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ORIGINAL ARTICLE

Association between Chronic Psychological Stress, Cortisol Dysregulation, and Risk of Breast Cancer Development in Women. A Case Control Clinical Study

MUHAMMAD HAMZA[1], USAMA NAEEM[2], SAMEEN ATHAR[3], HAMNAA AFZAL[4], AYESHA FATIMA NIAZI[5], JAVERIA ASLAM[6], MUHAMMAD UMAR ABBAS[7], AIMEN ABBAS[8]

[1]House Officer Physiotherapy Department, Shalamar Hospital, Lahore.
[2]House Officer Physiotherapy Department, Shalamar Hospital, Lahore. **Email:** nusama499@gmail.com
[3]House Officer Physiotherapy Department, Shalamar Hospital, Lahore. **Email:** sameenathar16@gmail.com
[4]House Officer Physiotherapy Department, Shalamar Hospital, Lahore. **Email:** hamnaafzal775@gmail.com
[5]House Officer Physiotherapy Department, Shalamar Hospital, Lahore. **Email:** ayeshafatimaniazi@gmail.com
[6]Associate Professor Physiotherapy, Shalamar School of Allied Health Sciences, Lahore. **Email:** Javeria.aslam@sihs.org.pk
[7]House Officer, Shalamar Hospital Pakistan. **Email:** drumar70@icloud.com, **ORCID:** 0009-0003-9279-9824
[8]MBBS Student, Akhtar Saeed Medical & Dental College, Lahore Pakistan. **Email:** aimenabas123@gmail.com, **ORCID:** 0009-0001-2460-5472
Correspondence to: Muhammad Hamza, **Email:** hamzariazpt@gmail.com, Cell: 03025013141

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ABSTRACT

Background: Chronic psychological stress has been seen as a more and more probable factor in the development of cancer via its impact on the hypothalamic-pituitary-adrenal (HPA) axis and dysregulation of cortisol. Nevertheless, there is limited evidence among clinical populations (especially in low- and middle-income nations).
Objectives: To assess the relationship between chronic psychological stress and cortisol dysregulation and the risk of breast cancer in women.
Methods: The present study is a hospital-based case-control study, comprising of 47 women with a newly diagnosed, histologically confirmed breast cancer and 47 age-matched healthy women, as controls. A structured proforma was used to record the sociodemographic variables, reproductive history and exposure to chronic stress. The Perceived Stress Scale (PSS-10) was used to measure psychological stress. Cortisol levels in the morning went through tests of chemiluminescent immunoassay and evening cortisol in a subset was taken to determine the diurnal rhythm. Dysregulation of cortisol was characterized by abnormal morning cortisol and/or flattened morning to evening cortisol ratio. The statistical tests were chi-square, independent t-test and multivariate logistic regression.
Results: PSS scores were much higher among breast cancer patients than they were among controls (24.8 vs. 17.2, $p < 0.001$). The cases were much more likely to have high psychological stress and long-term stressors in life. The mean morning cortisol levels were greater in cases (19.6 3g/dl) compared to controls (14.2 3g/dl) and cortisol dysregulation was more common in cases (61.7 vs. 27.6, $p < 0.001$). Multivariable regression demonstrated stress (AOR: 3.84) and dysregulated cortisol (AOR: 4.46) to be high predictors of breast cancer.
Conclusion: Cryptic psychological stress and dysregulation of cortisol are both of significant relevance in risking breast cancer. The stress and endocrine imbalance screening can be used to detect women who are at high risks and aid the preventive measures.
Keywords: breast cancer, stress, cortisol, HPA axis, women, psychological stress.

INTRODUCTION

Breast cancer is among the most critical issues of public health of women in the world that are increasingly being seen in both developed and developing nations[1]. Though the existence of more established risk factors like age, family history, reproductive hormone, obesity, and genetic predisposition are contributing factors in its development, new evidence has also pointed to the psychological factors of influence on breast cancer risk and specifically chronic stress[2]. Women in most places like the South Asia are often subjected to prolonged psychological stressors, which are caused by socioeconomic factors, care giving, interpersonal, financial and health related anxieties[3]. These chronic stress exposures can cause biological adaptations that can affect cancer proliferation and growth.

It has been known that chronic psychological stress activates the hypothalamic-pituitary-adrenal axis or HPA axis which leads to long-term release of cortisol [4]. Cortisol under normal conditions controls the metabolic activities, immune reactions, and inflammatory mechanisms. Nevertheless, the persistent increase of cortisol under the influence of constant stress may inappropriately regulate immunosurveillance, damage the process of DNA repair, facilitate oxidative stress, and disrupt hormonal balance all of which are biologically connected with carcinogenesis [5]. Additionally, it has been reported that abnormal cortisol rhythms, flattened diurnal variation, and loss of the normal morning peak have been recorded in people under chronic stress conditions which indicates endocrine dysfunction that can predispose women to the occurrence of tumors [6].

The psychosocial environment is also an important factor that determines physiological responses. Females in families with high stresses, with chronic emotional demands, or those subjected to work stress conditions could accrue increased levels of catecholamines and glucocorticoids circulating [7]. These stress hormones have been linked to increased tumor cell proliferation, angiogenesis and potential of metastasis in experimental models. Regardless of these results, the connection between chronic stress and dysregulation of cortisol and the risk of breast cancer in reality is poorly researched, especially in low- and middle-income groups such as Pakistan because in these countries the level of early detection is low, and the role of the psychosocial determinant of health is frequently neglected [8].

A case-control design gives a useful method of studying this association as well by comparing the level of stress and cortisol levels among women diagnosed with breast cancer compared to healthy controls. Knowledge of this relationship would aid in the development of risk factors that may be altered and therefore development of psychological and endocrine intervention that is specific to breast cancer to reduce its burden[9]. The proposed study thus seeks to assess the relationship between sustained psychological stress, cortisol pathophysiology, and the risk of developing breast cancer in women, which will offer new perspectives about the psycho-biological mechanisms that lead to the occurrence of the disease [10].

MATERIAL AND METHOD

The case control clinical study was undertaken in both the breast clinic and oncology units of the same tertiary care teaching hospital to investigate the relation of chronic psychological stress, cortisol dysregulation and risk of breast cancer among women. Forty-seven cases of newly diagnosed breast cancer with histological confirmation of the condition were recruited as the case group, and forty-seven age-matched healthy women with no history of malignancy had to be selected as the controls, comprising a total of 94 participants. The cases were sampled in line with the patients visiting the breast clinic and controls identified with the hospital staff, attendants and other visitors to the outpatient, in order to create similarity in age, socioeconomic exposure and the overall environment.

Both groups included women between the ages of 25 and 65 years. The eligibility criteria were that the cases should have been diagnosed with primary breast cancer in the past three months and had not undergone chemotherapy or radiotherapy. The controls were also included when they had no history of cancer or a major chronic disease. The exclusion criteria were as follows; pregnant or lactating, known endocrine diseases like Cushing syndrome or thyroid dysfunction, taking systemic corticosteroids or psychotropic drugs within six months, major surgery within one month or severe infection. Every participant was interviewed in a structured interview form through a pre-designed proforma after giving an informed consent. The information received was the sociodemographic, reproductive and menstrual, lifestyle factors, sleep, and family history of cancer. In the case of breast cancer, clinical information of the tumor laterality, stage, nodal involvement, and receptor profile were accessed in the hospital records. Measurement of height and weight was on standardized procedures and BMI was derived.

The Perceived Stress Scale (PSS-10) that was given by trained interviewers was used to measure chronic psychological stress. The scale was used to scale stress-related feelings experienced by the participants in the last month and the level of stress was low, moderate, and high. Other questions touched on chronic life stressors such as

financial, domestic, caregiving, workplace, and recent life traumatic events. Fasting venous blood samples were taken to test cortisol days regulation between 8:00 and 9:00 a.m. following at least eight hours of an overnight fasting. Samples were centrifuged, and serum kept at -20 o C awaiting analysis. Cortisol levels in serums were assessed by means of a standardized chemiluminescent immunoassay via the central laboratory of the hospital in accordance with an appropriate quality control process. where practicable, a second sample of blood was taken about 11.00 p. m. to test the effect of the time of day, and a ratio of morning to evening cortisol was determined in those who provided both samples.

Operationally, chronic psychological stress was considered to be a moderate to high score on the PSS-10 and maintained over a period of three months. Abnormal morning cortisol level outside laboratory reference range or decreased ratio of morning to evening cortisol level were considered as cortisol dysregulation as a sign of flattened diurnal cortisol rhythm. Cases were taken to be women who had proven cases of breast cancer and controls were taken to be women who had no malignancy or a significant chronic illness. The study ethics approval was granted by the Institutional approval Ref (IRB/2024/45E). and Review Committee and all the subjects were assured of confidentiality and voluntary participation. Any person who had significantly high stress levels or odd cortisol results was referred to psychological or endocrine consultation accordingly.

The statistical analysis was done in SPSS. Continuous variables like age, BMI, stress scores and cortisol levels were presented in the form of mean ± SD or median with interquartile range. The frequencies and percentages were used to summarize categorical variables. The independent-samples t test or Mann-Whitney U were used to compare cases and control in case of continuous variables; chi-square or exact test of Fisher was used in case of categorical variables. The multivariate logistic regression model was used to determine the independent relationships between chronic psychological stress and cortisol dys rule with breast cancer after controlling the confounding factors as age, BMI, reproductive and family history of cancer. The p-value of 0.05 was considered as statistically significant.

RESULTS

The study involved 94 women (from 47 cases and 47 controls of breast cancer). The calculation of mean age of the participants in the different groups matched as the two groups age matched successfully. Baseline sociodemographic and clinical variables demonstrated that the mean BMI of breast cancer patients was slightly higher than that of the controls, but the differences were not significant. Nonetheless, it was found there was a significant difference in family history of breast cancer whereby a higher percent of the cases reported positive family history as compared to controls. Reproductive variables were also captured including parity, breastfeeding history and menopausal status but none showed significant differences that affect matching validity.

Table 1 represents the demographic and clinical background details of the two groups. The age, BMI, residence, marital status and menopausal state did not differ statistically, thus indicating that the two groups were similar. Nonetheless, family history of breast cancer was found to be much more prominent among the cases (27.6) than among the controls (10.6), the p-value of 0.03 which represents a potential hereditary effect.

There were significant differences between groups in terms of the level of psychological stress. The mean scores of Perceived Stress Scale (PSS-10) were significantly higher in breast cancer patients compared to the controls. A much higher percentage of the cases were in the high stress category than the controls. Similarly, long-term exposure to stress in terms of financial pressure, burden of care givers and significant events in life were much more prevalent in cases.

As shown in Table 2, there is a very high significant difference in the level of stress among cases and controls. PSS scores were significantly higher in cases (24.8) as compared to those of controls (17.2). Over fifty percent of the cases (53.3) were of high psychological stress, and only 25.5 percent of the controls were of this type. Also, far more cases described persistent life violations like years of economic struggles or extreme domestic loads.

The level of serum cortisol did differ significantly in the two groups. The cortisol in the mornings had a huge difference in the breast cancer group, though a lower morning-evening ratio of cortisol was more common, implying the disruption of the diurnal clock. Cortisol dysregulation, which is defined as morning cortisol abnormality and/or flattened cortisol rhythm, was strongly more common in the cases.

Table 3 shows that breast cancer patients had a markedly greater mean level of morning cortisol levels and abnormal cortisol levels than controls. Abnormal morning cortisol was present in almost 50 percent (48.9) of the cases and more than 42 percent of the cases revealed a flattened diurnal rhythm. The cases (61.7% versus controls (27.6%) were significantly more prone to overall cortisol dysregulation, which would mediate a very close association between endocrine stress responses and risk of breast cancer.

To establish the independent predictive value of psychological stress, and cortisol dysregulation on breast cancer, a multivariate logistic regression analysis was carried out. Even after age, BMI, family history and reproductive factors, high psychological stress and dysregulation of cortisol were still strong predictors.

The regression findings demonstrate that women who were highly stressed psychologically were almost four times more likely to develop breast cancer than their counterparts who were not stressful. Cortisol dysregulation was also found to be an even more significant independent predictor, with women with that finding having more than four times the chance of breast cancer. Predictors were also chronic life stressors and positive family history which were statistically significant.

Table 1: Baseline Characteristics of Study Participants (N = 94)

Variable	Cases (n = 47)	Controls (n = 47)	p-value
Mean Age (years)	48.6 ± 9.2	47.9 ± 8.7	0.71
Mean BMI (kg/m²)	27.4 ± 4.8	26.1 ± 4.3	0.18
Urban Residence (%)	68.1%	63.8%	0.64
Married (%)	91.4%	87.2%	0.53
Family History of Breast Cancer (%)	27.6%	10.6%	0.03*
Postmenopausal (%)	44.7%	40.4%	0.68

Table 2: Comparison of Psychological Stress Between Cases and Controls

Stress Variable	Cases (n = 47)	Controls (n = 47)	p-value
Mean PSS Score	24.8 ± 6.4	17.2 ± 5.3	<0.001*
Low Stress (%)	6.3%	27.6%	0.004*
Moderate Stress (%)	40.4%	46.8%	0.54
High Stress (%)	53.3%	25.5%	0.006*
Chronic Life Stressors (%)	72.3%	40.4%	0.002*

Table 3: Cortisol Profile and Dysregulation Among Cases and Controls

Cortisol Variable	Cases (n = 47)	Controls (n = 47)	p-value
Mean Morning Cortisol (µg/dL)	19.6 ± 6.1	14.2 ± 5.4	<0.001*
Abnormal Morning Cortisol (%)	48.9%	21.3%	0.004*
Evening Cortisol (subset) (µg/dL)	7.1 ± 3.2	4.9 ± 2.8	0.01*
Flattened Cortisol Ratio (%)	42.5%	17.0%	0.006*
Overall Cortisol Dysregulation (%)	61.7%	27.6%	<0.001*

Table 4: Multivariable Logistic Regression Identifying Predictors of Breast Cancer

Predictor Variable	Adjusted OR (95% CI)	p-value
High Psychological Stress	3.84 (1.62–9.09)	0.002*
Chronic Life Stressors	2.91 (1.25–6.79)	0.01*
Cortisol Dysregulation	4.46 (1.87–10.62)	<0.001*
Family History of Breast Cancer	3.12 (1.02–9.54)	0.04*
BMI	1.07 (0.97–1.17)	0.18

DISCUSSION

The results of this case-control clinical trial demonstrate that there is a strong correlation between the constant psychological stress, dysregulation of cortisol, and the probability of breast cancer development in women. The findings revealed that the scores of Perceived Stress Scale (PSS) were significantly high among women with breast cancer than those who were not cancer patients and a significantly high percentage of the cases reported of having high levels of chronic psychological stress. This confirms the hypothesis that emotional or mental stress which may last a longer period of time can play a role in cancer pathogenesis by modulating several biological pathways. Stress is a physiological stimulus which causes the HPA (hypothalamic-pituitary-adrenal) axis to become active and the cortisol level to be elevated in the long term. Long-term cortisol hyperactivity may cause immune suppression, chronic inflammation, oxidative DNA damage, impaired apoptosis, and hormonal imbalance - mechanisms, which can combine to predispose to carcinogenesis.

Morning cortisol levels and the frequency of cortisol dysregulation were also highly increased and frequent among breast cancer patients, which was also observed in

the present study. Abnormal cortisol rhythms, especially an attenuated morning-to-evening ratio are an indication of impairment in normal circadian regulation of glucocorticoid release. It was found out that the diurnal fluctuation of cortisol may have a negative effect on immune protection by decreasing the functions of cytotoxic T cells and natural killer cells, which are essential in the recognition and destruction of abnormal or cancerous cells. Also, the distorted patterns of cortisol can modify estrogen, induce cell growth, and create an environment conducive to tumor growth. The observation that cortisol mal-regulation was a robust independent predictor of breast cancer, despite the influence of age, body mass index, and family history, is yet another indicator of the potential biological relevance of the stress-related endocrine derailment.

Besides, a greater number of breast cancer patients indicated that they had had some long-term stressors, including financial hardships, caring duties, and significant life events. The implications of such findings are that psychosocial strains might interact with the physiological mechanisms enhancing the negative impacts of chronic stress on the endocrine and immune systems. Although similar associations have been proposed in the previous research, findings are not consistent across populations. The variation in the results could be due to differences in the tools used in the measurement of stress and the differences between cultural backgrounds as well as the exposure to the environment. Nevertheless, statistically significant correlations in this paper are consistent with the new evidence in the world, which supports the idea that stress and cortisol deviations could serve as adjustable risk factors of breast cancer, Also, one should admit that breast cancer is a multifactorial one, and psychological stress cannot probably be one of the only factors of the development of the disease. Environmental, lifestyle, genetic and hormonal factors also contribute a lot.

However, the results of this paper highlight the importance of including psychological health, coping mechanisms, and early detection of endocrine disturbances in the prevention measures that are applied to prevent breast cancer. The strengths of this study are that it has the case-control design, validated psychological assessment tools, standardized cortisol measurements, and it has controlled the known confounders. Nevertheless, some restrictions are to be taken into account. The number of samples was relatively small, especially in the subgroup of the evening cortisol measurements. The cross-sectional information in data collection does not facilitate the determination of causality but emphasizes associations. Stress measure Self-reported measures of stress could also be subject to recall bias or underreporting. Although such limitations exist, the results offer significant information on the psycho-biological processes of risk of breast cancer and can be used to establish relationships through longitudinal studies in the future.

CONLUSION

This case-control study illustrated that there is a strong correlation between chronic psychological stress, cortisol dysregulation and breast cancer in women. Stress scores were higher among breast cancer patients, cortisol secretion abnormalities were significant and exposure to chronic life stressors were elevated among breast cancer patients more than healthy controls. High psychological stress as well as cortisol dysregulation were found to be strong predictors of breast cancer regardless of the presence of confounding factors. The results indicate that long-term emotional stress and impairment of HPA axis can be of significant contributory effect in the development of breast cancer.

The identification and treatment of chronic psychological stress can thus be a significant, but generally neglected, aspect of breast cancer prevention. Such measures as the inclusion of psychological screening, stress-reduction interventions, and endocrine assessment in the regular female health examinations might have the potential to allow the identification of at-risk individuals at earlier stages. To further investigate the causality of the relationship, and assess whether stress and cortisol regulation interventions can prevent breast cancer or enhance clinical outcomes, future, large-scale, prospective studies are required.

DECLARATION

Conflict of Interest
The authors declare no conflict of interest.

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Author's Contribution
All authors contributed equally in the complication of current study.

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Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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