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Psychological Stress, Cortisol Dysregulation, and Immune Alterations in Breast Cancer: A Biopsychosocial Analysis from a Low- and Middle-Income Country

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ABSTRACT

Background: In Pakistan, breast cancer is the most prevalent malignancy in women and has significant psychosocial and socioeconomic problems that could condition biological stress responses and disease outcomes. Psychological stress triggers hypothalamic-pituitary-adrenal (HPA) axis leading to the secretion of cortisol, which is important in the process of immune regulation and inflammation. Nevertheless, there are few facts on the interaction between psychological stress, cortisol mal-regulation, immune biomarkers, and social determinants in low- and middle-income breast cancer patients.

Methods: The study was a multicentred cross-sectional research done in both the public and private oncology hospitals in Punjab, Pakistan. The number of recruited participants was 320 people, 200 of them having histopathological confirmed breast cancer and 120 healthy people. A standardized scale that validated psychological stress was used to assess the stress and salivary and blood samples were measured by cortisol by use of enzyme-linked immunosorbent assay (ELISA). The analysis of immune biomarkers such as secretory immunoglobulin A (sIgA) and inflammatory cytokines was conducted using the standardized analysis approaches. The structured questionnaires and medical records were used to gather sociodemographic and clinical data including socioeconomic status (SES), area deprivation index (ADI) of community, stage of cancer, and mode of treatment. To compare groups and analyze associations, independent t-tests, chi-square tests, ANOVA and correlation analyses were employed. The p-value < 0.05 was assumed to be statistically significant.

Results: Breast cancer patients were found to have better cortisol level (13.8 ± 3.4 ng/ml) as opposed to the healthy controls (9.6 ± 2.7 ng/ml; p < 0.001), increased psychological stress (24.2 ± 6.1 vs. 16.8 ± 5.2) and decreased immune biomarkers (sIgA: 112.5 ± 25.6 vs. 138.2 ± 28.4). The cortisol (15.6 ± 3.7 nmol/L), inflammatory cytokines (12.7 ± 3.0) and the stress scores (26.7 ± 6.4) of advanced-stage patients were found to be significantly higher than those of the early-stage patients (p = 0.002). High deprivation areas and the low socioeconomic group accounted a higher percentage of breast cancer patients than the controls (p < 0.001). There was a positive correlation between psychological stress and cortisol levels and inflammatory markers and negative correlation between psychological stress and immune function markers.

Conclusion: Breast cancer patients, especially when they have advanced disease and are socioeconomically disadvantaged have great levels of psychological stress, cortisol problems, and immune distortions. The above results indicate a biopsychosocial model between social determinants and stress biology in cancer progression and the need to incorporate psychosocial support in oncology care in low-resource centers.

Keywords: Breast cancer, cortisol, psychological stress, immune biomarkers, socioeconomic status, Pakistan, psychoneuroimmunology.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women in all countries of the world and one of the leading causes of cancer-related morbidity and mortality. The incidence of breast cancer is of special concern to developing nations such as Pakistan where the country leads in incidences in Asia. The risk of developing breast cancer by Pakistani women is estimated to be 1 in 9, which is significantly large compared to most of its neighbours. Poor clinical outcomes among this population are caused by late-stage diagnosis, low-level screening programs, socioeconomic differences, and cultural barriers to accessing healthcare. Although biological and genetic factors are well defined causes of breast cancer, there has been the growing interest towards the role of psychosocial stress and the neuroendocrine mechanisms in the progression of breast cancer[1-3].

The activation of the hypothalamic-pituitary-adrenal (HPA) axis by psychological stress causes release of cortisol, which is an important stress hormone, and is responsible in regulating the immune system, inflammatory processes, and metabolism at homeostasis. Prolonged stress response system activation can cause the permanent elevation of cortisol which has been reported to suppress the immune system, produce more inflammatory cytokines, and also impair the ability of tumors to be surveyed. Recent findings indicate dysregulation of cortisol patterns and disease progression, responses to treatments, and survival rates in breast cancer patients. There are however limited studies that study these relationships in the Pakistani context[4-5].

The psychosocial stressors in Pakistan could be especially acute because of the socioeconomic factors, gender inequality, cultural demands, and the lack of access to healthcare. Female patients with breast cancer are usually emotionally distressed as a result of the fear of death, body image, financial and social stigma. Such stress triggers could be heightened in the groups of people who have low socioeconomic statuses or do not have adequate facilities, which might affect the physiological responses to stress and immune systems. Away from just considering the elements influencing the occurrence of psychological stress and social determinants on cancer progression, it is important to understand how the two interact with biological pathways in order to come up with holistic management modalities that are suitable to the local population[6-7]. In addition, advanced-stage patients exhibit significantly high levels of cortisol and inflammatory cytokines relative to patients with early-stage cancer implying that there is a very close correlation between the severity of the disease and dysregulation of biological processes in response to stress. Socioeconomic disadvantage was even more common with breast cancer patients and it points to the role of social determinants both as to the psychological and the physiological outcomes.

By such observations, the need to implement a biopsychosocial approach to managing breast cancer in Pakistan is emphasized. Inclusion of psychological analysis, stress coping interventions, and social support systems in services related to oncology can have effects of enhancing patient well-being and this could have an effect in the formulation of the biological pathways linked to the diseases progression[8-9]. Notwithstanding, this increasing popularity of psychosocial oncology worldwide, there is a paucity of empirical evidence in Pakistan that gives attention to the interaction of psychological stress, cortisol, immune activity and social factors in breast cancer patients.

Thus, the current paper was intended to examine how the psychological stress influences the level of cortisol, immune biomarkers, and social determinants in the patient with breast cancer in Punjab, Pakistan, and how these results are compared among patients at different stages of diseases and without the disease. The knowledge of these associations can be an important source of information to implement comprehensive culturally sensitive approaches to delivering cancer care within resource-constrained environments.

Objective

To examine the correlation among psychological stress, cortisol levels, immune biomarkers and socioeconomic determinants on breast cancer patients relative to healthy controls, and at various stages of the disease in Punjab, Pakistan.

MATERIAL AND METHOD

Study Design

The relationship between psychological stress, cortisol level, immune biomarkers and social determinants was analyzed in a cross-sectional analytical study to determine the relationship among the subjects who are HIV positive and those who are healthy.

Study Setting

The research was conducted at various cancer care clinics and tertiary care hospitals in Punjab, Pakistan of both the public and private sector health care facilities in order to have a representation of diverse population. The government-based oncology units were listed among the public hospitals which offered subsidized cancer treatment services as well as specialized cancer centers and oncology

clinics which offers cancer diagnostic and therapeutic services. This multi-center design provided an opportunity to recruit participants with different levels of socioeconomic background and clinical levels to increase the overall applicability of the results.

Duration of the Study
The research was carried out in the time of about 12 months, as of January 2024 until December 2024. This time period was sufficient to ensure proper recruitment of the participants, taking of the biologic samples, and also the analysis of the data.

Study Population
The target population was adult women with breast cancer who were either on treatment or follow-up care at the oncology centers, and controls were healthy women of the same age, who were recruited at the oncology centers and in the community as at the hospitals. The patients of breast cancer were covered in various clinical stages (Stage I-IV), and it was possible to compare the early and advanced conditions.

Sampling Technique
Eligibility to join the study was based on a non-probability consecutive method applied in recruiting appropriate individuals in oncology outpatient departments, chemotherapy unit and inpatient wards of selected hospitals. The recruitment of healthy controls was done through convenience sampling with the same hospitals and the communities with the aim of ensuring that the demographic characteristics were similar.

Sample Size
The overlap of the sample was determined based on a prevalence- based formula that will be applied when the study is carried out in a cross-sectional study with 5% margin of error and 95% level of confidence. With a medium assumption of the effect of cortisol between patients and controls it was estimated that the minimum size of sample needed was about 300 participants. The final population size in the study was 320 comprising 200 breast cancer patients and 120 healthy controls, and this was enough to support the statistical power in finding any significant differences between the two groups.

Inclusion Criteria
- Breast Cancer Patients
- Women between 18 years and older.
- Breast cancer known histopathologically.
- The patients who are already treated or under follow-up.

- Comprehension of the informed consent.
- Availableness to give biological samples.
- Healthy Controls
- Women over the ages of 18 years.
- Denies any cancer or chronic inflammatory history.
- No current acute illness
- Consent to take part, and give biological samples.

Exclusion Criteria
- Cancer-related psychiatric patients that were diagnosed with other psychiatric disorders.
- Patients that are on corticosteroids or immunosuppressants.
- Pregnant or lactating women
- Patients with chronic and severe autoimmune diseases or medical conditions.
- Incapacitated critically ill patients.

Study Measurements
The process of collecting data included the evaluation of the biological, psychological and social variables.

Biological Measurements
The levels of cortisol were of measurement on saliva and a blood sample that was gathered as per standard procedure. The samples of the salivary cortisol were gathered in sterilety and the samples of blood were gathered by qualified laboratory workers. To be accurate and reliable, samples were analyzed in certified laboratories through the enzyme-linked immunosorbent assay (ELISA) methods.

The biomarkers of immunity were seen to be secretory immunoglobulin A (sIgA) and inflammatory cytokines that have been quantified using well-validated laboratory methods. The choice of these biomarkers was informed by the fact that they are biomarkers that are related to immune functions and physiological reactions to stress.

Psychological Stress Evaluation
Psychological stress involved was determined by the help of a good standardized questionnaire, including the Perceived Stress Scale (PSS), that measures the perceived stress level during the past month. The instrument has proven to be highly reliable and valid in a variety of different populations and would be carried out in the local language where required.

Social Determinants Evaluation
Social determinants of health were assessed using structured questionnaires which covered indicators of socioeconomic status (SES), education, employment and residential deprivation. Community-level socioeconomic disadvantage was measured by the proxy scale, taken as Area Deprivation Index (ADI).

Clinical Variables

Medical records of patients with breast cancer provided their consent education to get clinical details such as cancer stage, treatment type, duration since diagnosis, and family history of breast cancer.

Data Collection Procedure

Participants were eligible and asked when they were visiting the clinic or hospital. The participants were taught to fill the questionnaire with the help of trained research staff (where necessary) and completed them with an informed written consent. The collection of the biological samples was done under controlled circumstances so as to reduce variation. This was anonymized and coded to guarantee confidentiality of all data.

Data Analysis

Th data were recorded and processed with the help of Statistical Package of Social Sciences (SPSS) version 25 (or other statistical software). Participant characteristics and study variables were summarized by using descriptive statistics such as means, Standard deviations, frequencies, and percentages.

To analyze the study findings with inference statistics, the following objectives and findings had been analyzed:

Cortisol, immune biomarkers, and stress scores were compared with the help of independent t-tests between the groups of breast cancer patients and healthy controls.

The difference in early and advanced cancer (stages of one way analysis of variance (ANOVA)) was used to analyze the difference.

Categorical Sociodemographic variables were analyzed using chi-square tests.

The Pearson correlation analysis was used to determine the association between psychological stress, cortisol levels, and immune biomarkers.

Several-linear regression analysis has been done to determine the independent predictors of cortisol levels, such as psychological stress and social determinants.

A p-value, below 0.05, was regarded as a statistically significant value.

Ethical Considerations

The study was started with the approval of the Institutional Review Board / Ethics Committee of the involved institutions following the protocol of ethical approval. All participants provided informed consent which was in writing form. The research was handled with a lot of confidentiality and anonymity and the subjects were aware that they could withdraw at any point without repercussions.

RESULTS

Table 1 shows the comparison between the sociodemographic and clinical variables in breast cancer patients (n = 200) and healthy controls (n = 120). The age variable of the sample size used was similar in both sets, as most respondents were in the 41 and above 55 and below age bracket in the breast cancer patients (46.0) and the controls (45.0). The mean age of the breast cancer patients (48. 6 ± 10.2 years) was slightly more than the age of controls (46.9 ± 9.8 years); but this was not significantly different (p = 0.12). Equally, there was no compelling difference in residential status in the two groups with almost similar proportions of study participants comprising urban and rural society (p = 0.91).

Conversely, there were large disparities observed in various socialdemographic variables. There was a statistically significant correlation with marital status where more percent (77.0) of breast cancer patients were married as compared to controls (71.7%). The level of education was also found to be significantly different across both groups (p = 0.02) with a higher percentage of breast cancer patients lacking any form of education (32.0) than among controls (21.7), with higher education level being more prevalent in controls. Another significant difference was found in employment status (p = 0.01) where breast cancer patients were more likely to be unemployed or housewives (74.0%) than were the controls (61.7%).

There were also significant socioeconomic differences. The percentage of patients with breast cancer was much higher than controls (62.0 vs. 40.0) with low socioeconomic status, middle, and high socioeconomic levels being predominant among controls (p < 0.001). Equally, the Area Deprivation Index (ADI) was observed to differ significantly across groups (p less than 0.001) with breast cancer patients living in densely deprived localities (59.0) more commonly than controls (36.7). These results indicate that there is a close relationship between breast cancer and socioeconomic disadvantage.

The clinical features of breast cancer patients revealed that most of them were diagnosed with Stage II (39.0%), and Stage III (30.0%) irrespective of the fact that the disease was already advanced at the time of diagnosis. Combination therapy was used by almost 50% (47.0) of patients, with chemotherapy, surgery and radiotherapy rated next (27.0), 15.0) and 11.0) respectively.

The occurrence of family history of breast cancer was also heavily more prevalent among the patients (36.0) in comparison to the controls (16.7) where the difference was highly important (p < 0.001), suggesting a possible genetic or familial predisposition within the group of patients.

In the Table 2, the analysis of biological, psychological, and social variables comparing the groups of participants

proved the important differences in the level of cortisol, immune biomarkers, and psychological stress. Active treatment patients with breast cancer showed significantly higher mean salivary cortisol (13.8 ± 3.4ng/ml) than their healthy counterparts (9.6 ± 2.7ng/ml) and this was statistically significant (p < 0.001). Likewise, there was a significant (p=.005) difference that was found between the patients of breast cancer (24.2 + -6.1) versus those of the controls (16.8 + -5.2) showing a higher perceived stress on the patient group. In contrast, the immune performance, which was one of the major indicators of secretory immunoglobulin A (sIgA) was reduced between the breast cancer patients (112.5 + 25.6) and the healthy persons (138.2 + 28.4), purportedly indicating the effects of stress on the immune functions.

On further stratification in terms of stage of disease, difference was also noticeable. Even the more advanced patients (Stages III -IV) showed significant differences in cortisol levels (15.6 ± 3.7 nmol/L) and cytokine levels (12.7 ± 3.0) being lower in patients with early-stage (Stages I -II) breast cancer. Psychological stress measurements were also in a similar pattern, whereby, patients with advanced stages were found to have the greatest psychological stress levels (26.7 ± 6.4) than patients with early stages (20.5 ± 5.8). All these differences were statistically significant (p = 0.002), which suggested that severity of the disease is closely correlated with physiological stress responses as well as inflammatory activity.

**Table 1.** Sociodemographic and Clinical Characteristics of Study Participants by Disease Status

Variable	Category	Breast Cancer Patients (n = 200) n (%)	Controls (n = 120) n (%)	p-value
Age (years)	≤ 40	58 (29.0)	42 (35.0)	0.18
	41–55	92 (46.0)	54 (45.0)	
	> 55	50 (25.0)	24 (20.0)	
Mean Age (years)	—	48.6 ± 10.2	46.9 ± 9.8	0.12
Marital Status	Single	22 (11.0)	20 (16.7)	0.04*
	Married	154 (77.0)	86 (71.7)	
	Widowed/Divorced	24 (12.0)	14 (11.6)	
Education Level	No education	64 (32.0)	26 (21.7)	0.02*
	Primary	46 (23.0)	30 (25.0)	
	Secondary	58 (29.0)	38 (31.7)	
	Higher	32 (16.0)	26 (21.6)	
Employment Status	Employed	52 (26.0)	46 (38.3)	0.01*
	Unemployed/Housewife	148 (74.0)	74 (61.7)	
Residence	Urban	112 (56.0)	68 (56.7)	0.91
	Rural	88 (44.0)	52 (43.3)	
Socioeconomic Status (SES)	Low	124 (62.0)	48 (40.0)	<0.001*
	Middle	56 (28.0)	52 (43.3)	
	High	20 (10.0)	20 (16.7)	
Area Deprivation Index (ADI)	High deprivation	118 (59.0)	44 (36.7)	<0.001*
	Moderate	54 (27.0)	46 (38.3)	
	Low	28 (14.0)	30 (25.0)	
Cancer Stage	Stage I	36 (18.0)	—	—
	Stage II	78 (39.0)	—	
	Stage III	60 (30.0)	—	
	Stage IV	26 (13.0)	—	
Treatment Type	Surgery	30 (15.0)	—	—
	Chemotherapy	54 (27.0)	—	
	Radiotherapy	22 (11.0)	—	
	Combination	94 (47.0)	—	
Family History of BC	Yes	72 (36.0)	20 (16.7)	<0.001*
	No	128 (64.0)	100 (83.3)	
Significant at p < 0.05				

Table 2. Participant Characteristics and Biological Measures Across Study Groups

Participant Group	Sample Type	Cortisol Level (Mean ± SD)	Immune Biomarkers (Mean ± SD)	Psychological Stress Score (Mean ± SD)	Social Determinants (SES/ADI)	Disease Status	p-value
Breast Cancer Patients (n=200)	Saliva	13.8 ± 3.4 ng/ml	sIgA: 112.5 ± 25.6	24.2 ± 6.1	Low SES: 62%	Active treatment	<0.001*
Healthy Controls (n=120)	Saliva	9.6 ± 2.7 ng/ml	sIgA: 138.2 ± 28.4	16.8 ± 5.2	Mixed SES	No disease	—
Early-Stage BC (I–II)	Blood	11.2 ± 2.9 nmol/L	Cytokines: 8.4 ± 2.1	20.5 ± 5.8	Moderate SES	Stable	0.002*
Advanced Stage BC (III–IV)	Blood	15.6 ± 3.7 nmol/L	Cytokines: 12.7 ± 3.0	26.7 ± 6.4	Low SES		

Table 3. Association Between Cortisol, Immune Biomarkers, Psychological Stress, and Social Determinants

Variable	Outcome Variable	Correlation Coefficient (r)	Regression β	95% CI	Statistical Significance
Psychological Stress Score	Cortisol Level	0.52	0.48	0.32 − 0.64	p < 0.001*
Socioeconomic Status (Low)	Cortisol Level	0.39	0.35	0.18 − 0.52	p = 0.001*
Area Deprivation Index (ADI)	Cortisol Level	0.41	0.37	0.21 − 0.53	p < 0.001*
Cortisol Level	sIgA	−0.46	−0.40	−0.58 − −0.22	p < 0.001*
Cortisol Level	Cytokine Levels	0.49	0.44	0.27 − 0.61	p < 0.001*
Psychological Stress	Immune Biomarkers	−0.35	−0.30	−0.48 − −0.12	p = 0.003*

Distribution of Cancer Stages Among Breast Cancer Patients
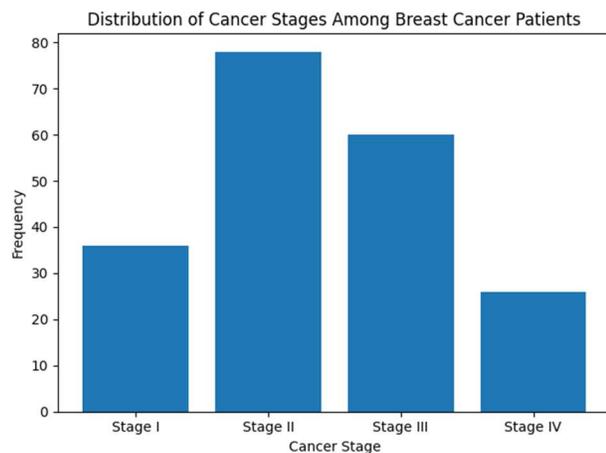
Social determinants were also dissimilar among the groups with a greater percentage of breast cancer patients mainly with advanced disease falling within the low socioeconomic status (SES) groups. Contrary, the comparison was made between healthy controls, who occupied mixed SES categories. The implication of this finding is that socioeconomic disadvantage could act as a predisposing factor to stress and disease pathway, possibly via chronic psychosocial stress and insufficient healthcare facilities.

The relationship between the biological (cortisol and immune biomarkers) and psychological stress and social determinants are found in Table 3. The results showed that the scores of psychological stress had a strong positive relation with the value of cortisol (r = 0.52, p < 0.001), which showed that the higher the perceived stress level, the higher the perceived physiological stress response was measured by the value of cortisol secretion. Cortisol levels were also substantially associated with socioeconomic disadvantage and greater deprivation of the area (0.35 and 0.37, respectively; p 0.001), indicating that poor social conditions might be one of the contributing factors of neuroendocrine dysregulation.

Moreover, cortisol levels recorded significant low correlation with the immune functioning indicators, which included secretory immunoglobulin A (sIgA) (r = -0.46, p less than 0.001), implying low immune functioning with elevated levels of cortisol. On the other hand, there was a positive correlation between cortisol and the inflammatory cytokines (r = 0.49, p < 0.001) as having more inflammatory reactions in people with higher stress hormone levels in the body. There was also a negative relationship between immune biomarkers and psychological stress (=0.30, = 0.003), which once again confirms the relationship between psychological distress and immune-suppressive functions.

All these show that psychological stress and social determinants have a huge impact on cortisol levels which consequently leads to changes in immune functions and inflammatory processes. The findings are in favor of the hypothesis that psychosocial stress can be linked to biological dysregulation via the activation of hypothalamic-pituitary-adrenal (HPA) axis; therefore, this might have an effect on disease progression and patient outcomes.

DISCUSSION

The current research examined the correlation between psychological stress and cortisol level, immune biomarker and social determinants between the breast cancer

patients in Punjab, Pakistan, and the healthy test subjects and among the disease stages. Results showed that the level of cortisol and psychological stress scores were considerably high in breast cancer patients in contrast with healthy people along with low markers of immune functionality and high levels of inflammatory cytokines. In addition, patients with metastatic-stage breast cancer showed significantly increased cortisol and inflammatory biomarker levels in comparison to patients with a small tumor. Breast cancer patients were also found to be disadvantaged socioeconomically and the areas they lived in were also more in need. All these facts indicate the interplay relationships of complex factors, both psychological, biological and social in breast cancer and it shows the importance of including a biopsychosocial model in the treatment of cancer in the Pakistani setting.

Among the major results of this study was a greater level of cortisol in the breast cancer patients as compared to their well counterparts. One of the major hormones that react in response to stress is cortisol that is triggered by the hypothalamic-pituitary-adrenal (HPA) axis. With long term cortisol secretion caused by chronic psychological stress, suppression of immune system, metabolic imbalances, and inflammatory reaction have been linked to this type of secretion. The high level of cortisol in the research is related to the prior studies suggesting that in most cases, cancer patients have neuroendocrine responses that are dysregulated[10-11]. Within the Pakistani context, stress factors including the financial strain, a lack of healthcare accessible resources, the fear of becoming diseased, and cultural stigma related to cancer can play a role in long-term activation of stress mechanisms, hence cortisol[1-2].

The analysis also noted a large difference in the scores of psychological stress between the breast cancer patients and controls favoring the former. One of the most acceptable forms of life stressors experienced by cancer patients is the diagnosis of cancer, which is usually accompanied by a certain level of uncertainty, anxiety, and emotional distress. Women diagnosed with breast cancer in Pakistan might encounter other problems associated with the body image, marital ties, social demands, and unawareness of the treatment outcomes. Cultural aspects can also tend to discourage frank talk about an ailment and instead encourage emotional repression, which causes amplified psychological burden[11-14]. These results shed a lot of light on the relevance of the psychosocial assessment as a part of cancer management especially in low-resource countries where mental health services are scarce.

Reduction of the immune function markers on the form of secretory immunoglobulin A (sIgA) in breast cancer patients was found to be another significant observation when breast cancer patients were compared to their healthy counterparts. It has been documented that chronic stress and high levels of cortisol are the factors that inhibit immune responses, by decreasing the activity of lymphocytes and also by compromising mucosal immunity[14-15]. The observation of lower levels of sIgA in the group of patients points to the lack of immune defense mechanisms and can be considered a predisposing factor to disease development and susceptibility to infections. An addition, the study also found elevated levels of inflammatory cytokines in patients with advanced-stage disease, which is a major indication of amplified inflammatory reactions in relation to resolutions of tumor progression. The role of inflammation in cancer biology is very critical, as it has effects on tumor proliferation, angiogenesis, and metastasis. Concurrent elevations of cortisol and rising levels of inflammatory cytokine indicate lack of control of immune endocrine interplay in the case of breast cancer patients[15-16].

The comparison made with the early-stage and advanced-stage breast cancer patients also added new insights into the changes that were related to the disease physiologically. Patients having late-stage cancers showed much better cortisol levels, inflammatory cytokines and high score on psychological stress in contrast to patients with early-staged cancer. According to this finding, the severity of the disease can escalate the stress reaction and neuroendocrine dysregulation. The treatments of patients at advanced stages are more aggressive, have more physical symptoms, and carry a strain on the wallet, as well as uncertainty about prognosis, all of which might add to the psychological distress. Moreover, the progression of the disease could trigger the biological stress responses, and it could be in both directions, with disease burden accelerating the illness, and an altered illness accelerating the physiological response to the disease[16-18].

In this study, social determinants were applied as one of the key issues that affected patient outcomes. Higher percentage of the breast cancer patients were in low socioeconomic status (SES) and high area deprivation groups as opposed to healthy controls. The socioeconomic disadvantage can also cause a later diagnosis, restriction in access to screening programs, lack of proper adherence to treatments, and psychological stress. The unequal conditions in healthcare services between urban and rural regions, financial reasons, and the insufficient insurance cover in Pakistan have the potential of aggravating the fate of the diseases, especially among the unfortunate segments of the population. The persistent activation of the effects of stress hormones as a result of chronic exposure to socioeconomic stressors can also affect the physiological pathways, therefore, leading to cortisol dysregulation[17-19]. These results point to the necessity to eliminate social inequalities through complete cancer management measures.

The reported correlation between psychological stress, cortisol levels and immune biomarkers validate the theoretical context of psychoneuroimmunology which makes sense of the impact of psychological factors on the immune and endocrine system. The constant pressures trigger the HPA axis and sympathetic nervous system causing the hormonal composition to respond to the immune functions and inflammatory conditions. These biological processes are also potentially relevant to cancer progression as well as response and recovery to treatment. Thus, the psychological stress interventions can potentially benefit not only the emotional well-being but also have some physiological effects and clinical outcomes[18-20].

Clinically, the results of this study have a significant implication on the treatment of cancer in Pakistan. Oncology services should be integrated with regular psychological and emotional appraisal of stress levels and psychological functionality especially in patients with advanced illnesses or socioeconomic deficiency. Psychosocial stress interventions, including counseling, cognitive behavioral therapy, mindfulness stress reduction and support groups have been reported to decrease stress and cortisol levels of cancer patients. Such interventions could be introduced in oncology centers and are likely to enhance the quality of life and possibly balance the biological responses of stress. In scenarios with limited resources, community-based interventions based on appropriate cultural practices as well as patient education might be an effective cost-efficient solution to psychosocial needs[20-21].

The paper also indicates the significance of multidisciplinary models of care including psychological, social, and medical elements. Oncologists, psychologists, nurses and social workers cooperating with each other can be assistive in supporting the holistic needs of patients. Also, the implementation of public health activities with the aim to raise awareness, early diagnosis, and lessen stigmatization related to breast cancer can contribute to alleviating mental suffering and enhancing the outcome of treatment. The interventions at the policy level that will promote access to affordable cancer care and decrease socioeconomic differences are also necessary in enhancing patient outcomes in Pakistan[2,3] (Figure 1).
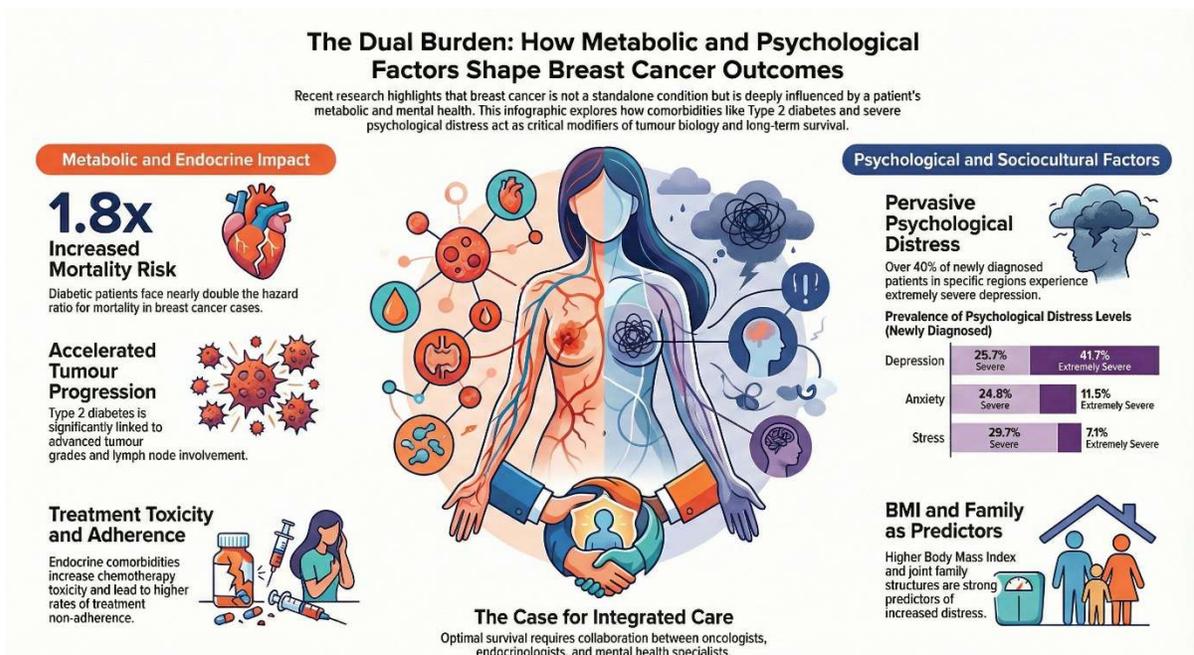

Figure 1: Factor influence on breast cancer

Although it has contributed, the study has had a number of limitations, which ought to be taken into consideration. The cross-sectional design does not allow the development of causal relationships between psychological stress, cortisol level, and the alterations of immune. The longitudinal studies are required to assess the time-related relations and the effects of stress throughout the disease progression and treatment. The convenience sampling can be problematic to the generalization to the wider population of breast cancer patients. Also, one-time measurement of cortisol could not be able to fully represent the changes in hormone secretion across the day. Future research ought to use more than one time of sampling. The self-reported questionnaires were used to measure psychological stress where they could be prone to reporting bias. Moreover, other psychosocial factors like

anxiety, depression, coping, and social support were not researched in depth and could lead to more information about patient experiences[2,3,22-23].

The next line of future research needs to be oriented towards longitudinal studies, interventional studies, to specify whether a reduction of psychological stress will result in quantifiable changes in cortisol regulation, and immunologic efficacy in breast cancer patients. It would also be of value to investigate how the culturally specific psychosocial interventions can be beneficial in the Pakistani groups. Besides, the investigation of genetic, environmental, and lifestyle determinants could be an even more comprehensive explanation of breast cancer results.

CONLUSION

This paper has shown that women with breast cancer in Punjab, Pakistan are highly burdened with psychological stress and cortisols in comparison with the healthy controls, and have lower immune responses and high levels of inflammatory processes. Poor socioeconomic status and late stage of the disease were closely linked with increased neuroendocrine and immune deregulation. The findings confirm the biopsychosocial model of cancer and substance of the need to combine psychological and social support in oncology care as a means of enhancing patient well-being and potentially better clinical outcomes.

Recommendations
- Psychological-stress screening should become a routine of providing oncological care.
- Breast cancer patients should receive psycosocial interventions in the form of counseling, stress management programs and support groups.
- Particular emphasis must be placed on patients with low socioeconomic status and advanced disease at a greater risk of having complications that may be related to stress.
- The teams of psychologists, social workers, and oncology professionals multidisciplinary care should be created.
- Sensitization of the population should be used to de-stigmatize and encourage early detection of breast cancer.
- The healthcare policies must aim at enhancing access to affordable cancer care by disadvantaged populations.

Implications
Clinical Implications
The results indicate that comprehensive type of cancer management should be developed, which incorporates psychological stress as well as treatment. Observation of cortisol and signs of stress could be used to elaborate effective care strategies and detect high-value patients.

Public Health Implications
Socioeconomic inequalities are one of the major factors contributing to patient vulnerability, hence community-based interventions and sensitizations could aid in decreasing the inequalities and increasing the outcomes of early detection and care.

Policy Implications
Mental health services should be incorporated into oncology programs by the healthcare policymakers and resources should be channeled towards psychosocial support services especially in places like Pakistan that do not have many resources.

Limitations
- The cross-sectional study does not allow causal interpretation of stress and cortisol and immune modifications.
- The ease of use could lower generalizability to the general population.
- The cortisol values were collected at one instance that did not necessarily indicate the diurnal variation.
- Self-reported measures were used to assess psychological stress, thereby, creating the issue of bias in the responses.
- There was a lack of thorough observation of other psychosocial factors like depression, coping patterns and social support.

Future Research
The longitudinal designs used in future research works should focus on causation of the relationship between psychological stress with cortisol regulation and cancer development. It is suggested that interventional research with evaluation of the efficacy of psychosocial and stress-reduction programs on biological effects of breast cancer patients be examined. More in-depth research on genetic, environmental, and lifestyle determinants of stress responses of Pakistani population would also contribute to knowledge and carry out culturally appropriate interventions.

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