19	11.65
	Stage III	26	15.95
	Stage IV	50	30.67

Table-4: Risk factor analysis using conditional logistic regression.

	Characteristics	Categories	Cases	Controls	Crude OR (95% CI)	P-value	*Adjusted OR (95% CI)	P-value
Reproductive Risk Factors	Age of menarche	>12	32	31	Reference		Reference	
		≤12	131	132	0.96(0.56-1.65)	0.890	0.70(0.12-3.77)	0.665
	Breastfeeding per	<12	126	61	Reference		Reference	
	child***	≥12	21	93	0.11(0.06-0.21)	0.000	0.04(0.01-0.24)	0.000
	History of miscarriages	No	91	118	Reference		Reference	
		Yes	72	45	2.14(1.30-3.44)	0.002	3.29(0.74-14.65)	0.117
	Parity	Parous	150	157	Reference		Reference	
		Nulliparous	13	6	2.27(0.84-6.12)	0.106	1	
	Age at first full term	≥20	119	112	Reference		Reference	
	pregnancy	<20	31	45	0.62(0.35-1.09)	0.098	0.33(0.06-1.71)	0.192
Hormone Related Risk Factors	Hormonal Replacement	No	22	18	Reference		Reference	
	therapy**	Yes	30	31	0.84(0.35-1.99)	0.701	0.73(0.22-3.19)	0.692
	Age of menopause (Late	<55	7	1	Reference		Reference	
	Menopause)**	≥55	45	48	9.29(1.83-83.17)	0.009	6.08(0.18-195.72)	0.308
	History of Oral	No	122	130	Reference		Reference	
	Contraceptive Pills	Yes	41	41	1.35(0.78-2.33)	0.272	1.64(0.36-7.49)	0.519
Medical Related Risk Factors	Hypertension	No	100	150	Reference		Reference	
		Yes	63	13	7.06(3.68-13.54)	0.000	9.55(4.16-29.92)	0.000
	Family History	No	102	142	Reference		Reference	
		Yes	61	21	4.32(0.24-7.76)	0.000	3.40(1.65-6.98)	0.001
	Personal History for past	No	153	153	Reference		Reference	
	non-cancerous diseases	Yes	10	10	1(0.40-2.46)	1.000	0.71(0.21-2.18)	0.522
Lifestyle Risk Factors	Night Shift Working	No	161	160	Reference		Reference	0.890
		Yes	2	3	0.66(0.10-4.01)	0.654	0.87(0.12-6.17)	
	Smoking	No	154	160	Reference		Reference	
		Yes	9	3	3(0.81-11.08)	0.099	1.99(0.39-10.14)	0.405
	Alcoholic	No	162	163	Reference		Reference	
		Yes	1	0	1.04e+15(0)	1.000	81016.04(0)	0.988
	Hookah	No	156	160	Reference		Reference	
		Yes	7	3	2.47(0.61-10.01)	0.203	2.21(0.27-18.09)	0.457
	Naswar	No	149	159	Reference		Reference	
		Yes	14	4	4.51(1.26-16.04)	0.020	2.70(0.49-14.79)	0.250
	Physical Activity	Vigorous Intensity	17	35	Reference		Reference	
		Light Intensity	90	88	2.02(1.06-3.82)	0.030	7.50(2.87-19.60)	0.000
		Moderate Intensity	56	40	2.72(1.3-5.43)	0.004	4.04(1.65-9.85)	0.002
Anthropometric Risk Factors	BMI kg/m^2	Underweight	1	16	0.03(0.00-0.307)	0.002	0.04(0.00-0.57)	0.016
		Normal	47	29	Reference		Reference	
		Overweight	43	24	1.17(0.59-2.37)	0.643	2.91(1.12-7.54)	0.028
		Obese	72	94	0.50(0.29-0.88)	0.015	0.64(0.32-1.29)	0.221
Demographic Related Risk Factors	Sub-ethnicity	Saraiki	71	71	Reference		Reference	
		Punjabi	70	71	0.98(0.58-1.65)	0.959	1.20(0.59-2.41)	0.603
		Muhajir	22	21	1.05(0.50-2.20)	0.894	1.08(0.40-2.88)	0.872

CI: Confidence Intervals; OR: odds ratio.

*Odds ratios adjusted for ethnicity, socio-economic status, age at menarche (continuous), menopausal status and age at menopause combined (menopause before and at age 55), parity (parous, nulliparous), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years), family history of breast cancer (yes/no), and body mass index (<25, 25-29, ≥30 kg/m^2).

**Among postmenopausal women.

***Among breastfeeding women.

controls. The mean age for both the groups was identical at 46.04±10.62 years (range: 26-80 years). Baseline characteristics of all the subjects were noted (Tables-1a - 1b). Mean age at menarche in the cases was 12.15±0.75 compared to 12.08±0.69 in the controls, while mean age at menopause in the cases was 48.60±3.63 compared to 49.31±3.03 in the controls (Table-2).

Among the cases, left breast was affected in 92(54.6%) patients, right breast in 65(39.9%), and there were 6(3.6%) bilateral cases. Also, 136(83.4%) of the cases presented with breast lump, while breast lump and nipple discharge

was noted in 16(9.8%). Only 5(3%) patients had fungating tumour.

According to histopathology reports, 142(87.1%) patients were diagnosed with invasive ductal carcinoma, while 21(12.9%) were diagnosed with invasive lobular/colloid/ medullary carcinoma or Paget's disease of breast. Further, 92(56.4%) patients had tumour size 6-8cm. Metastasis to axillary lymph nodes was observed in 121(74.2%), and metastasis to other lymph nodes in addition to axillary was observed in 25(15.3%) patients. Finally, 74(45.7%) patients were diagnosed at stages III and IV (Table-3).

Duration of breastfeeding per child, history of miscarriages, delayed menopause, HTN, family history of disease, intensity of physical activity and BMI were significantly associated with breast cancer risk ($p<0.05$). Multivariate analysis showed that family history, HTN, intensity of physical activity, breastfeeding and BMI were significantly associated with breast cancer development ($p<0.05$) (Table-4).

Discussion

There has been a huge increase in breast cancer cases in Asia over the last few decades.[17] Lack of resources for diagnosis and management of the disease has increased the mortality rate in Pakistani population as well.[12] The relationship between breast cancer and various aetiological factors have been reported previously.[9,10] Among the contributing factors, some preventable causes are related to the socio-cultural context and require study within different populations. None of the previous studies on potential breast cancer risk factors from Pakistan was based on southern Punjab population.[6,18] However, geographical variations in incidence and mortality rates of breast cancer are reported worldwide and thus, the present study was planned to investigate epidemiology, clinical characteristics and reported potential breast cancer risk factors in women from southern Punjab through matched case-controls using conditional logistic regression.[19]

Of the 163 breast cancer cases, 53(32.5%) were aged 26-40 years, 84(57.7%) were aged 41-60 years, and 15(9.2%) were aged 61-80 years. Average age at diagnosis differs among populations with mostly reported is 60 years,[11] but in the current study the average age was 46 years. Among clinical subtypes, 142 (86.7%) cases had invasive ductal carcinoma which is in line with literature.[20] None of the 163 patients was at stage I, 19(11.5%) were stage II, 26(31.75%) stage III and 50(30%) were at stage IV. Further, 71(42.8%) patients were not completely evaluated for staging, but tumour size based on biopsy reports placed them in stages III and IV. Late-stage diagnosis is one of the key factors in disease metastasis.[11] High mortality rate linked to metastasis[3] emphasises the need of in-time diagnosis to increase patient survival.

Five risk factors remained significantly associated with breast cancer in multivariate analysis in the current study, including breastfeeding duration per child, HTN, family history, physical activity and BMI. Previously, meta-analysis of more than 50,000 patients and 96,000 controls concluded that relative risk of breast cancer is decreased by 4.3% for every 12 months of breastfeeding.[21] This inverse relationship between breast cancer risk and breastfeeding was also supported by other studies[22,23] as well as the present study. Reduction in breast cancer risk was significantly associated with optimum period of lactation. However, link between molecular subtype of breast cancer and breastfeeding duration was not explored in this study unlike literature.[9]

Several conflicting results have been reported for breast cancer and HTN,[24] while our results showed that HTN was significantly associated with breast cancer. Previously, Han et al. documented that the effect of HTN varied in pre- or post-menopausal women perhaps due to the difference in hormonal exposure,[24] but the current study found HTN irrespective of the menopausal status. Various mechanisms have been proposed to explain the association of breast cancer with HTN, like sharing of common patho-physiological pathway by HTN and breast cancer which may be mediated by adipose tissue.[25] Furthermore, HTN is considered to be implicated in apoptotic deregulation and, hence, may increase breast cancer risk by affecting the regulation of cellular turnover,[24] but no plausible explanation has been proposed.

In the current study, positive family history of breast cancer was recorded for 61(37.4%) patients and 12(12.9%) controls. The data is in line with literature, indicating that women with positive family history are more prone to the disease.[4]

Menopausal data of cases indicated that maximum patients had pre-menopausal status. Late menopause was found strongly associated with breast cancer in the current study. Women who attain menopause at or >55 of age are six times more likely to be diagnosed with breast cancer compared to those who attain it before that age.[9] Average age of attaining menopause among Pakistani females ranges 40-49 years.[6,18] Delay in menopause increases the period of exposure to steroid hormones which enhance the risk of cancer by 3%.[9,10] Adipose tissue is correlated with excessive oestrogen which refers to the BMI. High BMI and delayed menopause are reported to

have a positive association with breast cancer risk, but the current results did not indicate that, which may reflect a more complex relationship involving menopause, BMI and other related factors. Obesity has been inversely associated with the risk of breast cancer among pre-menopausal women.[26,27] Data showed that 0.6% patients were underweight, 28.8% had normal BMI, 26.4% were overweight and 44.2% were obese. The current results support earlier findings[27,28] of complicated association between breast cancer risk and obesity among pre- and post-menopausal women. In the current study, 68% cases were pre-menopausal, but lack of association could be due to increased BMI of the controls compared to the cases.

Various reproductive factors, like delayed menarche and early age at first full-term pregnancy, tend to decrease breast cancer risk, while nulliparity increases the risk,[29] but the current results showed no significant association between these factors and breast cancer. History of miscarriage is a controversial risk factor.[30] Two recent meta-analysis of multiple epidemiological studies are contradictory to each other regarding the association of miscarriages with breast cancer development.[31] The current results showed no significant association of this factor with breast cancer risk. Extensive studies including details about age, stage and number of miscarriages etc., are required to explore the link between miscarriages and breast malignancy.

Usage of oral contraceptive pills (OCPs) is also a controversial risk factor as a number of studies have reported positive association[31] while others have reported a negative association.[29] Our results showed positive but non-significant association. Deviation of results may reveal population difference or unrealistic answers provided by the participants. No significant association was found between HRT and increased breast cancer risk, as the number of post-menopausal HRT-obtaining females was equal in the two groups.[29]

Among habits, smoking is one of the well-known risk factors for cancer development[28] which was also evident in the current study, but the frequency of smokers was too small to validate the significance of this association. Similarly, using 'hookah' and 'naswar' was found to be associated, though non-significantly, with increased breast cancer risk. Verification of the findings requires detailed analysis using large sample size. Alcohol consumption was found to be the variable of least importance in the current study because of social and religious norms. Only one patient gave positive response for alcohol though it is an established risk factor for breast cancer.[5,23]

Conclusion

There was positive association of HTN and family history with increased breast cancer risk, while breastfeeding, increased BMI and intense physical activity decreased the risk in women from southern Punjab. Lifestyle and reproductive risk factors may take many years before their contribution to cancer incidence is noticed. Preventive measures and awareness campaigns are indispensable to reducing breast malignancy.

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