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Impact of Tumor-Secreted Molecules on Suicide Behavior

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Abstract

Lung cancer is one of the most common and deadly types of cancer worldwide and accounts for a substantial proportion of cancer-related mortality; a fraction of these deaths are attributable to suicide among affected patients. Beyond severe physical complications, lung cancer is associated with profound psychological consequences that markedly impair quality of life. Emerging evidence suggests that inflammatory processes and tumor-associated immune signaling—particularly cytokines released within the lung tumor microenvironment—may influence central nervous system function through neuroimmune and neuroendocrine pathways. We hypothesize that lung cancer–associated secreted molecules, including pro-inflammatory cytokines and tumor-derived signaling factors, contribute to increased suicidality by inducing neuroinflammation and dysregulation of stress- and mood-related neural circuits. Integrating epidemiological data with biological mechanisms may facilitate the development of innovative biomarkers and targeted preventive strategies to reduce suicide risk in this vulnerable population.

Keywords: Tumor-Secreted; Molecules; Suicide; Inflammatory; Cytokine.

1.Introduction

Suicide is a severe and complex psychological outcome in patients with cancer and represents a critical concern in comprehensive oncological care. According to a large population-based study conducted in the United States between 2000 and 2016, among nearly eight million individuals with cancer, approximately 47.5% died during follow-up and 0.3% of deaths were attributed to suicide. Suicide risk was highest during the first two years after diagnosis and was particularly elevated in cancers with poor prognosis and high symptom burden, including lung, oral cavity and pharynx, pancreas, esophagus, and stomach cancers, whereas prostate and thyroid cancers showed a lower risk compared with the general population (1). Biologically, accumulating evidence suggests that cancer and suicide may be linked through shared genetic, inflammatory, and neurobiological pathways (2). Cadherin and cholecystokinin receptor (CCKR) signaling pathways (3), along with cancer-associated pro-inflammatory mediators, have been implicated in depression and suicidal behavior through several mechanisms, including activation of the kynurenine pathway (4), disruption of hypothalamic–pituitary–adrenal (HPA) axis feedback inhibition (5), and glutamate-mediated excitotoxicity (6). In advanced non-small cell lung cancer, particularly stage IV disease, the severity of depressive symptoms has been shown to correlate with systemic inflammatory indices such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and advanced lung cancer inflammation index. Importantly, inflammation not only contributes to psychiatric morbidity but also represents an independent prognostic factor for survival in lung cancer patients (7). Measurement of C-reactive protein plays a significant role in identifying inflammation-associated depression and predicting clinical outcomes (8). Moreover, antidepressant strategies targeting inflammatory pathways have demonstrated potential benefits for both psychological well-being and survival in cancer patients (9). Elevated levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-17 have been reported in patients with lung cancer and are weakly but consistently associated with anxiety and depressive symptom severity (10). Chronic pulmonary inflammatory conditions, including chronic obstructive pulmonary disease, pneumonia, and viral infections such as SARS-CoV-2, are also associated with mood and cognitive disturbances through microglial activation and neuroinflammation (11,12). Recent studies further support a broader association between systemic inflammation and suicidality across clinical populations (13). Beyond its respiratory function, the lung acts as an active immunological and secretory organ capable of releasing cytokines, hormones, neuropeptides, and other signaling molecules into the systemic circulation. These lung-derived mediators may directly or indirectly influence brain function and behavior (14). Accordingly, a focused examination of lung cancer–associated inflammation and lung–brain communication pathways may provide novel insights into the biological underpinnings of suicidality in this population.

Recent evidence has further strengthened the link between inflammatory processes and suicidal behavior, demonstrating consistent associations between elevated inflammatory markers and suicidality across clinical populations (15).

2.Hypothesis

We hypothesize that lung cancer–associated inflammatory and tumor-induced signaling molecules—including pro-inflammatory cytokines such as TNF-α, IL-1β, IL-17, and acute-phase proteins such as C-reactive protein—can directly or indirectly modulate the function of brain regions involved in mood regulation. Through neuroimmune and neuroendocrine interactions, these mediators may exacerbate anxiety and depressive symptoms and ultimately increase suicidal tendencies beyond psychosocial stressors alone. Accordingly, lung-derived inflammatory biomarkers are proposed as potential tools for suicide risk screening, early identification, and prognostic stratification in patients with lung cancer. Improved characterization of these molecules and their downstream molecular and cellular pathways may facilitate the development of targeted interventions, including anti-cytokine therapies, anti-inflammatory agents, or neuromodulatory approaches such as vagus nerve stimulation.

3.Hypothesis Evaluation

Assessment of suicide risk in lung cancer patients should rely on ethically feasible and clinically applicable approaches, including multivariate measurement of inflammatory mediators in bronchoalveolar lavage fluid and peripheral blood samples (15). Rather than invasive brain tissue sampling, advanced neuroimaging techniques—such as structural and functional magnetic resonance imaging—may be used to identify alterations in brain regions involved in emotional regulation, including the amygdala and prefrontal cortex (15). At the molecular level, cytokine quantification using sensitive immunoassays, gene expression profiling via quantitative PCR or RNA sequencing, and proteomic approaches can provide insight into immune and inflammatory signaling pathways associated with psychiatric vulnerability. When combined with validated psychometric instruments—such as the Patient Health Questionnaire-9 for depression severity and the Columbia-Suicide Severity Rating Scale for suicide risk. These multidimensional data may support integrative predictive models while distinguishing biologically mediated suicidality from psychological reactions to severe illness, pain, hypoxia, or fear of death .

4.Conclusion

Based on the available evidence, it can be hypothesized that lung cancer cells, through the secretion of inflammatory mediators and tumor-associated signaling molecules, may influence central nervous system function and disrupt neuroimmune pathways, thereby potentially increasing vulnerability to suicidality. This biologically grounded framework complements psychosocial explanations and highlights inflammation-driven mechanisms as potential independent contributors to suicide risk in lung cancer. Precise identification of these molecules and their mechanisms may advance understanding of the interaction between tumor biology and mental health and support the development of sensitive diagnostic tools and targeted interventions to reduce suicide risk. Such an interdisciplinary approach underscores the need for collaboration among oncologists, immunologists, psychiatrists, and neuroscientists.

5.Ethics statement

No ethics committee approval was required as this manuscript does not involve human subject research.

Consent for publication

No consent was obtained as this manuscript does not involve human subject research.

Declaration of Generative AI and AI-assisted technologies in the writing process

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CRediT authorship contribution statement

Mohammad Reza atashzar: Conceptualization, Methodology, Supervision . **Fatemeh moghimi :** Data curation, Writing- Original draft preparation , **Hamid Arshadinezhad :** Writing- Reviewing and Editing

Declaration of competing interest

The author declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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