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Association of Breastfeeding and Breast Cancer: A Case- Control Study

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ABSTRACT

Objectives: To find the association of breastfeeding and the risk of breast cancer in our population.
Study Design: Case-control study.
Place and Duration of Study: Oncology Ward-4 at Jinnah Postgraduate Medical Center, Karachi Pakistan, from Jun 2018 to Jun 2019.
Methodology: All patients with diagnosed Breast Cancer visiting the outpatient department were enrolled in this study. Controls were randomly selected from the community. Demographic characteristics, reproductive history, breastfeeding pattern, and hormonal status of cancer were collected from all participants.
Results: Among patients who had a positive history of breastfeeding were three times more likely to develop breast cancer than those with no history of breastfeeding [Odds Ratio 3.315 (95% Confidence Interval: 2.094-5.249)]. 69.7% of participants in our study breastfed for more than 2 years. There was also a weak inverse association between lactation amenorrhea and breast cancer risk. Women who experienced lactation amenorrhea had only half the risk of women who did not experience lactation amenorrhea [Odds Ratio 0.685 (95% of Confidence Interval: 0.397-1.182)].
Conclusion: There was a negative relationship between breast cancer and breastfeeding. Further research should explore the genetic and cultural differences and the risk of breast cancer.

Keywords: Amenorrhea, Breast carcinoma, Breastfeeding, Lactation, Prognosis.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer globally, contributing to 11.6% of the total cases in 2018. It is reported that the incidence rates of breast cancer are highestin Australia and Northern Europe.[1] There are large variations in incidence and mortality across different parts of the world with a greater incidence rate in the developed world whereas a higher mortality in the developing world.[2]

In Pakistan, it is estimated that about one in every nine women are expected to develop breast cancer at least once in their life.[3] Earlier data showed that breast cancer was the most frequent cause of cancer in females in the country, accounting for about one-third of the overall cases.[4] A recent survey done in all districts of Karachi, reported that breast cancer accounts for 49.5% of all cancers in women.[5]

Despite the progress made during the last decade, including the advanced imaging options and better treatment, has decreased the mortality rates world-wide, however, it remains a substantial burden on the community.[6]

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There are a variable number of risk factors, reproductive and menopausal, associated with breast cancer. The factors that increase the rate include the early menarche and late menopause, null parity, fewer children, use of alcohol or exogenous hormones as frequently reported in studies whereas, breastfeeding is reported to have a protective effect against breast cancer.[8] The risk of breast cancer is also seen to increase in women who use hormonal contraceptives.[9]

Considerable importance has been placed on investigating the association of breastfeeding with breast cancer. Recent reviews and meta-analyses have shown that breast cancer significantly reduces the risk of breast cancer in Asian women. The incidence of breast cancer was estimated to be about 11% lower in women who breastfeed compared to those who have never breastfed.[10] There have been many studies conducted in the past to assess the factors associated with incidence of breast cancer, particularly the effect of breastfeeding. However, to date there have been very few studies conducted on Pakistani population, a country where breastfeeding practice is very common, to determine its effect on breast cancer risk. Our study was planned to find the association of breastfeeding and risk of breast cancer in our population.

METHODOLOGY

The case-control study was conducted at Jinnah Postgraduate Medical Center, Karachi, Pakistan from December 2018 to June 2019 with the approval of Institutional Ethical Review Board (IERB certificate number; CPSP/REU/ONC-2017-186-162).

Inclusion Criteria: All patients with diagnosed Breast Cancer visiting the JPMC On-cology Department were enrolled in this studyusing. Controls were defined as those with no history of breast cancer and had similar demographic characteristics as that of the case group.

Exclusion Criteria: None

Data was collected and recorded through a preformed proforma after taking informed consent from the participants meeting the identification criteria for both control and case. A preformed proforma was used to take a detailed history regarding the subject's family history of breast cancer, breastfeeding habits including the number of children breastfed, number of breastfeeds per day, duration of breastfeeding, presence of lactational amenorrhea, etc.

Controls were selected from the community who matched with the demographic profile of the case subjects. After obtaining informed consent, each control subject were asked about her reproductive and breastfeeding histories, as well as detailed information on other potential breast cancer risk factors including the use of contraceptives, and family history of cancer. Family history of breast cancer was considered to be positive if the subject had a mother or sister who had been diagnosed with breast cancer.

Statistical Package for the Social Sciences (SPSS) v.23 was used to analyze data. Conditional logistic regression analysis was used to estimate odds ratios (ORs) for the risk of breast cancer. The *p*-value of ≤0.05 was considered as significant.

RESULTS

A total of 165 participants were enrolled in the study with a mean age of 47.2±11.6 years. 161(97%) of the patients were married with an average number of four children. 56(33.9%) bore their first child at the age of 18 or younger while 46(27.9%) bore their first child between the ages of 18 to 25 years. 120(72.7%) women had a history of breastfeeding their newborn. The average duration of breastfeeding among patients was 6.0±4.01 years. Majority of the participants had a history of early menarche and were premenopausal at diagnosis (Table-I).

Table-I: Demographics and Clinical Profile of Case and Control Groups (n=165)

Variable	Cases	Controls
Mean±SD	47.2±11.6 years	45.6±6.5 years
Marital Status		
Unmarried	4(2.4%)	16(9.7%)
Married	161(97.6%)	149(90.3%)
Education Status		
Yes	78(47.3%)	89(53.9%)
No	87(52.7%)	76(46%)
Age of Menarche		
8-10 years	5(3%)	4(2%)
10-12 years	78(47.3%)	66(40%)
13-16 years	72(43.8%)	81(49%)
>16 years	10(5.9%)	14(9%)
Number of Children		
0	44(26.6%)	69(41.8%)
1-2	21(12.7%)	17(10.3%)
>2	100(60.6%)	79(47.9%)
Age at First Child		
<18	56(33.9%)	47(28.5%)
18-25	46(27.9%)	50(30.3%)
26-35	27(16.4%)	10(6.1%)
>35	3(1.8%)	6(3.6%)
N/A	33(20%)	52(31.5%)
Mean age at Diagnosis	46.30±11.48 years	–
Menstrual Status at Diagnosis		
Premenopausal	108(65.4%)	
Postmenopausal	57(34.5%)	–
Habit of Breastfeeding		
Yes	120(74.5%)	74(49.66%)
No	41(25.5%)	75(50.3%)
Mean duration of Breastfeeding	5.78±4.23 years	2.6±2.5 years
Lactational Amenorrhea		
Yes	34(20.6%)	34(45.9%)
No	98(77%)	40(54.1%)
Family History of Breast Cancer		
Positive	13(7.9%)	41(24.8%)
Negative	152(92.1%)	124(75.2%)
Contraceptive History		
Positive	13(8.1%)	19(12.7%)
Negative	148(91.9%)	130(87.2%)
Method of Contraceptive Use		
Pills	5(38.5%)	7(36.8%)
Injectables	4(30.8%)	4(21.1%)
Subdermal Patch	1(7.7%)	3(15.8%)
IUD Copper T-Wire	2(15.4%)	5(26.3%)
Hysterectomy	1(7.7%)	-

In Table-II, we observed an association between Breastfeeding and various risk factors of breast cancer. It was found that participants who had given birth more than twice in their lifetime were only half as likely to develop breast cancer as those who were nulliparous [OR: 0.504 (95% CI: 0.312-0.814)]. Among

patients who had a positive history of breastfeeding were three times more likely to develop breast cancer than those with no history of breastfeeding. A total of 92(69.7%) participants in our study breastfed for more than 2 years.

We also report a weak inverse association between lactation amenorrhea and breast cancer risk. Women who experienced lactation amenorrhea had only half the risk of women who did not experience lactation amenorrhea (Table-II).

Table-II: ORs and 95% CIs for selected breast cancer risk factors among participants (n=165)

Risk Factors	Cases	Controls	Odds ratio (95% CI)
Number of Children			
No children	44(26.6%)	69(41.8%)	10.504
More than 2 children	100(60.6%)	79(47.9%)	(0.312-0.814)
History of breastfeeding			
No	41(25.5%)	75(50.3%)	13.315
Yes	120(74.5%)	74(49.6%)	(2.094-5.249)
Lifetime years of breastfeeding			
0	12(9.1%)	11(9.7%)	_
<1 year	8(6.1%)	24(21.2%)	_
1-2 years	20(15.2%)	34(30.1%)	_
>2 years	92(69.7%)	44(38.9%)	_
Lactational Amenorrhea			
No	98(77%)	40(54.1%)	10.685
Yes	34(20.6%)	34(45.9%)	(0.397-1.182)
Histological Grade			
Grade I	_		
Grade II	79(47.9%)	_	_
Grade III	86(52.1%)		
Hormone Receptor Status			
Triple Negative	38(23%)		
Triple Positive	22(13.3%)		
ER Positive	96(58.2%)	_	_
PR Positive	85(51.5%)		
HER2 Neu Positive	60(36.4%)		
History of Contraceptive use			
Negative	148(91.9%)	130(87.2%)	0.601
Positive	13(8.1%)	19(12.7%)	(0.286-1.264)

In the study, 17(77.3%) women with a positive history of breastfeeding were triple positive, 28(73.7%) were triple negative, 60(72.3%) were ER/PR positive, while 45(75%) had HER2/neu positive breast cancer. However, there was no significant association between breastfeeding and triple negative or Her2/neu positive breast cancers (Table-III).

DISCUSSION

The importance of breastfeeding on the health of the child as well as the mother has been widely recognized. The evidence behind the protective effects that breastfeeding confers upon the mother have evolved over the past few decades. Previous literature has reported an association between breastfeeding and reduced risk of ovarian cancer and maternal depression.[11]

This current study was conducted with an aim to identify breastfeeding as an independent risk factor of breast cancer among our population. In our study, 120(74.5%) breast cancer patients had a positive history of breastfeeding their infants while; only 41(25.5%) patients had never breastfed their children. Upon comparison with the control group, it was found that the women who had a positive history of breastfeeding were about three times more at risk of developing breast cancer than those who had a negative history of breastfeeding their offspring (odds ratio [OR]=3.315, 95% confidence interval [CI]=2.094-5.249). Our results were in accordance with the study conducted in Bangkok, South Asia where no association between breast cancer and breastfeeding was reported.[12] Another study from Brazil, reported similar results to ours, concluding that breastfeeding did not have a protective effect against breast cancer in women in their population (p>0.05).[13] Our results contradict the majority of the Western studies wherein a strong link has been established between breastfeeding and its protective effects against breast cancer.[14-16]

Table-III: Association of Subtypes of Breast Cancer and Breastfeeding among participants (n=165)

Hormone Receptor Status	Breastfeeding		*p*-value*
	Yes	No	
Triple Positive			
Yes	17(77.3%)	5(22.7%)	
No	103(72.0%)	40(28.0%)	0.410
Triple Negative			
Yes	28(73.7%)	10(26.3%)	
No	92(72.4%)	35(27.6%)	0.529
ER/PR Positive			
Yes	60(72.3%)	23(27.7%)	
No	60(73.2%)	22(26.8%)	0.519
HER2/neu Positive			
Yes	45(75.0%)	15(25.0%)	
No	75(71.4%)	30(28.6%)	0.380

This protective effect of breastfeeding was more frequently observed with hormone receptor-negative cancers which have a poorer prognosis.[14] In the current study, ER receptor was the most prevalent hormone receptor among the women who had a positive history of breastfeeding. Triple negative cancer was observed in 23% women while Her2/neu was observed in 36.4% women. The majority of the patients had ER/PR positivity as concurred by previous literature.[15] Previously,

breastfeeding was linked to decreased risk of estrogen receptor–negative/progesterone receptor–negative breast cancers and an associated decreased risk of triple-negative cancers.[16-17] However, we did not find any significant correlation between breastfeeding and triple negative or Her2/neu positive cancers (p>0.05) Table-III.

Our study results contradict those of Bernier *et al*., who found that compared with parous women who never breastfed, women who had breastfed were at reduced risk of breast cancer (odds ratio [OR] = 0.90, 95% confidence interval [CI]=0.86 to 0.94).[18] Similarly, another large analysis reported that breastfeeding caused a minimal reduction in breast cancer risk, among women with four or more deliveries.[19] The differences in the results of this study with other studies regarding the effect of breastfeeding on breast cancer may be due to the genetic and epigenetic differences in each region or country.

One of the largest studies conducted to determine this association is the collaborative reanalysis of 47 studies from 30 different countries with a sample size of more than fifty-thousand women with invasive breast cancer. The study showed there is a 4.3% reduction in relative risk of breast cancer for every 12 months of breastfeeding .[20] This study was conducted on a very large sample size, comprising of data from different ethnicities and races, therefore, the results speak volumes and are quite substantial evidence which are contradictory to our study findings. Gajalakshmi et al. reported that breastfeeding reduced the incidence of breast cancer in premenopausal women, but no significant relationship was observed in postmenopausal women.[21]

The link between breastfeeding and breast cancer risk is difficult to understand and has been a topic of research for decades. There have been different mechanisms proposed to examine this correlation. Breastfeeding can be linked with differentiation of breast tissue, leading to more branching, increased number of lobules or ductal elongation that occurs during pregnancy and lactation.[22] One hypothesis suggests that the greater involution of terminal duct lobular units (TDLU) seen in parous women promoted by long term breastfeeding may contribute to a reduced risk of breast cancer.[23]

In the present study, we also observed that 77% of the women did not experience lactational amenorrhea, whereas only 20.6% of them did experienced lactational amenorrhea during breastfeeding. In the present study, cessation of menstrual cycles was mostly associated with exclusive breastfeeding whereas, early return of menstrual cycles after delivery was seen with combined feeding practices and early weaning.

The contradictory findings in our study may be attributable to the fact that most of the study population belonged to the low socioeconomic class with practices to start early weaning in infants, not feeding on demand, reduced number of feeds per day, and also because early return of menstrual cycles.

Based on the contradictions between studies, in assessing the association between breast cancer and breastfeeding factors, gene mutations status of the individuals should also be taken into consideration, which was not done in the present study. It is recommended that future studies focus on this issue. On the other hand, the small sample size with the history of breastfeeding in this study was a factor that could have affected the interpretation of the results.It is recommended that large sample size studies should be undertaken in the future.

CONCLUSION

The results showed that there was a negative relationship between breast cancer and breastfeeding. Most of our study population belonged to younger age group who are more predisposed to genetic alterations. Due to the difference between the findings of this research and other researches, genetic, epigenetic, and cultural differences must be considered in the evaluation of risk factors for breast cancer.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SB: & GH:, Conception, drafting the manuscript, approval of the final version to be published.

MN: & KA:, Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

KM: & AS:, Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

MA: & RDA: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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