ORIGINAL RESEARCH ARTICLE

Breast cancer risk factors based on reproductive and non-reproductive profiling of Pakistani women: A hospital based case control study

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Abstract

Breast cancer (BC) is a global public health problem attributed to varying risk factors. The designing of a targeted screening program focused on at-risk women can be cost-effective in reducing its burden. A hospital based case control study was conducted on 138 cases of breast cancer and 169 healthy controls to investigate the reproductive and non-reproductive risk factors for breast cancer in Pakistani women. The odds ratios (ORs) and 95% confidence intervals (CIs) were computed with unconditional logistic regression. Almost all i.e. 97.83% of cases were married (OR=5.03),70.29% were illiterate (OR=1.88), 73.19% were aged >35 years (OR=0.632) and 81.16% belonged to the poor class(OR=1.81). Early age at menarche (OR, 2.55; 95% CI 1.50-4.31, P=0.0001), hormone replacement therapy (OR=2.057, 95% CI 1.283-3.295, P= 0.002) early pregnancy (OR,2.23, 95% CI 1.29-3.88, P=0.004), history of miscarriage (OR, 2.11, 95% CI 1.32-3.39,P=0.002) & oral contraceptive use (OR, 2.76, 95% CI 1.54-4.92, P= 0.006) were significantly associated with BC. The study highlights the dire need for effective public health programs for high-risk women to address this highly fatal disease. *(Afr J Reprod Health 2023; 27 [10]: 57-64).*

Keywords: Breast cancer, women, risk factors, reproductive, non-reproductive, profiling

Résumé

Le cancer du sein (BC) est un problème de santé publique mondial attribué à divers facteurs de risque. La conception d'un programme de dépistage ciblé axé sur les femmes à risque peut s'avérer rentable pour réduire son fardeau. Une étude cas-témoins en milieu hospitalier a été menée sur 138 cas de cancer du sein et 169 témoins sains pour étudier les facteurs de risque reproductifs et non reproductifs du cancer du sein chez les femmes pakistanaises. Les rapports de cotes (OR) et les intervalles de confiance (IC) à 95 % ont été calculés par régression logistique inconditionnelle. La quasi-totalité soit 97,83% des cas étaient mariés (OR=5,03), 70,29% étaient analphabètes (OR=1,88), 73,19% étaient âgés de >35 ans (OR=0,632) et 81,16% appartenaient à la classe pauvre (OR=1,81). . Âge précoce aux premières règles (OR = 2,55 ; IC à 95 % 1,50-4,31, P = 0,0001), traitement hormonal substitutif (OR = 2,057, IC à 95 % 1,283-3,295, P = 0,002) grossesse précoce (OR , 2,23, IC à 95 % 1,29-3,88, P=0,004), les antécédents de fausse couche (OR, 2,11, IC à 95 % 1,32-3,39, P=0,002) et l'utilisation de contraceptifs oraux (OR, 2,76, IC à 95 % 1,54-4,92, P= 0,006) étaient significativement associé à la Colombie-Britannique. L'étude souligne le besoin urgent de programmes de santé publique efficaces destinés aux femmes à haut risque afin de lutter contre cette maladie hautement mortelle. *(Afr J Reprod Health 2023; 27 [10]: 57-64).*

Mots-clés: Cancer du sein, femmes, facteurs de risque, reproducteur, non reproductif, profilage

Introduction

Breast cancer is the result of unchecked epithelial proliferation of breast parenchyma and its ductal epithelium[1]. Worldwide this is the second most prevalent cancer and the prime determinant of mortality in women . About 2 million new cases of breast cancer were reported in 2018, as per statistics from the Breast Cancer Research Foundation[2] which is quite alarming. A report from India estimated the age adjusted incidence rate of breast cancer in females in Delhi as 41 per 100,000 followed by females of Chennai (37.9/100,000) and Bangalore (34.4/100,000)[3]. The estimated

prevalence of breast cancer among females in Bangladesh is 22.5 per 100,000 women[4] while the same was reported as 13.1 per 100,000 women in Sri Lanka[5]. The risk factors for cancer of breast tissue might vary among the countries. The good understanding of the risk factors in local context may help to adopt more informed interventional strategies based on scientific evidence of prevention of breast cancer[6]. Being the sixth most populous country in the world, Pakistan is facing an increased burden of breast cancer owing to socio-demographic and lifestyle related factors[7]. It is the most commonly diagnosed malignancy in Pakistan occuring in one out of every nine women[8]. Health care system in Pakistan is not so efficient in detecting diseases early, therefore cumulatively identifying the risk factors will help to inform global health institutions for intervention particularly in the field of cancer[9,10]. Few studies are conducted to explore the role of potential risk factors associated with breast cancer among Pakistani women[7,11]. Various studies reported a significant association of breast cancer with being unmarried, lack of breastfeeding to the new born, and late menopause[11-13]. These studies focused on the population of highly urbanized areas. The demographic and reproductive risk factors for breast cancer may differ amongst diverse populations. The stratification of women according to the risk of developing breast cancer can improve risk prediction and early intervention by screening strategie targeting those most likely to benefit[14].

The published literature shows several factors involved in the emergence of breast cancer that cause mutation and abnormal amplification of both oncogenes and antioncogenes of the human genome[15]. Genetics account for 5–10% of BC cases[16]. The genetic mutations increase the risk of BC tenfold especially in those whose are posing reproductive and non-reproductive risk factors[17]. Sindh is the second most populous province of Pakistan. Breast cancer data has been published only from urban areas of Karachi city. To date no single study has been carried out to investigate the risk factors associated with breast cancer in the population of the rest of province. There is scarcity of literature relating reproductive and non-reproductive risk factors with well-known relation with genetic risk factors for breast cancer. Furthermore, the delay in reporting of breast cancer is also increasing the severity of the breast cancer in

females. Despite rising trends in BC in this developing country, less work on its preventive side has been undertaken. Hence, there was a dire need to have the data to represent the population of rural areas, living in dverse socio-demographic circumstances. In order to accomplish this task, the study was carried out to understand the risk factors associated with breast cancer.

Methods

Study design and setting

The matched case control study was conducted at the Nuclear Institute of Medicine and Radiotherapy (NIMRA) Jamshoro, Pakistan from April 2019 to March 2020. The NIMRA is the only center in Jamshoro where cancer patients are referred from all over Sindh province for treatment alongwith financial support to the patients.

Study participants, inclusion and exclusion criteria

The 138 women referred for management of confirmed primary breast cancer based on histological reports at NIMRA were recruited for the study period of one year. The sample size was calculated by using prevalence-based formula; the cumulative prevalence of BC in multiple centers in Pakistan was reported as 8 percent[18] ; (n= Z^2 X p X q /e^2), n = required sample size;; p= prevalence of breast cancer in Pakistan (9%); q=100-p = (91%); e= margin of error=5%. The power of study was 80%. Initially sample size was calculated as 125; considering the factor of attrition, the final sample size was computed as 138. Patients getting admission in NIMRA, with complete details of reproductive and non-reproductive risk factors and those with original biopsy reports were included in study. Recurring instances and cases with insufficient information were excluded from the research. The 169 female attendants of the patients were harmonized by age (year of birth±five years), with no known preceding history or symptoms suggestive of breast cancer were enrolled as the control group and it was ensured that the cases and controls were from the same socio-demographic areas. If no female attendant of matching age group was available, the control was selected randomly. Patient herself and her hospital files were the sources of information. Among reproductive risk

factors, 13 years of age was taken as cut-off for age of menarche; the menarche reported at age <13 years was labelled as early menarche; the menopause reported at +55 years was labelled as late menopause; similarly marriage at age <18 years was categorized as early marriage. Women at hormone replacement therapy (HRT) for atleast one years were categorized as subjects with history of HRT; similar was the cut-off period for positive history of oral contraceptives.

Procedure

It was an interview-based study, questionnaire was available in the local languages (Sindhi and Urdu). The data collection team was constituted at the Department of Physiology, University of Sindh, Jamshoro,Pakistan. The data collectors were trained about how to collect the data from cases and controls. First, the participants were briefed about the objectives of the study and assured about the confidentiality of the information. Secondly, literate participants were given a written consent form and illiterate participants were asked for verbal consent and by taking thumb impressions. The subjects declining to take part in the study were not included in the research. The study was carried after approval by the Institutional Review Board (IRB) of the University of Sindh,Pakistan (No:Physiol/IRB/02 dated 11.02.2019). The consent procedure was also approved by the same IRB.

Questionnaire and study variables

The questionnaire was divided into sections in order to probe demographic profiles and reproductive and non-reproductive risk factors. The demographic section comprised of questions about age, education, marital, economic status and residential status. The breast cancer risk factor section comprised items about trauma; the word trauma was used for any type of injury, received on the breast either as domestic violence or accident. Other risk factors included early menarche, early pregnancy, number of full time pregnancies, hormonal replacement therapy (HRT), history of miscarriage, late menopause, lack of breast feeding, use of oral contraceptives and delayed initiation of intervention. All the questions were posed in a non-judgmental style.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 23.0 was used to analyze data. We performed descriptive statistics including the calculation of central tendencies i.e. means ± standard deviations and relative frequencies. In bivariate analysis, we used the χ^2 test to examine the association between reproductive & non-reproductive variables among cases & controls with a probability of 95% with explanatory variables including age, education, and place of residency, etc. The P value ≤ 0.05 was considered for statistical significance.

Results

A total of 307 participants joined the study including 138 patients with cancer of breast and 169 controls. The overall participation rate was >92%. The sociodemographic characteristics of the study participants are detailed in Table 1. The mean age for the case group was 46.02±12.24 years and the mean age for the control group was 41.15±9.27years. The illiterate participants accounted for 70.29% of all the cases as compared to 55.62% of controls. The majority of the cases as well as controls belonged to poor economic class (81.16% and 70.41% respectively). Over half (56.52%) of the cases and 51.49% of controls belonged to rural regions. Majority (97.83%) of the cases were married and 57.97% of them were married befor 18 years.

The potential reproductive predictors of breast cancer identified in bivariate analysis are reported in Table 2. The 64.49% cases reported age of menarche later than 13 years. In relation to this reference class, the risk of breast cancer among those of early menarche was greater (OR,2.55; 95% CI, 1.50 - 4.31; P=0.0001). Surprisingly, the highest potential of acquiring cancer of breast was seen in unmarried women (OR, 95% CI, 1.44-1.75, P=0.008). Noticeably, no association of breast cancer was seen for late menopause and breast feeding for period lesser than 12 months.

Among cases of breast cancer, those who underwent trauma accounted for 22.46% of all the cases (OR=3.20 95% CI 1.62-6.31, P < 0.0001). However, rural-urban residential disparity was not reported as associated to breast cancer (OR, 0.81; 95% CI, 0.51-1.282; P=0.42).

Table 1: Sociodemographic characteristics of participants

Variable	Cases n(%)	Controls n(%)	Total n(%)
Age category, Years			
≤ 35	37 (26.81%)	62 (36.68%)	99 (32.25%)
> 35	101 (73.19%)	107 (63.32%)	208 (67.75%)
Educational Status			
Illiterate	97 (70.29%)	94 (55.62%)	191 (62.21%)
Literate	41 (29.71%)	75 (44.38%)	116 (37.79%)
Economic Status			
Poor class	112 (81.16%)	119 (70.41%)	231 (75.24%)
Middle class	26 (18.84%)	50 (29.59%)	76 (24.76%)
Residence Status			
Urban	60 (43.48%)	82 (48.52%)	142 (46.25%)
Rural	78 (56.52%)	87 (51.49%)	165 (53.75%)
Marital Status			
Married	135 (97.83%)	152 (89.94%)	287 (93.49%)
Unmarried	3 (2.17%)	17 (10.06%)	20 (6.51%)
Age at Marriage			
<18 years	80 (57.97%)	48 (28.40%)	128 (41.69%)
≥18 years	58 (42.03%)	121 (79.60%)	179 (58.31%)

Table 2: Reproductive risk factors of breast cancer

Factors	Cases	Controls	OR	95% CI	P values
Menarche					
≤13	49 (35.51%)	30 (17.75%)	2.55	1.50-4.31	0.0001
>13	89 (64.49%)	139 (82.25%)	1.0 (Ref)		
Late Menopause					
Yes	14 (10.14%)	20 (11.83%)	0.84	0.40-1.73	0.716
No	124 (89.86%)	149 (88.17%)	1.0 (Ref)		
Hormone Replacement Therapy					
Yes	63 (45.65%)	49 (28.99%)	2.05	1.28-3.29	0.002
No	75 (54.35%)	120 (71.01%)	1.0 (Ref)		
Marital Status					
Married	135 (97.83%)	152 (89.94%)	5.03	1.44-1.75	0.008
Unmarried	3 (2.17%)	17 (10.06%)	1.0 (Ref)		
Age at marriage					
<18	80 (57.97%)	48 (28.40%)	2.23	1.29-3.88	0.004
≥18	58 (42.03%)	121 (79.60%)	1.0 (Ref)		
Number of full term pregnancies					
≤ 5	89 (64.49%)	116 (68.64%)	0.60	0.35-1.00	0.06
> 5	49 (35.51%)	53 (31.36%)	1.0 (Ref)		
History of Miscarriage					
Yes	81 (58.69%)	63 (37.28%)	2.11	1.32-3.39	0.002
No	57 (41.31%)	106 (62.72%)	1.0 (Ref)		
Breastfeeding					
≤12 months	115 (83.33%)	133 (78.70%)	0.82	0.41-1.61	0.60
>12 months	23 (16.67%)	36 (21.30%)	1.0 (Ref)		
Oral Contraceptive Use					
Yes	46 (33.33%)	39 (23.08%)	2.76	1.54-4.92	0.0006
No	92 (66.67%)	130 (76.92%)	1.0 (Ref)		

Table 3: Non-reproductive risk factors of breast cancer

Factors	Case	Control	OR	95% CI	P-values
Age group(years)					
>35	101 (73.18%)	107 (63.32%)	0.63	0.38-1.03	0.06
≤ 35	37 (26.81%)	62 (36.68%)	1.0 (Ref)		
Education					
Illiterate	97 (70.29%)	94 (55.62%)	1.88	1.17-3.03	
Literate	41 (29.71%)	75 (44.38%)	1.0 (Ref)		0.009
Economic Class					
Poor class	112 (81.16%)	119 (70.41%)	1.81	1.05-3.10	0.03
Middle lass	26 (18.84%)	50 (29.59%)	1.0 (Ref)		
Residential Status					
Urban	60 (43.48%)	82 (48.52%)	0.81	0.51-1.28	0.42
Rural	78 (56.52%)	87 (51.49%)	1.0 (Ref)		
Trauma					
Yes	31 (22.46%)	14 (8.28%)	3.207	1.62-6.31	< 0.0001
No	107 (77.54%)	155 (91.72%)	1.0 (Ref)		
Early Intervention					
No	35 (25.36%)	-	-	-	-
Yes	103 (74.64%)	-	-	-	-

Discussion

Overall, the burden of breast cancer incidence and mortality is rapidly increasing worldwide[19] which necessitated the thorough investigation of underlying risk factors for it.

Reproductive factors of breast cancer

Early menarche (≤13 years) and late menopause (55+ years) are considered to be risk factors for acquiring breast cancer[20.] In contrast to current study, the cross sectional research conducted by Admoun C fixed 50+ years as cut-off age for late menopause; this could have resulted in more recruitment of cases of BC as compared to current study. In the present study, 35.51% of breast cancer patients had an early menarche while 10.14% of breast cancer patients were at late menopausal age. These risk factors have been consistently reported by several previously published studies[21, 22]. This result might be due to longer estrogen exposure to the breast from earlier age. Surprisingly, our study revealed late menopause was not associated with breast cancer (OR=0.84). The reason of this contrasting finding might be attributed to the low sample size and also selecting the controls from the neighbors of the patients. The result also indicates that the estrogen exposure to breast at an earlier age may play a critical role in inducing breast cancer more than the extended periods of estrogen

exposure. Another study endorsed our finding showing early menopause as a significant risk factor for breast cancer (OR=2.55)[23]. Similarly, hormonal replacement therapy is also a proven risk factor for breast cancer[24, 25]. In the undertaken study 45.65% of breast cancer patients had HRT. This has also been confirmed by another study in the same country i.e. Pakistan[26].

The reproductive history of a female is the strongest modifier of her breast cancer risk. The mean age at marriage is a strong determinant of age at first pregnancy. Early pregnancy is regarded as a protective factor against breast cancer. In this study 57.97% participants who had early pregnancy at the age of <18 years were the breast cancer patients. Mean age at first pregnancy varies with the cultural context in South Asian and Western countries. In a study conducted in India by Bhadoria *et al* reported the mean age at marriage in India as 18.42±3.97 years and the women who married at age ≤ 20 years, accounted for 72.5% of breast cancer cases[27]. This shows that there is a need to reconsider the role of early pregnancy as a protective factor as it varies with geographical distribution and cultural context. The relationship between early pregnancy, age and breast cancer has to be further studied. A higher number of full-term pregnancies is thought to lower the risk of this disease in the long run[28]. The current study reveals that 35.51% of breast cancer cases were those who had a history of full-term pregnancies (>5); despite this we find lower parity

as not being a risk factor for breast cancer (OR= 0.60) which is not in line with findings from other studies that suggest subsequent full term pregnancies lower the risk of breast cancer by 10%+ [29, 30]. The breast cancer risk is higher among women with repeated pregnancy losses as compared to those reporting live births[31]. In this study, cases of miscarriages accounted 58.69% of all breast cancer cases. We however did not addressed miscarriages as risk factor for breast cancer due to low sample size. Studies from India[27], China[32], Central African Republic[33] have reported 61.2%, 59.5% and 65.5% respectively of breast cancer cases in females with history of miscarriages. Nevertheless, further research is required to examine the biochemical connection underlying miscarriage and breast cancer. The likelihood of developing breast cancer is thought to be increased by the use of contraceptives. In this research, 33.33% of all breast cancer cases were among those who reported taking oral contraceptives (OR 2.76; 95% CI 1.54-4.92; P=0.0006). Several studies have also reported the usage of contraceptives as a risk factor for breast cancer[27,33,34].

Non-reproductive risk factors

Older age is a potential factor playing a role in the development of cancer of breast. This study revealed the mean age of cases of breast cancer as 46.02±12.24 years while Shamsi et al report mean age of cases of breast cancer as 46±10.1 years[35]. Badar, et al. (2015) have reported the mean± standard deviation of reported cases of breast cancer as 48.6±12.2 years[36]; while another study reported this data as 29.1±9.3 years[37]. These consistent findings show that the occurrence of breast cancer in an earlier age is a public health point of concern which if not prevented would strike women at their highly fertile and productive age. Another study indirectly endorsed the findings by pointing out that 49+ years significantly increase the trend of breast cancer incidence rate[38]. Demographic factors associated with breast cancer including being illiterate (OR=1.88) and lower socioeconomic status (OR=1.81), urban dwelling (OR= 0.81) were also explored in this study. These factors have been reported as risk factors by other studies as well[37,39].

Trauma is considered a risk factor for developing breast cancer[40]. In our study, 22.46% of breast cancer patients reported a history of trauma to the breast, the cause of which could not be further explored. A link between physical trauma and cancer can be possible. In developing countries of South Asia, physical abuse on females is prevalent[41].

Early intervention can be used to treat breast cancer. The higher prevalence of breast cancer in low and middle income countries (LMIC) has been linked to the reporting delay and later initiation of breast cancer[42]. Due to illiteracy, low-income profile, lack of basic knowledge about cancer biology and prevention, the females of South Asia are more prone to delayed reporting of symptoms of breast cancer. Most females who need medical care are hesitant because most of the health workforce comprises of males[43,44]. This result has also been confirmed by a recently published study in which authors have shown that breast cancer patients also delayed reporting their disease to healthcare providers[7,43].

Some limitations must be considered to explain the findings of current study. Firstly, the study was carried out on a small number of subjects; therefore known risk factors might not be the perfect representative of the general population. Secondly, as is evident in analytical studies, the chances of information bias can not be over ruled. Selection of controls accompanying the cases of BC might be suffering from pre- BC stage which might have distorted results of our study owing to selection bias. However, despite all these perceived limitations, results arising from this research can be useful as it can contribute to the ongoing large scale breast cancer research in low resource country like Pakistan. Moreover, the work done on some modifiable reproductive risk factors like age at marriage, number of pregnancies and using oral contraceptives etc can provide useful information to the general population.

Conclusion

This study confirmed only a few of the well-established risk factors for developing breast cancer in Pakistani women, such as early menarche, miscarriages, hormone therapy and breast trauma. The current study by pin-pointing the highly prevalent and preventable risks in population, will help in formulating the risk-factor screening and health education program to the masses. This will in turn reduce financial cost due to treament of breast cancer.

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Competing interests

Funding

Availability of data

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