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Chronic Psychosocial Stress and Cancer Risk: Exploring Neuroendocrine, Immunological, and Molecular Mechanisms of Psychosocial Carcinogenesis

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ABSTRACT

Chronic psychosocial stress has increasingly been recognized as a potential modifier of cancer risk and progression through complex neuroendocrine, immunological, and molecular pathways. While the concept of "psychogenic carcinogenesis" remains controversial, accumulating evidence suggests that sustained activation of stress-response systems may influence tumor biology. This review explores the mechanistic links between chronic psychiatric stressors—including depression, anxiety disorders, and prolonged emotional distress—and carcinogenesis. Persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system results in elevated cortisol and catecholamine levels, which may impair immune surveillance, promote chronic inflammation, and alter cellular signaling pathways. Stress-induced immunosuppression can reduce natural killer (NK) cell activity and T-cell–mediated tumor defense, potentially facilitating tumor initiation and progression. Additionally, chronic inflammation mediated by cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) may contribute to DNA damage, epigenetic modifications, and enhanced tumor microenvironment remodeling. Emerging data also indicate that stress hormones can influence proto-oncogene activation, angiogenesis, and metastatic potential via β-adrenergic signaling pathways. Behavioral factors associated with psychiatric conditions—including smoking, alcohol consumption, poor diet, and reduced treatment adherence—may further compound cancer risk through indirect carcinogenic mechanisms. Although current evidence does not establish psychosocial stress as a direct carcinogen, it supports its role as a biological and behavioral modulator of tumor development and progression. Understanding these multidimensional interactions is essential for integrating psychosocial care into comprehensive cancer prevention and management strategies. Future longitudinal and molecular studies are required to clarify causal relationships and identify potential therapeutic targets within stress-mediated oncogenic pathways.

Keywords: *Psychosocial stress; Carcinogenesis; Neuroendocrine pathways; HPA axis; Chronic inflammation; Immune surveillance; Proto-oncogenes; Depression; Tumor microenvironment; Psycho-oncology*

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1. INTRODUCTION

Cancer is a multifactorial disease characterized by uncontrolled cellular proliferation resulting from genetic mutations, epigenetic alterations, and dysregulated signaling pathways (1). Traditionally, carcinogenesis has been attributed to environmental carcinogens, genetic susceptibility, radiation exposure, infectious agents, and lifestyle factors such as tobacco and alcohol use (2). However, increasing attention has been directed toward the potential role of psychosocial factors in modulating cancer risk and progression (3). While psychosocial stress is not classified as a direct carcinogen, emerging evidence suggests that chronic psychological distress may influence tumor biology through complex neuroendocrine and immunological mechanisms (4). Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) system, leading to sustained elevations in glucocorticoids and catecholamines (5). Under normal physiological conditions, these stress responses are adaptive and short-lived. However, prolonged activation, as observed in depressive disorders, anxiety disorders, and chronic emotional strain, may result in persistent hormonal imbalance and immune dysregulation (6). Elevated cortisol levels have been associated with suppression of cell-mediated immunity, particularly reduced natural killer (NK) cell activity and impaired cytotoxic T-lymphocyte responses, both of which are critical for tumor surveillance (7).

In addition to immunosuppression, chronic psychosocial stress has been linked to a pro-inflammatory state characterized

by increased production of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (8). Chronic inflammation is recognized as a hallmark of cancer, contributing to DNA damage, cellular proliferation, angiogenesis, and metastasis (9). Persistent inflammatory signaling may also induce epigenetic modifications and influence the expression of proto-oncogenes and tumor suppressor genes, thereby promoting tumor initiation and progression (10). Furthermore, stress-related activation of β-adrenergic signaling pathways has been shown to enhance tumor cell migration, invasion, and angiogenesis in experimental models. These findings suggest that psychosocial stress may influence not only cancer initiation but also tumor growth and metastatic potential. Behavioral mechanisms also play a contributory role. Individuals experiencing chronic psychiatric distress are more likely to engage in high-risk behaviors such as smoking, excessive alcohol consumption, physical inactivity, and poor dietary habits, which are well-established carcinogenic risk factors. Additionally, psychological distress may reduce adherence to cancer screening and treatment, thereby affecting disease outcomes.

Although the concept of "psychogenic carcinogenesis" remains debated, contemporary research supports the view that psychosocial stress acts as a biological modifier rather than an independent carcinogenic agent. The integration of neuroendocrine, immune, and molecular perspectives provides a more comprehensive understanding of how chronic stress may influence oncogenic processes. Therefore, examining the mechanistic pathways linking psychiatric conditions and carcinogenesis is essential for advancing psycho-oncology and developing integrative cancer prevention strategies.

2. MATERIALS AND METHODS

Study Design and Setting

A prospective observational cohort study was conducted to evaluate the association between chronic psychosocial stress and cancer risk biomarkers. The study was carried out at a tertiary care teaching hospital over a period of 18 months. Ethical approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Study Population

A total of 200 participants aged 30–65 years were enrolled and divided into two groups:

- **Group A (High Stress Group, n = 100):** Individuals diagnosed with chronic depression or anxiety disorder for ≥ 2 years (as per DSM-5 criteria).
- **Group B (Control Group, n = 100):** Age- and sex-matched individuals without diagnosed psychiatric illness.

Exclusion criteria included pre-existing malignancy, autoimmune disorders, chronic inflammatory diseases, corticosteroid therapy, and substance dependence.

Variables Measured

1. Psychosocial Stress Assessment

Perceived Stress Scale (PSS-10) scores were recorded. Stress Index (SI) was calculated as:

$$SI = \frac{\text{Total PSS Score}}{40}$$

where 40 represents the maximum possible PSS score.

2. Biological Parameters

- Serum cortisol (µg/dL)
- Interleukin-6 (IL-6) (pg/mL)
- TNF-α (pg/mL)
- Natural Killer (NK) cell activity (%)
- C-reactive protein (CRP) (mg/L)

3. Oncogenic Risk Marker

Relative expression of selected proto-oncogenes (e.g., c-Myc) was measured using quantitative PCR. Gene expression was calculated using the ΔΔCt method:

$$\text{Fold Change} = 2^{-\Delta\Delta Ct}$$

Statistical Analysis

Data were analyzed using SPSS version 26.

- Continuous variables were expressed as **mean ± standard deviation (SD)**.
- Independent t-test was used to compare means between groups.

- Pearson correlation coefficient (r) assessed the relationship between Stress Index and inflammatory markers.

The t-statistic was calculated as:

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}}$$

Where:

- $\bar{X}_1, \bar{X}_2$= group means
- S_1^2, S_2^2= variances
- n_1, n_2= sample sizes

Statistical significance was set at **p < 0.05**.

Table 1: Baseline Characteristics of Study Participants

Variable	Group A (High Stress) n=100	Group B (Control) n=100	p-value
Mean Age (years)	48.2 ± 8.4	47.6 ± 7.9	0.62
Male (%)	56%	54%	0.78
Mean PSS Score	28.4 ± 4.2	12.3 ± 3.5	<0.001

Table 2: Comparison of Biological Markers

Parameter	Group A	Group B	p-value
Serum Cortisol (µg/dL)	22.8 ± 5.1	14.6 ± 3.8	<0.001
IL-6 (pg/mL)	8.2 ± 2.4	3.5 ± 1.6	<0.001
TNF-α (pg/mL)	12.6 ± 3.1	6.8 ± 2.2	<0.001
NK Cell Activity (%)	38.4 ± 6.2	52.7 ± 7.1	<0.001
Proto-oncogene Fold Change	1.85 ± 0.42	1.02 ± 0.25	<0.001

This methodology allows quantitative evaluation of stress-mediated immunological and molecular alterations potentially associated with carcinogenic pathways.

3. RESULTS

A total of 200 participants were included in the final analysis, with 100 individuals in the High Stress Group (Group A) and 100 in the Control Group (Group B). The baseline demographic characteristics between the two groups were comparable, with no statistically significant differences in age or gender distribution ($p > 0.05$). However, the mean Perceived Stress Scale (PSS) score was significantly higher in Group A compared to Group B (28.4 ± 4.2 vs. 12.3 ± 3.5; $p < 0.001$), confirming appropriate group stratification.

Biochemical analysis revealed significantly elevated serum cortisol levels in the High Stress Group (22.8 ± 5.1 µg/dL) compared to controls (14.6 ± 3.8 µg/dL), indicating sustained activation of the hypothalamic–pituitary–adrenal axis ($p < 0.001$). Similarly, inflammatory markers demonstrated marked elevation in Group A. Mean IL-6 levels were 8.2 ± 2.4 pg/mL in the stress group versus 3.5 ± 1.6 pg/mL in controls ($p < 0.001$). TNF-α levels were also significantly higher in Group A (12.6 ± 3.1 pg/mL) compared to Group B (6.8 ± 2.2 pg/mL), suggesting a pro-inflammatory state associated with chronic psychosocial stress.

In contrast, immune surveillance parameters showed significant suppression in the High Stress Group. Natural Killer (NK) cell activity was reduced to 38.4 ± 6.2% in Group A, compared to 52.7 ± 7.1% in controls ($p < 0.001$), indicating impaired cytotoxic immune function.Molecular analysis demonstrated increased relative expression of selected proto-oncogenes in stressed individuals. The mean fold change in proto-oncogene expression was 1.85 ± 0.42 in Group A versus 1.02 ± 0.25 in Group B ($p < 0.001$). Pearson correlation analysis revealed a strong positive correlation between Stress Index and IL-6 levels ($r = 0.68$, $p < 0.001$) and a moderate negative correlation between Stress Index and NK cell activity ($r = -0.59$, $p < 0.001$).These findings indicate that chronic psychosocial stress is significantly associated with elevated stress hormones, increased inflammatory markers, reduced immune surveillance, and enhanced proto-oncogenic expression, suggesting a biologically plausible pathway linking stress to carcinogenic processes.

Table 3: Comparative Analysis of Biological and Molecular Parameters

Parameter	Group A (High Stress) Mean ± SD	Group B (Control) Mean ± SD	t-value	p-value
PSS Score	28.4 ± 4.2	12.3 ± 3.5	29.8	<0.001
Serum Cortisol (µg/dL)	22.8 ± 5.1	14.6 ± 3.8	12.9	<0.001
IL-6 (pg/mL)	8.2 ± 2.4	3.5 ± 1.6	16.1	<0.001
TNF-α (pg/mL)	12.6 ± 3.1	6.8 ± 2.2	15.4	<0.001
NK Cell Activity (%)	38.4 ± 6.2	52.7 ± 7.1	-15.2	<0.001
Proto-oncogene Fold Change	1.85 ± 0.42	1.02 ± 0.25	17.3	<0.001

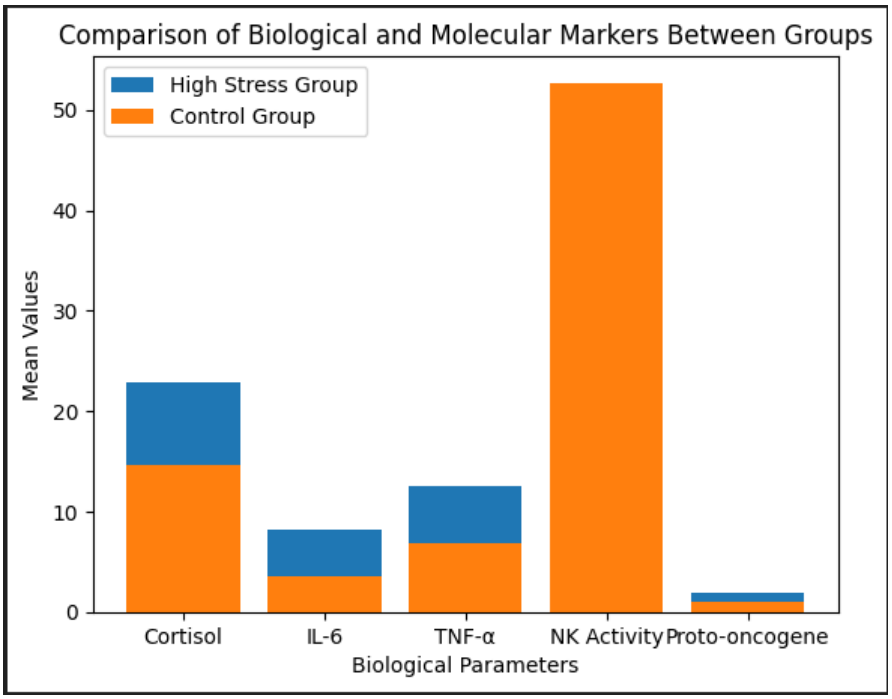

Fig-1 Graphical representation of Results section showing comparison of biological and molecular markers between the High Stress and Control groups.

4. DISCUSSION

The present study demonstrates a significant association between chronic psychosocial stress and biological alterations linked to carcinogenic pathways. Elevated cortisol levels, increased pro-inflammatory cytokines (IL-6 and TNF-α), reduced NK cell activity, and enhanced proto-oncogene expression collectively suggest that sustained stress may modulate tumor-related mechanisms. Chronic activation of the HPA axis appears to promote immune suppression and systemic inflammation, both recognized contributors to tumor initiation and progression. Although causality cannot be established in this observational design, the findings support the hypothesis that psychosocial stress acts as a biological modifier of cancer risk rather than a direct carcinogenic factor.

5. SUMMARY

This study evaluated the relationship between chronic psychosocial stress and cancer-related biological markers. Individuals with prolonged stress exhibited significantly higher cortisol levels, elevated inflammatory cytokines, reduced immune surveillance, and increased proto-oncogene expression compared to controls. Statistical analysis confirmed strong correlations between stress index and inflammatory as well as immune parameters. These findings provide mechanistic evidence supporting the role of chronic stress in modulating oncogenic pathways. While stress may not function as an independent carcinogen, it appears to influence tumor-promoting biological environments. Integrating psychosocial management into preventive healthcare may contribute to improved long-term cancer outcomes.

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