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Socio-Demographic, Physical and Clinical Risk Factors of Breast Cancer Patients in Pakistan

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ABSTRACT

Introduction: With high incidence rates seen globally but disproportionately higher death rates in underdeveloped countries like Pakistan, breast cancer is a serious worldwide health concern. Comprehensive local evidence on the socio-demographic, physical, and clinical risk factors unique to the Pakistani population is still lacking despite its prevalence. In order to close this gap, this study will identify and clarify the complex range of risk factors linked to the development of breast cancer in Pakistan.

Objectives: The present study was conducted to determine the socio-demographic and risk factors in breast cancer patients from local population of Pakistan so that potential disparity in healthcare access and outcomes can be identified.

Material and Methods: A cross-sectional comparative study was conducted at Cancer care hospital, Lahore in which diagnosed cases of breast cancer (study group, N= 150) and age matched healthy females (control group, N=150) were enrolled. Socio-demographic, physical and clinical characteristics were obtained from structured questionnaire and medical record review. The study utilized Minitab 2021 and SPSS 27.0 for data recording and analysis. Categorical variables were analysed using frequencies, percentages, and Chi-square tests, while quantitative data were assessed for normality using Shapiro-Wilk statistics. Normally distributed data were compared using the student t-test, and non-normally distributed data with the Mann-Whitney U test, with a significance threshold set at $p < 0.05$. To validate findings and assess the impact of significant variables, Minitab was used for regression analysis, descriptive analysis, ANOVA, and graphical representation through Pareto charts and graphs.

Results: The mean age of the cases at the time of presentation was 52 ± 11.2 years as compare to the control group in which the mean age was 46.87± 11.63. History of breastfeeding, history of breast cancer, history of diabetes, OCP use and hepatitis C are the major predictors, while the other factors are not significantly associated with Breast cancer.

Conclusion: The study's conclusion emphasizes the critical need for all-encompassing approaches to address the rising incidence of breast cancer, especially in developing nations where inequities in access to healthcare worsen the situation.

Key words: 1. Breast cancer, 2. Pakistan, 3. Socio-demographic factors, 4. Risk factors, 5. Comparative study, 6. Healthcare disparity, 7. Statistical analysis

Introduction:

Breast cancer is one of the most common cancers reported worldwide and leading cause of death in women globally. According to the global cancer burden estimates, a staggering 2.26 million new case of breast cancer were reported worldwide in 2020 (Sung et al., 2021). The incidence of breast cancer is higher in the developed countries compared to the developing countries. However, the untoward finding in terms of mortality shows a much higher rate in the developing countries (Wilkinson & Gathani, 2022). Pakistan bears the unfortunate distinction of having the highest risk of breast cancer development among all Asian nations (Mubarik et al., 2019). The occurrence rate of breast cancer in Pakistan is 1 in every 9 women. In Pakistan, approximately 34,066 new cases of breast cancer had been reported in women (Khan, Duan, Wu, & Ji, 2021). The majority of women with breast cancer present with a palpable breast mass. Other signs and symptoms include orange peel appearance of skin (peau d' orange appearance), skin dimpling, erythema, edema, blisters, nipple changes such as bloody discharge or nipple retraction (Katsura, Ogunmwonyi, Kankam, & Saha, 2022).

The onset of breast cancer is associated with multifaceted array of risk factors which can trigger genetic mutations and abnormal amplifications of genes involved in abnormal cellular processes leading to development and progression of breast cancer (Khan et al., 2021). Scientific studies have proved that advancing age is paramount risk factor for breast cancer, with incidence escalating significantly among older women(Fakhri et al., 2022). However, a multifaceted array of additional risk factors also contributes substantially to breast cancer development including positive family history of cancer/ breast cancer, no or less period of breast feeding, estrogen and reproductive factors, obesity, smoking, use of oral contraceptive pills, excessive alcohol consumption, smoking, exposure to radiations, lifestyle and genetic factors. All of the above are significantly linked to the development of breast cancer (Cohen, Stoll, Anandarajah, Doering, & Colditz, 2023).

Despite the availability of international data, local evidence on breast cancer socio-demographic, physical and clinical risk factors is fragmented and inconclusive. This underscores the need for community-specific research to elucidate the distinct determinants of breast cancer. By identifying and addressing these risk factors in a local population, we can develop targeted interventions to mitigate the devastating consequences of breast cancer and improve health outcomes at the community level. The present study endeavoured to ascertain the above-mentioned risk factors that heighten the risk of breast cancer in a local setting.

MATERIALS AND METHODS

This collaborative study utilized a cross-sectional comparative study design. The Ethical Review Committee at the University of Lahore provided approval for this research study. A total of 150 cases of histologically diagnosed breast cancer patients (N=150) and age matched healthy females (N=150) controls were enrolled in the study through non-random convenience sampling with written informed consent taken from each patient. The inclusion criteria for the cases were females with histologically confirmed diagnosis of breast cancer, aged between 30-70 years. Females with diagnosis of any malignancy other than breast cancer such as ovarian tumor, pregnancy or any recurrent disease and medically unstable patient were excluded from the study. Age matched 150 healthy females, with absence of documented cancer who visited the hospital for medical checkup without any clinical signs and symptoms of breast cancer were selected as controls (N=150).

Socio-demographic information, clinical history (such as history of Diabetes, Hypertension, Hepatitis B, C or any other co-morbidities) and pertinent physical examination parameters (such as weight and height for BMI Calculation) of each participant were recorded on a specifically designed subject data sheet providing accurate and comprehensive dataset for each participant. The blood pressure of the enrolled subjects was obtained using an automated blood pressure monitor, ensuring accurate readings. Measurements of height in meters and weight in kg were taken as part of the anthropometric assessment for Body Mass Index (BMI) calculation. A stadiometer (Seca 213) was utilized to measure the heights of the enrolled subjects in meters. Weight was measured using a weighing scale. Without shoes and with the bare minimum of clothing, weight was measured in kilograms. Before collecting any measurements, all of the instruments were calibrated to zero. The body mass index was calculated by dividing the weight in kilos by the height in meters square (Tahir, Nawaz, Sikandar, & Shah, 2019)

Statistical analysis:

Two software programs, Minitab 2021 version 20.3 and SPSS version 27.0 (statistical package for social sciences), were used for data recording and analysis. First, using SPSS, frequencies and percentages were used to represent categorical variables. The Chi-square test was used to determine whether the two groups' qualitative/categorical data were related. The significance level was established as a probability, and the chi-square value (X^2) was given in numerical form. A difference between the groups was considered significant if X^2 was larger than or equal to the critical value, and not significant if X^2 was less than the critical value. Shapiro-Wilk statistics were employed to verify the data's normality. For quantitative variables that were normally distributed, the mean ± Standard Deviation (SD) and median ± Inter Quartile Range (IQR) were to be provided, respectively. The student t test was to be used to compare groups of normally distributed data. To compare groups for quantitative variables that were not normally distributed, the Mann-Whitney U test was employed. For all purposes, a p-value of less than 0.05 was deemed statistically significant. One sample T-test was applied to check the differences of means. In order to estimate the degree of difference, ANOVA was applied on the significant variables. The results of ANOVA are represented in the form of graphs. Regression analysis was used to find out the nature of relationships, their impact, scores and direction. Pareto chart was made giving a graphical representation of the impact.

Results:

As Table 1 indicates, the association of factors such as lesser education, living in more rural environment, post-menopause, oral contraceptive pills' (OCPs) consumption, family history of Breast Carcinoma (CA Breast), having Diabetes, having Hepatitis C and being a smoker was significant with CA breast. Table 2 shows findings in quantitative parameters. The mean age, weight and BMI was higher in CA Breast patients as compared to controls. There was significant association between CA Breast and the above-mentioned quantitative parameters i.e. older age, people with more weight and those having higher BMI.

Table 1: Table showing Frequencies of categorical variables of patients and controls used in the study

Characteristics	**Categories**	**Patients (150)**	**Controls (150)**	**Statistics**	
		Frequency/ percentage N (%)	Frequency/ percentage N (%)	**X***	P value**
Education Level	Illiterate	51 (34)	27 (18)	**11.728***	**0.008****
	Primary	65 (43)	70 (46.7)		
	Secondary	26 (17)	41 (27.3)		
	Higher education	8 (5)	12 (8)		

Residence	Urban	51 (54)	71 (47.3)	**7.473***	**0.024****
	Semi-urban	51 (54)	49 932.7)		
	Rural	48 (42)	30 (20)		
Marital status	Unmarried	5 (3)	11 (7.3)	2.48*	0.288**
	Married	121(81)	118 (78.7)		
	Widowed	24 (16)	21 (14)		
Parity	Nulliparity	13 (8.7)	17 (11.3)	0.669*	0.716**
	Uni/ bi parity	16 (10.7)	17 (11.3)		
	Multiparity	121 (80.7)	116 (77.3)		
Age at menarche	Less than 13 years	87 (58)	77 (51.3)	1.345*	0.246**
	More than 13 years	37(42)	73 (48.7)		
Menopause	Pre-menopausal	52 (34.7)	82 (54.7)	**12.132***	**0.000****
	Post-menopausal	98 (65.3)	68 (45.3)		
OCPs use	Yes	55 (36.7)	28 (18.7)	**12.143***	**0.000****
	No	95 (63.3)	128 (81.3)		
Use of HRT	Yes	28 (18.7)	22 (14.7)	0.864*	0.353**
	No	122 (81.3)	128 (85.3)		
History of breast feeding	Yes	72 (48)	104 (69.3)	**14.076***	**0.000****
	No	78 (52)	46 (30.7)		
Family history of cancer	Yes	15 (10)	11 (7.3)	0.674*	0.412**
	No	135(90)	139 (92.7)		
Family history of breast cancer	Yes	16 (10.7)	3(2)	**9.496***	**0.002****
	No	134 (89.3)	147 (98)		
History of Hypertension	Yes	38 (25.3)	33 (22)	0.461*	0.497**
	No	112 (74.4)	117 (78)		
History of Diabetes Mellitus	Yes	47 (31.3)	29 (19.3)	**5.71***	**0.017****
	No	103 (68.7)	29 (80.7)		

History of smoking	Yes	11 (7.3)	3 (2)	**4.795***	**0.029****
	No	139 (92.7)	147 (98)		

*value generated according to chi square
**p-value generated by Chi square score

Table 2: Data distribution and comparison of quantitative demographic parameters between controls and patients

Parameter	**Patients (45)**	**Controls (45)**	**P-value**
	Mean ± SD	Mean ± SD	
	Median (IQR)	Median (IQR)	
Age (years)	52 ± 11.2	46.87± 11.63	**0.00[a]**
	52.5 (44-61)	46 (36-56)	
Height (meters)	1.58 ± 0.06	1.59±0.05	0.08[a]
	1.59 (1.59-1.64)	1.61 (1.57-1.65)	
Weight (Kg)	69.7 ± 18.76	64.82±17.79	**0.01[a]**
	67.0 (67-79)	60 (52-78)	
BMI(kg/m2)	27.68 ± 7.14	25.23±6.56	**0.00[a]**
	26.65 (26.65-31.6)	23.4 (20.35-29.7)	

[a]p-value generated by Mann-Whitney U Test
[b]p-value generated by Independent Sample "t"-Test
p-value ≤ 0.05 is considered statistically significant

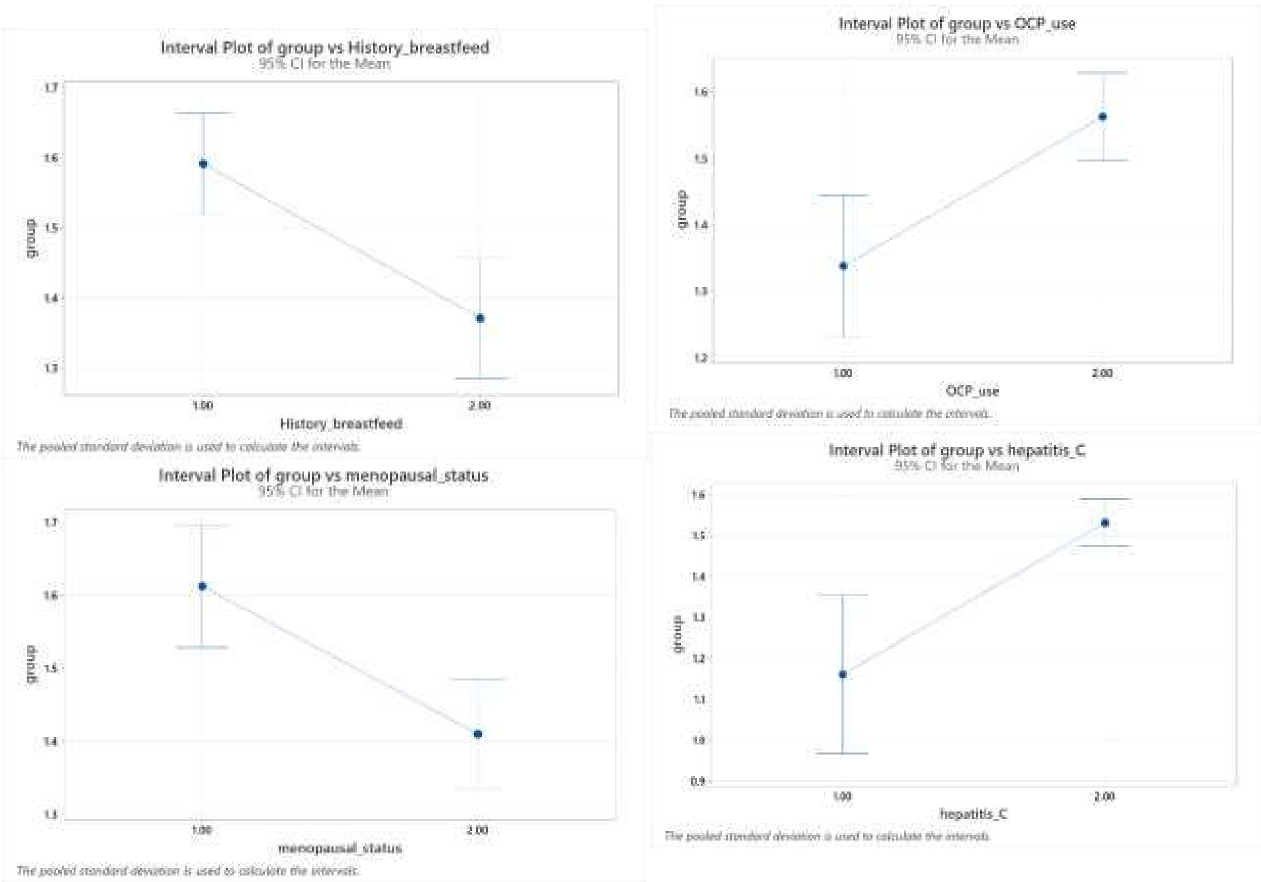
Using Minitab, one sample T test verified the significant factors from previous results. To find out the measure of difference between the patients and controls, ANOVA was applied on means of the significant factors.

ANOVA to Visualize the Differences in Means

The Analysis of Variance (ANOVA) results provide further evidence of a significant difference in residence scores between the case and control groups. Each variable demonstrates a significant impact on the dependent variable. Variables such as history of breastfeeding, menopausal status, OCP use, and history of hepatitis C exhibit most significant effects on the dependent variable, with F-values ranging from 12.57 to 14.67 and all p-values being less than 0.05 and the lowest amongst all. Education, history of breast cancer, and history of diabetes mellitus show significant but relatively lower effects, with F-values ranging from 4.01 to 9.74 and all p-values being marginally bigger than the previous factors. Lastly, age, residence and history of smoking also have significant effects, but to a lesser extent, with F-values of 1.97, 3.79 and 4.84, respectively, and all p-values although being less than 0.05 yet bigger than earlier factors. Overall, these results suggest that each independent variable contributes to explaining variations in the dependent variables.

Figure 1 shows the graphical representation of findings of ANOVA for the most significant 4 factors.

Figure 1: Graphical representation of ANOVA for Menopause, OCP use, Breast feeding and Hepatitis C



Regression Equation

This regression equation summarizes the relationship between various independent variables and the dependent variable.

Regression Equation

group	=	0.180 + 0.00497 Age + 0.0 Rural residence + 0.0820 Semi-rural residence + 0.0259 Urban residence + 0.0 Education- Higher Education + 0.174 Education- Illiterate + 0.024 Education-Primary Education + 0.003 Education-Secondary Education + 0.0 menopausal status-Post-menopausal - 0.0772 menopausal status- Pre-menopausal + 0.0 OCP use-yes + 0.1516 OCP use-No + 0.0 History of breastfeeding- No - 0.1992 History of breastfeeding-Yes + 0.0 History of breast cancer-No + 0.366 History of breast cancer- Yes + 0.0 History of Diabetes Mellitus-No + 0.1542 History of Diabetes Mellitus-Yes + 0.0 History of smoking- No + 0.172 History of smoking- Yes + 0.0 Hepatitis C No + 0.2288 Hepatitis C -Yes

Coefficients

Term	**Coefficient**	**SE Coefficient**	**T-Value**	**VIF**
Constant	0.180	0.197	0.91	
Age	0.00497	0.00264	1.88	1.40
residence				
Semi-rural	0.0820	0.0953	0.86	2.96
Urban	0.0259	0.0905	0.29	2.90
Education				
Illiterate	0.174	0.133	1.31	5.00
Primary Education	0.024	0.111	0.21	4.46
Secondary Education	0.003	0.118	0.03	3.56
Menopausal status				
Pre-menopausal	-0.0772	0.0631	-1.22	1.45
Use of OCPs				
Yes	0.1516	0.0613	2.47	1.10
History of breastfeeding				
Yes	-0.1992	0.0564	-3.53	1.13
Family history of breast cancer				
Yes	0.366	0.110	3.32	1.06
History of Diabetes Miletus				
Yes	0.1542	0.0610	2.53	1.03
History of smoking				
Yes	0.172	0.131	1.31	1.13
Hepatitis C				
Yes	0.2288	0.0968	2.36	1.05

The overall R-squared value of this model is 14.66%, which means that these factors can cater for as much as 15% of the reasons for cases. Residence, Education, Menopausal Status, OCP Use, History of Breastfeeding, History of Breast Cancer, History of Diabetes Mellitus (DM), History of Smoking, Hepatitis C are categorical variables representing different characteristics or factors. Positive coefficients indicate that being in a particular category of the variable is associated with a higher likelihood of belonging to the group, while negative coefficients indicate a lower likelihood.

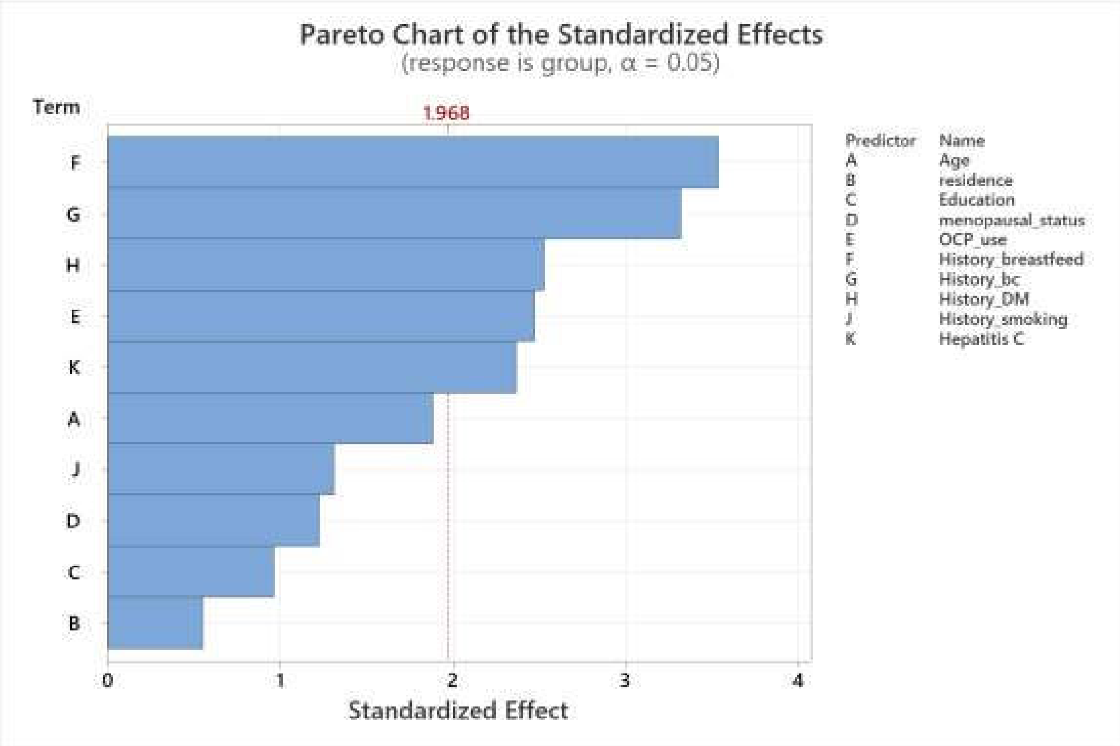
It is clearly visible that history of breastfeeding, history of breast cancer, history of diabetes, use of oral contraceptives and hepatitis C, to some extents are the major predictors, while the other factors are not significant. The regression equation includes coefficients for each category of these variables compared to their respective reference categories. For example, having history of breastfeed (compared to a reference category, likely no history of breastfeed) is associated with a lower likelihood of being a case, as indicated by the positive coefficient of -0.1992. Conversely, having a history of breast cancer is associated with a higher likelihood of belonging to the group, as indicated by the positive coefficient of 0.366. Same is for the use of oral contraceptives and diabetes, and hepatitis C with coefficients 0.1516, 0.1542 and 0.2288 respectively.

Pareto chart:

To make the scores of Regression Analysis easier to understand, Pareto chart is drawn and presented in Figure 2.

This graph makes it clearer to visualize the impact of regression. History of breastfeeding, history of breast cancer, history of diabetes, OCP use and hepatitis C to some extents are the major predictors, while the other factors are not significant.

Figure 2: Pareto chart of the standardized effects:



Discussion:

The problem of Breast CA is running rampant globally. Although the incidence is pretty much the same in developed or underdeveloped countries, however the indicators such as disability adjusted life years (DALY) show that more burden is shared by the underdeveloped countries (Kulothungan et al., 2024). In developing countries, this menace goes up a notch because of lack of screening facilities, lack of education and awareness among the masses. This leads to inability to appreciate cancer in earlier stages ultimately leading to lower survival rates (Nandakumar et al., 2017). This also causes the diagnosis to be made at later stages making the treatment and management far more expensive, therefore unaffordable for most people(Weth et al., 2024). Many a time, it is too little too late and the treatment can no longer suffice saving lives. Pakistan is this regard is no different and has one of the worst numbers in the region as well as in the world (Khan et al., 2021). Traditionally there are many risk factors that are associated with probability for someone to end up with CA breast. Our study found similar associations like those reported in many previous studies, to the extent that it feels like stating the obvious. However there are fewer studies from this part of the world so adding to the available knowledge in the local context gives a perspective to the findings(Fan, Goss, & Strasser-Weippl, 2015). Having said that, our study unearthed few untoward associations as well. For instance, the people living in semi-urban or rural areas shows more incidence of CA breast. However, this finding did not have an impact. Similarly, the age at menarche is said to have a strong association with CA breast (Kim et al., 2024). Our study did not appreciate this association. After passing our data through rigorous sequence of statistical tests through 2 soft wares, the results were reported.

It can be seen quite evidently that we can chalk out the five most important factors which have the most significant association with Breast CA. First is Breast feeding. Our study showed that more women who had not breastfed their children had Breast CA. This is in line with many studies. The most recent one is a contemporary review published in 'Frontiers in Oncology' asserting the same association. (Nicolis, De Los Angeles, & Taramasco, 2024). The second factor identified in our regression analysis as significant is having a pertinent family history i.e. mother, grand-mother, a sister or a cousin sister had breast CA as well. (Padamsee et al., 2024) The family history of breast CA is associated with mutation in BRCA1 and BRCA2 genes, which run in families and is a well-studied association. (Yu et al., 2024). In the next place is the co-morbidity of Diabetes mellitus. The incidence of CA breast in diabetics was more than that in non-diabetics. (Thomas, Scalzo, & Wellberg, 2024). Some of the mechanisms by which diabetics tend to be more prone to developing breast cancer include the following: 1) Insulin resistance leading to increased levels of insulin in the blood. Insulin is a growth factor and can induce growth in breast tissue. 2) Persistent hyperglycaemia in the blood can lead to inflammation in the body and this constant inflammatory environment in the body can lead to cancerous transformation of breast cells. 3) Diabetics are prone to obesity and obesity leads to more estrogen. Estrogen hormone can increase growth of hormone receptor positive breast cancer cells.(Xiong et al., 2024) Next in line is consumption of Oral Contraceptive pills. The women who had history of prolonged oral contraceptive drugs use had more CA breast than those who had not.(Najm, 2024) In addition to other factors, this can be due to the hormones in OCPs that can influence breast cells. In the list of most impactful factors, the last one is the comorbidity of Hepatitis C. Patients who had hepatitis C had more CA breast than the others. This was in line with a similar finding in another study which showed a similar impactful correlation between Hepatitis C and the outcome of Breast cancer. Hepatitis C virus can accelerate breast cancer progression by increasing p53 and c-Myc oncoproteins circulating levels. (Fathy, Abdelrazek, Attallah, Abouzid, & El-Far, 2024)

Conclusion

The study's conclusion emphasizes the critical need for all-encompassing approaches to address the rising incidence of breast cancer, especially in developing nations where inequities in access to healthcare worsen the situation. The study emphasizes context-specific findings, shedding light on connections like the effect of breastfeeding practices and the comorbidity of hepatitis C on breast cancer incidence, despite the universality of risk factors like family history and diabetes mellitus. These revelations highlight the significance of customized therapies and increased public awareness initiatives to target both known risk factors and recently discovered correlations, with the ultimate goal of reducing the catastrophic impact of breast cancer on people and communities around the globe.

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