Original Article

Breast Cancer: Epidemiology, Risk Factors and Survival Analysis in the Pakistani Population

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Abstract

Objective: To find out the association of genetic, reproductive and socio demographic factors with breast cancer in Pakistani women along with the survival percentage of patients having breast cancer.
Methodology: A case control study was carried out for a period of 3 years. Data were collected from different hospitals in Pakistan and the survival rate was determined by having direct contact with patients through telephone calls. For the estimation of survival probability Kaplan-Meier curve was used.
Association of various demographic and epidemiological factors with breast cancer occurrence was estimated by using the odds ratio (OR) and 95% confidence interval (CI). Various tests used to find out the significance of results included student t-test, chi square test, Fisher exact test and ANOVA. A statistical tool SPSS version 22 was used to analyze the date and results orientation.
Results: The mean age for breast cancer diagnosis 47.3±11.8 years of age was found as mean age for breast cancer diagnosis. Higher Body Mass Index (BMI) was the major contributing factors in developing breast cancer (OR=3.5, 95% CI=2.6-4.5). Significant risk factors found to be associated with the breast cancer include dlong reproductive period (menarche to meno- pause), family history of disease and habit of passive smoking (P<0.05). Out of 448 married patients, 23% were nulliparous and 26% of patients did not have a lactation history. Chemotherapy along with radiotherapy and surgery have been found to be effective methods for breast cancer treatment (80% survival).
Conclusion: Present study concluded that age, body mass index, oral contraceptives usage, lactation duration, reproductive duration and marital status of the female are significant factors in developing breast cancer in Pakistani women.

Keywords: Breast Cancer, Nulliparous, Chemotherapy, Radiotherapy, Surge

Introduction

Breast cancer is the carcinoma of the breast which originates in breast tissue. This carcinoma is mostly found in the inner lining of milk producing ducts. In this carcinoma a single cell is transformed into multiple abnormal cells with high potential of malignancy.[1] Breast cancer has high incidence (23% of the total cancer) as well as mortality rate due to which it is considered as a major health problem throughout the world.[2] After lungs cancer, breast cancer has the highest mortality rate in Asia.[3] Among the list of Asian countries, Pakistan is at the top in breast cancer morbidity and mortality rate with 2.1 million new cases and 627,000 deaths in 2018.[4] Lack of awareness is associated with delayed diagnosis that may be attributed to personal, sociocultural and economic factors.[5]

Epidemiological studies showed correlation between various risk factors and breast cancer development.[4,5] These genetic and enviromental factors that interact with each other contributing in increasing risk of developing breast cancer. These factors also contribute to the variability in incidence of the disease onset.[6] Early and late events in life also contribute to breast cancer on set, but the mechanism of differential susceptibility has not been fully explored.[7] Those women who have family history of this carcinoma, women who used exogenous hormones, those who have first child at older age and obese women are more prone to developing breast cancer.[8,9] In order to understand the etiology of breast cancer, risk factors contributing in breast cancer need to be evaluated properly.

Age at the time of diagnosis is one of the most important factor contributing in increasing breast cancer mortality. In Asian countries breast cancer is found to be diagnosed in younger age of 40-50 years, whereas in western countries breast cancer is usually diagnosed in late ages of 60-70 years.[10] Geographic location was observed to be contributing in varying breast cancer incidence, therefore breast cancer risk factors in different populations are also varying. Population based cancer registries have not been formulated in Pakistan; available data is gathered from small groups of population.[11] So, it is important to explore the potential risk factors contributing in the onset of breast cancer in Pakistan.

Knowing the breast cancer susceptible groups of Pakistani women and factors contributing in causing breast cancer will increase awareness among women at high risk, promote early diagnosis and decrease cancer probability. It will also help in formulating programs for public health improvement.

Purpose of this study was to find out the asso- ciation of breast cancer with various epidemi- ological, reproductive and demographical risk factors in Pakistani women. Factors which are particularly focused in

this case-control study include age, reproductive age (menarche/meno-pause age) or duration, age of women when she gave first birth, number of pregnancy, lactation history, use of oral contraceptives and passive smoking. This study also analyzed the survival probability of breast cancer patients.

Methodology

Study design: The Inclusion/exclusion criteria and data collection. In the present study standardized, structured questionnaire was used for information collection from histologically confirmed breast cancer patients. Questionnaire was comprised of questions about different factors including personal and family detail as well as disease history of each candidate. Study approval was taken from the ethical committees of Fatima Jinnah Women University (FJWU) and Rawalpindi Medical College (RMC) and Allied Hospitals (Holy family, Benazir Bhutto and District Headquarter Hospitals). These hospitals were visited to collect data from breast cancer patients and age match controls. An informed consent was signed by all the participants who were being interviewed. A total of 1000 individuals (500 histologically positive patients and 500 age matched controls) were interviewed. Only those individuals were included in the study who had been confirmed by oncologists as breast cancer patients. However, control data was collected to monitor any age related factor. Study participants were contacted personally through telephone calls for determination of their vital status (alive or dead). Death dates of the participants were recorded for survival analysis of breast cancer patients. Samples were collected for the duration of 3.5 years (January 2017 to July 2020).

Statistical analysis

SPSS 25 was used to perform statistical analysis of the data collected from patients and controls. Variables were compared by using Fisher exact, chi-square and t-test. Frequencies and percentages were used to describe the categorical variables whereas mean and standard deviations were used for analyzing continuous variables. Odds ratios and 95% CI were used to estimate the association between breast cancer and different risk factors. Kaplan-Meier curve was used to find out the survival probability of breast cancer patients. Results with P values less than 0.05 were considered as statistically significant (Table 1).

Results

A total of 1000 individuals (500 cases and 500 age match con- trols) were selected for the study and they were interviewed for the specific questions. The mean age of patients and healthy women was found as 47.6+12.2 years and 46.6+12.01 years re- spectively. Significant association was found by multivariate analysis between increased age (≥40 years) and breast cancer risk (P=0.03). Highest number of patients was found in the age group of 36-45 years with the mean age 42.1±1.51 years (Figure 1). Body mass index (BMI) of the patients as well as controls was calculated by recording their weight in kg and height in cm. Al- most twice increase in breast cancer risk was found as associated with obesity (OR=2.3, 95% CI=1.6-3.3). Significant association of marital status was found with risk of breast carcinoma (p<0.05). Large number of the patients were married (82%), only few were unmarried. However, number of pregnancies didn't play role in the cause of breast cancer as only 5% cases were nulliparous in the current study (Figure 1).

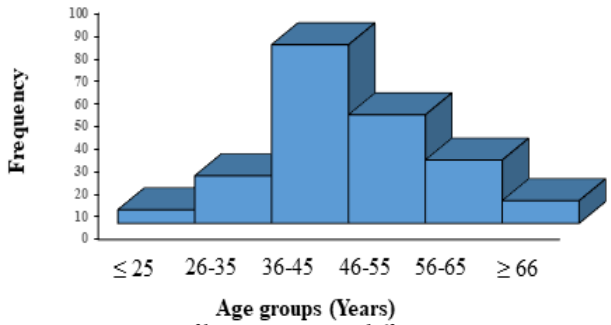

Figure 1: Frequency of breast cancer in different age groups

Among parous 26.2% females had no lactating history, which could be considered as the cause of breast cancer in them. Mean age of the patients at first birth was 21.3± 0.3 years. Majority women had 3 to 4 live births with mean 3.8± 2.2. Family history, consuming oral contraceptives and passive smoking were the factors that had significant association (P<0.05) with increased risk of disease (Table 1). In the current study, none of the patients were active smokers. Few passive smokers had double risk of breast cancer compared to patients who did not smoke (OR=2.0, 95% CI=1.5-2.6). Pictorial data for the various factors associated with breast cancer are shown in Figure 2.

Although both peri and post-menopausal breast cancer cases were found, with large number of patients having an early men- arche or late menopause. Females with late menopause (after 55 years of age) had more than double risk of developing breast cancer compared to women having early menopause (OR=2.5, 95%, CI=1.7-3.7). In the same way an early menarche (<12 years of age) doubled the risk of developing breast cancer as compared to late menarche of ≥12 years of age (OR=2.0, 95%=1.5-2.6).

In the conducted survival analysis of breast cancer patients utilizing the Kaplan-Meier curve, the mean survival time was determined by calculating the interval between sample collection (T0) and the maximum time (Tmax). The median survival time, the point at which the probability of patient survival is reduced by half, was found to be 23 months. This crucial metric was derived from assessing the survival rates under three different treatments: surgery, chemotherapy, and radiotherapy. Statistical tests, including the log-rank, Breslow, and Tarone-Ware tests, were employed to evaluate the impact of these treatments on breast cancer survival. Significantly, all three treatments demonstrated notable effects on survival rates (p<0.05).

It is truly remarkable and noteworthy that the most elevated de-

gree of survival was observed and documented when the three in- terventions were implemented and utilized simultaneously, which strongly suggests and implies that there may exist significant synergistic effects that greatly enhance and augment the overall outcomes and results for patients who are undergoing treatment. It is of utmost importance and necessity to accurately and precisely capture and record instances and cases of patient mortality in order to provide and present a clear and visual representation of the patients' outcomes. These instances and cases are meticulously documented and effectively portrayed on the widely recognized and accepted Kaplan-Meier curve, which serves as a powerful tool and method to display the progression and status of patients where data was censored and not fully available.

Table 1: Cross-sectional analysis of epidemiological and socio demographic factors in breast cancer patients and healthy controls

Cases			Controls		
Risk factors	**Mean/ Frequency**	**Standard deviation%**	**Mean/ Frequency**	**Standard deviation/%**	**P-Value**
Diagnosis age	47.6 years	+12.23	46.6 years	+12.01	0.21#
Menarche age	11.8 years	+0.79	12.7 years	+0.8	0.33#
Body Mass Index	29	+3.9	24.3	+2.7	<0.01#*
Married Children	410	82.0%	351	70.0%	<0.01+*
None	87	21.2%	11	3.1%	<0.01@*
≤ 4	228	55.6%	116	33.0%	
5-9	95	23.1%	224	63.8%	
Menopausal status					
Pre	206	41.2%	299	59.8%	<0.01+*
Post	294	58.9%	201	40.2%	
Menopausal Age					
≥ 50 years	181	61.5%	106	52.7%	0.05+*
Breast Carcinoma					
History in family	192	38.4%	46	9.2%	<0.01+*
Usage of oral contraceptives	238	47.6%	117	23.4%	<0.01+*
1st pregnancy age					
Less than 30 years	260	80.4%	290	85.2%	0.21+
Passive smokers	312	62.4%	115	23%	<0.01+*

*#T-test*Significant difference the specific risk factor in two groups (cases and controls).\ +Fisher's exact test @Annova*

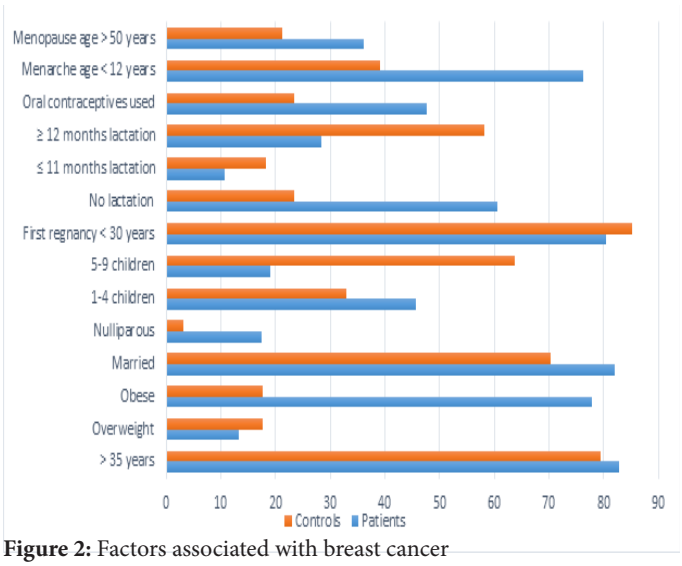

Figure 2: Factors associated with breast cancer

Fisher extract test showed significant association between reproductive period (menarche to menopause) and increased breast cancer risk (P<0.01). For the follow-up 447 participants were contacted, some of them lost during study. In order to check survival rate, patients were followed up for 3 years (after interview date), through telephone calls and found that 77% of the patients survived (Table 2).

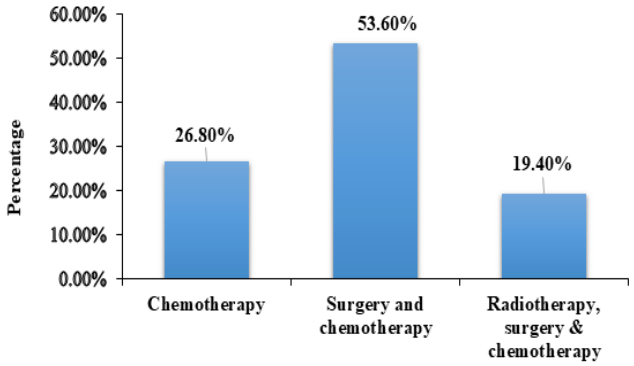

Figure 3: Percentages of the patients receiving different treatments is illustrated

This comprehensive and all-encompassing analysis and examination of the data and results obtained from different treatments and interventions offers invaluable and highly valuable insights and knowledge into the effectiveness and efficacy of these various approaches. Furthermore, this analysis also strongly emphasizes and highlights the potential advantages and benefits of adopting and implementing a combined and integrated approach in order to significantly improve and enhance the rates of survival for individuals who are adversely and severely impacted by the devastating effects of breast cancer (Figure 3 and 4).

Table 2: Statistical analysis of different treatments given to breast cancer patients and association of these treatments with breast cancer survival

Treatment	Mean	95% CI	Median	95% CI	P-Value
Chemotherapy	17.4 ± 0.2	16.8-17.9	18.0 ± 0.2	17.4-18.5	<0.01
Chemotherapy and Surgery	23.0 ± 0.3	22.3-23.7	25.0 ± 0.6	23.7-26.2	
Chemotherapy, Surgery and Radiotherapy	27.2 ± 0.6	25.8-28.5	25.0 ± 0.6	23.7-26.2	
Overall	22.8 ± 0.3	22.2-23.5	22.0 ± 0.3	21.2-22.5	

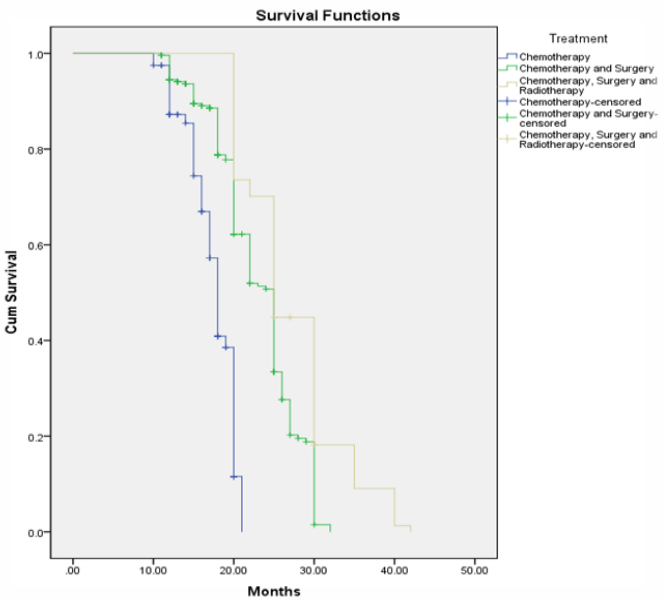

Figure 4: Survival analysis curve, after 3-year follow-up.

Discussion

In Pakistani females, breast carcinoma is the most frequently diagnosed cancer. The rate of breast carcinoma is promptly increasing almost everywhere, especially in less developed countries.[12] Ratio of breast cancer in Asian countries is lower than European countries, however death rate due to breast cancer in Asian countries is comparable to European countries.[13] Five Asian countries having highest breast cancer death rates are Pakistan, Armenia, Lebanon, Jordan and the Syrian Arabic Republic.[14] Pakistan is at the top list, due to this alarming situation its need of hour to adopt preventive strategies.[15] World wide breast cancer has been studied widely but disagreement is found about breast cancer risk factors and its development. Most important risk factor listed for different cancers is age.[16] Although no age is specified for the development of breast cancer, but ¾ number of cases diagnosed after 50 years of age.[17] However average age of breast cancer diagnosis for different countries is different, for US it is 61 years 18 for Iran it is above 44 years[19] and for Brazil it is 55.8 years old.[17] Mean age at the time of diagnosis of breast cancer in the current study was re- corded as 47.3±11.8 (Table 1) which is in accordance with the previous studies.[20] Diagnosis age in the present study (as well as previous studies in Pakistan) is almost ten years earlier than the diagnosis age in Western countries. Further studies are needed to find out the reason of breast cancer diagnosis in younger ages in Pakistan. Another major health issue globally is obesity, elevated BMI gives rise to different diseases including cancer.[21]

It was estimated that if obesity is prevented, breast cancer occurrence rate could be 50% reduced in European Union alone.[22] Studies conducted on relation between obesity and breast can- cer reported that obesity increased the risk of breast cancer in women above 50 years of age.[23-25] Current report also showed an association of obesity with breast cancer risk (OR 3.5, 95% CUI=2.6-4.5) (Table 1). Previously, Bhaskaran et al.,[26] and Xia *et al.*,[27] also found association of high body mass index with in- creased risk of breast cancer, it might be due to the activity of excess aromatase in the peripheral adipose tissue, that produced higher levels of free estrogen.[28]

In Asian countries important risk factors associated with breast cancer include menarche at younger age, menopause at late age, first birth at older age and few live births.[29] Contrast has been found in the marital status and breast cancer in different studies. Marriage somehow affects the health of women, however association of breast cancer risk with marital status has not been investigated comprehensively. Similar to the results of Aizer et al., we also found that married women have less chances of developing breast cancer (OR=0.35, 95% CI=0.2-0.6) (Table 1). But in contrast to the previous studies, we found equal probability of breast cancer in both nulliparous females and females with vary- ing number of children (OR=1, 95% CI=0.7-1.3). It is reported in literature that many women effected with breast cancer have lactation history.

In the present study we also found that major- ity cases were having lactation history (OR=0.8) (Table 1). But further studies are required to investigate the mechanism that how breastfeeding effects breast cancer. There is no direct link between menopause and breast cancer but menopause at older ages increased the risk of developing breast cancer. We found that early menarche and late menopause increases the chances of developing breast cancer, (Table 1) these results are in accor- dance with the findings of Khalis et al., It can be said that repro- ductive duration (menarche to menopause) plays fundamental role in breast cancer which may be due to the production of steroids during reproductive ages. Steroid's hormones are produced by ovaries and they effect the function and development of the breast. In previous studies, family history is also reported as one of the important risk factors of breast cancer. Familial history of breast cancer in first degree relative is considered an independent risk factor for the development of the breast carcinoma. In this study only few patients had family history of breast cancer (Table 1).

It has been reported that most of the familial breast cancer cases are caused by mutations in the BRCA-1 and BRCA-2 genes.[30] In the present study, chemotherapy was found as most common method of treatment. Chemotherapy was given to patients at three different times, i.e.; at initial stages to destroy cell, before surgery to shrink tumor size and after surgery to destroy remaining cancer cells. In order to avoid spreading of cancer across the body some patients had removed their effected breasts by

surgery. Few patients were given radiotherapy, after chemotherapy and surgery (Table 2). All the treatments were effective, and their combination resulted in good overall survival rate (80%).

Conclusion

Present study concluded that age, body mass index, oral contraceptives usage, lactation duration, reproductive duration and marital status of the female are significant factors in developing breast cancer in Pakistani women. Survival analysis revealed that combination of different treatments. Overall survival analysis showed that different treatments conferred good impact on patient's survival. Breast cancer susceptible groups have been identified in the current study, these groups should be focused on priority basis to avoid breast cancer development.

Authors' Contribution: SZ did experimental work and write up. NM designed and supervised research work. JSK contributed in samples collection. I. performed statistical analysis of the data. AY contributed in conception and designing.

Conflict of interests: The authors show no conflict of Interest.

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