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Persistent severe stress and carcinogenesis: a prisma-based systematic review of biological mechanisms and epidemiological evidence

Abstract

Background: Chronic severe psychological stress has long been hypothesized to contribute to cancer development and progression via neuroendocrine, immunological, and inflammatory pathways. However, evidence remains inconsistent and a comprehensive synthesis is lacking.

Objective: This review aims to systematically evaluate existing preclinical and clinical literature, elucidating biological mechanisms by which persistent severe stress may influence carcinogenesis, and to assess epidemiological associations between chronic stress exposure and cancer incidence, progression, or survival.

Methods: We conducted a systematic search of MEDLINE (PubMed), Embase, Web of Science, and publisher databases (Elsevier, Wiley, SAGE, BMC) up to May 2025. Search terms included combinations of "psychological stress," "chronic stress," "stressful life events," "cancer," "carcinogenesis," "tumour progression," and related immunologic, neuroendocrine, and molecular keywords. Two independent reviewers screened titles/abstracts and full texts, applied predefined inclusion and exclusion criteria, extracted data, and assessed risk of bias. The review was carried out following PRISMA guidelines. Both mechanistic (animal / in vitro) and human (observational, clinical) studies were included.

Results: Of 4,312 records identified, 38 full-text articles met inclusion criteria (preclinical mechanistic studies, observational cohort/case–control studies, and systematic reviews). Mechanistic evidence consistently shows that chronic stress induces activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS), elevates catecholamines and glucocorticoids, impairs cytotoxic immune surveillance, elevates pro-inflammatory cytokines, promotes angiogenesis and extracellular matrix remodeling, and creates a tumor-permissive microenvironment, thereby facilitating tumor initiation, growth, and metastasis. Clinically, epidemiological findings are mixed: some large meta-analyses report modest positive associations between psychosocial stressors (e.g., depression, anxiety) and overall cancer incidence or mortality, while others find no consistent association. The quality of evidence is limited by heterogeneity in stress definitions, measurement methods, and confounding by lifestyle factors.

Conclusion: Preclinical and translational evidence supports biologically plausible pathways linking persistent severe stress with carcinogenesis and tumor progression. However, human epidemiological evidence remains inconsistent and insufficient to establish causality. Well-designed prospective studies with validated stress measures and biomarker assessment, as well as interventional trials targeting stress pathways, are needed.

Implications for Nursing: Screening for chronic stress, integrating stress-management interventions, and facilitating psychosocial support may contribute to cancer prevention strategies and improve outcomes in clinical care.

Keywords: chronic psychological stress, carcinogenesis, neuroendocrine–immune mechanisms, hypothalamic–pituitary–adrenal axis, tumor progression, epidemiological evidence

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Introduction

Cancer remains one of the most significant global health challenges, constituting a leading cause of morbidity and mortality across both developed and developing countries. Traditionally, cancer etiology has been explained primarily through genetic predisposition, exposure to environmental carcinogens, and modifiable lifestyle-related risk factors such as tobacco use, unhealthy dietary patterns, alcohol consumption, and physical inactivity. However, an increasing body of scientific inquiry has begun to explore the contribution of psychosocial determinants of health—particularly chronic and severe psychological stress—as potential modulators of cancer initiation, progression, and clinical outcomes.[1]

Psychological stress is an inherent component of human life and, in acute forms, represents an adaptive response that enables individuals to cope with perceived threats. In contrast, persistent or severe stress may exert deleterious effects on multiple physiological systems. Chronic stress is characterized by sustained activation of biological stress pathways, leading to cumulative physiological wear and tear, often described as allostatic load.[2]

The hypothesis that chronic psychological stress may contribute to cancer development and progression has gained renewed attention through advances in psychoneuroimmunology and behavioral oncology.[1] Psychoneuroimmunology provides a conceptual framework for understanding how psychological processes interact with the nervous, endocrine, and immune systems to influence health and disease.[3]

Within this framework, chronic stress disrupts homeostatic regulation through prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), resulting in sustained elevations of glucocorticoids and catecholamines.[2]

Activation of the HPA axis leads to increased secretion of cortisol, which exerts profound effects on immune regulation, inflammation, metabolism, and cellular growth.[2,3] Under chronic stress conditions, these mediators may impair cytotoxic immune surveillance mechanisms critical for eliminating transformed cells.[1,3] Chronic stress is also associated with dysregulated inflammatory responses and persistent low-grade inflammation, which may contribute to DNA damage and tumor-promoting microenvironments.[1]

At the cellular and molecular levels, prolonged exposure to stress hormones influences processes directly relevant to carcinogenesis and tumor progression, including alterations in proliferation, apoptosis resistance, angiogenesis, extracellular matrix remodeling, and metastatic potential. The tumor microenvironment is increasingly recognized as a dynamic determinant of cancer behavior.[4] Chronic stress may reshape this microenvironment through neuroendocrine–immune interactions, thereby favoring tumor growth and dissemination.[1]

In parallel with mechanistic research, epidemiological studies have examined whether chronic stress and related psychosocial factors are associated with increased cancer risk or poorer outcomes. Some investigations report modest associations between psychosocial stressors and cancer incidence or mortality, whereas others fail to demonstrate consistent relationships.[1]

The inconsistency of epidemiological findings has generated considerable debate. Psychological stress is a complex and multidimensional construct that is difficult to measure uniformly.[5] Moreover, stress exposure is intertwined with behavioral risk factors that independently influence cancer risk, raising concerns about residual confounding.[1]

Despite these challenges, converging evidence from experimental and translational research supports the biological plausibility of a link between chronic severe stress and carcinogenesis.[2,4] Therefore, this systematic review aims to synthesize mechanistic evidence elucidating biological pathways linking chronic stress and cancer, critically evaluate epidemiological associations, and derive implications for nursing practice and future interdisciplinary research.

Methods

Protocol and registration

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor, transparency, and reproducibility.[6] The PRISMA framework was applied across all stages of the review process, including study identification, screening, eligibility assessment, data extraction, synthesis, and reporting. Adherence to PRISMA principles was intended to minimize selection bias, enhance the clarity of reporting, and facilitate critical appraisal by readers and reviewers.

A detailed review protocol was developed a priori before initiating the literature search. The protocol defined the research questions, eligibility criteria, search strategy, study selection procedures, data extraction plan, quality assessment methods, and synthesis approach. Developing the protocol in advance was intended to reduce the risk of selective reporting and analytical bias.[6] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) to promote transparency and prevent unnecessary duplication of research efforts. At the time of manuscript preparation, the PROSPERO registration number was pending (registration ID: pending/2025).

Any deviations from the original protocol during the review process were carefully documented and justified. However, no major protocol amendments were required, as the predefined methodology was sufficiently robust to accommodate the diversity of evidence identified in the literature.

Eligibility criteria

Eligibility criteria were established using a structured framework encompassing study design, exposure, outcomes, publication characteristics, and language. These criteria were designed to capture a comprehensive body of evidence addressing both biological mechanisms and epidemiological associations between persistent psychological stress and carcinogenesis.[7,8]

Study design

Eligible studies included a broad range of research designs to allow integration of mechanistic and clinical evidence. Specifically, the following study types were considered:

i. **Preclinical studies**: Including animal models and in vitro experiments, that investigated the biological effects of chronic stress or stress-related neuroendocrine mediators on cancer initiation, tumor growth, angiogenesis, immune modulation, invasion, or metastasis.[6,7]

ii. **Observational human studies**: Including prospective and retrospective cohort studies, case–control studies, and population-based analyses examining associations between chronic psychological stress and cancer-related outcomes.[9]

iii. **Clinical studies**: Including non-randomized interventional or translational studies, where stress-related exposures or biomarkers were evaluated in relation to cancer progression or survival.[10]

iv. **Previously published systematic reviews or meta-analyses:** That explicitly examined relationships between psychological stress, psychosocial factors, or stress-related biological pathways and cancer outcomes.[11]

This inclusive approach was adopted to enable triangulation of evidence across experimental, observational, and synthesized data.

Exposure

The primary exposure of interest was chronic or persistent psychological stress. Eligible studies were required to operationalize stress using one or more of the following approaches:

• Validated psychometric instruments measuring perceived stress, chronic stress burden, depression, anxiety, psychological distress, or related constructs.[9]

• Assessment of prolonged exposure to adverse life events, such as bereavement, caregiving burden, social isolation, chronic occupational stress, or sustained psychosocial adversity.[9]

• Experimental induction or modeling of chronic stress conditions in preclinical studies, including social defeat, restraint stress, isolation stress, or chronic unpredictable stress paradigms.[6,7]

• Measurement of stress-related biological correlates, such as dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic nervous system (SNS) activation, or chronic elevation of stress hormones.[8]

Studies focusing exclusively on acute or short-term stress responses were excluded, as the review specifically aimed to evaluate the effects of persistent stress exposure relevant to long-term carcinogenic processes.[7]

Outcomes

Eligible studies were required to report one or more cancer-related outcomes relevant to carcinogenesis or tumor progression, including:

- Tumor initiation, growth, invasion, angiogenesis, or metastasis.[6,7]
- Cancer incidence, recurrence, progression, or stage at diagnosis.[9,11]
- Cancer-specific mortality or all-cause mortality among cancer patients.[9]
- Immunological, inflammatory, neuroendocrine, or molecular biomarkers with established relevance to carcinogenesis (e.g., immune surveillance markers, pro-inflammatory cytokines, angiogenic factors, or extracellular matrix remodeling indicators).[8,12] Studies that examined stress in relation to lifestyle factors without direct measurement of stress or without reporting cancer-related outcomes were excluded.

Publication characteristics

Only English-language, peer-reviewed publications were included. The literature search covered studies indexed in selected databases up to May 2025, without restrictions on year of publication. Conference abstracts, editorials, commentaries, letters without original data, and unpublished manuscripts were excluded to ensure methodological quality and data completeness.[6]

Search strategy

A comprehensive and systematic electronic search strategy was developed in consultation with established systematic review methodologies.[6] Searches were conducted across multiple biomedical and interdisciplinary databases to maximize coverage of relevant literature.

The search strategy combined controlled vocabulary terms and free-text keywords related to psychological stress and cancer. Stress-related terms and biological pathway descriptors were informed by mechanistic literature describing neuroendocrine–immune interactions in tumor biology.[7,8]

Boolean operators (AND/OR), truncation, and database-specific indexing terms were applied to refine and optimize the search. Manual hand-searching of reference lists and citation tracking were also conducted to identify additional relevant studies.[6]

Study selection

The study selection process followed a two-stage screening procedure in accordance with PRISMA recommendations.

In the first stage, titles and abstracts were independently screened by two reviewers. In the second stage, full-text articles were assessed against predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion or consultation with a third reviewer to ensure methodological rigor and minimize bias.[6]

Data extraction and quality assessment

Data extraction: A standardized data extraction form was developed and pilot-tested prior to full data extraction. Extracted data included study design, stress measurement, cancer outcomes, biomarkers, and effect estimates.[9]

Quality and risk of bias assessment: Methodological quality and risk of bias were assessed using validated tools appropriate to each study design:

I. Newcastle–Ottawa Scale (NOS) for cohort and case–control studies.[9]

II. Standardized evaluation criteria for preclinical studies examining tumor growth and stress biology.[6,7]

III. AMSTAR-2 for systematic reviews and meta-analyses.[11]

Quality assessments were conducted independently by two reviewers.

Data synthesis

Due to substantial heterogeneity in study designs, populations, stress definitions, and outcome measures, a narrative synthesis was undertaken rather than a quantitative meta-analysis.[6] Preclinical studies were grouped according to major biological pathways implicated in stress-related carcinogenesis, including neuroendocrine activation, immune modulation, inflammatory signaling, and tumor microenvironment remodeling.[7,8,12] Human observational studies were synthesized with emphasis on associations between chronic stress and cancer incidence, progression, recurrence, or mortality.[9,11] This structured narrative approach enabled comprehensive integration of mechanistic and epidemiological evidence while respecting methodological diversity.[6]

Results

Study selection

The systematic search strategy yielded a total of 4,312 records from electronic databases, including MEDLINE (PubMed), Embase, Web of Science, and major publisher platforms. Screening was conducted independently by two reviewers in accordance with established systematic review standards.[13]

Of the 142 full-text articles assessed, 38 studies met the predefined inclusion criteria and were included in the final synthesis. These comprised 14 preclinical mechanistic studies, 16 human observational studies, and 8 prior systematic reviews or meta-analyses examining chronic psychological stress and cancer-related outcomes.[13,14] Articles were excluded primarily due to insufficient stress characterization, lack of cancer-related endpoints, cross-sectional designs without temporal inference, or inadequate methodological quality. The overall study selection process is summarized in (Table 1).

Evidence from preclinical studies – biological mechanisms

Preclinical evidence provides a robust and biologically coherent framework supporting the hypothesis that persistent severe stress can facilitate carcinogenesis and tumor progression. Across animal models and cellular systems, chronic stress consistently alters neuroendocrine

signaling, immune competence, inflammatory status, and the tumor microenvironment(TME).[14]

Table 1 Characteristics of included studies

Study type	Number of studies	Primary models / populations	Main outcomes
Preclinical mechanistic	14	Animal models, in vitro systems	Neuroendocrine activation, immune suppression, TME changes
Human observational	16	General population, cancer patients, survivors	Cancer incidence, progression, recurrence, mortality
Reviews / Meta-analyses	8	Systematic reviews, umbrella reviews	Synthesized evidence on stress–cancer associations

Neuroendocrine activation

Chronic psychological stress results in sustained activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), leading to prolonged elevation of circulating glucocorticoids and catecholamines.[14]

Experimental models demonstrate that prolonged stress exposure enhances adrenergic signaling within tumor tissues. Elevated catecholamines activate β-adrenergic receptors on tumor cells and stromal components, promoting intracellular pathways associated with proliferation, survival signaling, and metabolic adaptation.[14,15]

Stress-induced neuroendocrine activation also alters the metabolic and angiogenic profile of the tumor microenvironment, promoting tumor growth and dissemination.[14]

Immunosuppression and immune dysregulation

One of the most consistent findings in preclinical models is impairment of anti-tumor immune surveillance under chronic stress conditions. Sustained stress reduces natural killer (NK) cell cytotoxicity and CD8+ T-cell activity, both essential for eliminating transformed cells. Chronic stress also promotes expansion and recruitment of immunosuppressive cell populations, including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages (TAMs), thereby facilitating tumor immune evasion.[14] Within the TME, these stress-induced immune alterations contribute to reduced immune-mediated tumor control and increased metastatic potential.[15]

Inflammation, oxidative stress, and tumor microenvironment remodeling

Chronic stress is associated with persistent low-grade inflammation characterized by elevated pro-inflammatory cytokines and oxidative stress markers.[14] Sustained inflammatory signaling increases reactive oxygen species (ROS), contributing to DNA damage and genomic instability.

Experimental evidence further demonstrates that stress-related signaling enhances angiogenesis and extracellular matrix remodeling, thereby facilitating tumor invasion and metastasis.[15] These coordinated changes reinforce the biological plausibility of a mechanistic link between chronic stress exposure and advanced cancer phenotypes.[14] The principal biological mechanisms identified across preclinical studies are summarized in (Table 2).

Table 2 Key biological mechanisms linking chronic stress and cancer (preclinical evidence)

Mechanism	Stress-induced changes	Implications for cancer
Neuroendocrine activation	Elevated glucocorticoids, catecholamines	Enhanced tumor growth, survival signaling
Immune suppression	Reduced NK and CD8+ T-cell activity	Impaired immune surveillance
Immunosuppressive cells	Increased MDSCs, Tregs, TAMs	Tumor immune evasion
Inflammation & oxidative stress	Elevated cytokines, ROS, DNA damage	Tumor initiation and progression
TME remodeling	Angiogenesis, ECM and lymphatic remodeling	Metastasis and invasion

Evidence from human studies – epidemiology

Human epidemiological studies provide mixed findings regarding the relationship between chronic psychological stress and cancer outcomes. Variability in stress measurement and confounder adjustment complicates interpretation.[13,15]

Cancer incidence

A PRISMA-guided meta-analysis of prospective cohort studies reported no consistent association between perceived stress or stressful life events and overall cancer risk across multiple cancer types.[13]

In contrast, umbrella reviews and meta-analyses have suggested generally consistent evidence linking depression, anxiety, and psychosocial stress with increased cancer incidence and mortality.[15,16] These discrepancies appear influenced by differences in stress conceptualization, duration of exposure, and analytic adjustment strategies.

Large pooled analyses have not consistently identified synergistic interactions between psychosocial stressors and traditional behavioral risk factors, suggesting that stress may operate independently of lifestyle-related pathways.[15]

Cancer progression, recurrence, and survival

Evidence linking psychological stress to cancer progression and survival appears somewhat stronger, though still heterogeneous. Systematic reviews report moderate associations between psychological distress variables and increased recurrence risk among cancer survivors.[16]

Several meta-analyses indicate that individuals with depression or anxiety exhibit a modestly increased risk of cancer incidence and cancer-specific mortality.[15,16] However, these associations may still be influenced by residual confounding and observational study limitations.[13] A synthesis of epidemiological findings is presented in (Table 3).

Table 3 Summary of epidemiological evidence on stress and cancer outcomes

Outcome	Overall evidence	Key limitations
Cancer incidence	Inconsistent	Heterogeneous stress definitions, confounding
Cancer progression	Moderate association	Limited number of studies
Recurrence	Suggestive but mixed	Small samples, cancer-type specificity
Cancer mortality	Modest increased risk	Residual confounding, observational design

Interpretation of mechanistic evidence

The preclinical and translational literature synthesized in this review provides strong and convergent evidence that persistent severe psychological stress can profoundly alter biological systems implicated in carcinogenesis and tumor progression.[4,8] Across animal models, in vitro experiments, and translational studies, chronic stress consistently activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), resulting in sustained elevations of glucocorticoids and catecholamines.[6,9] These neuroendocrine mediators exert pleiotropic effects on immune regulation, inflammation, angiogenesis, extracellular matrix remodeling, and intracellular signaling pathways that collectively shape a tumor-permissive microenvironment.[7,10]

One of the most robust findings across mechanistic studies is the detrimental impact of chronic stress on anti-tumor immune surveillance.[8,11] Elevated glucocorticoids and catecholamines have been shown to suppress cytotoxic T lymphocyte and natural killer (NK) cell activity, reduce antigen presentation, and impair immune recognition of transformed cells.[9,12] Concurrently, chronic stress promotes the expansion and functional dominance of immunosuppressive cell populations, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[11,12] These alterations shift the immune balance from tumor elimination toward immune tolerance, thereby facilitating tumor initiation and progression.[8]

Inflammation represents another critical mechanistic bridge between chronic stress and cancer biology.[6,15] Prolonged activation of stress pathways is associated with increased production of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and C-reactive protein.[15,16] While acute inflammation serves protective and reparative roles, chronic low-grade inflammation is widely recognized as a hallmark of cancer development.[7,15] Stress-induced inflammatory signaling can promote oxidative DNA damage, enhance cellular proliferation, inhibit apoptosis, and activate oncogenic pathways, thereby increasing malignant transformation risk.[10,16] Furthermore, inflammatory mediators influence stromal and immune components within the tumor microenvironment (TME), reinforcing pro-tumorigenic feedback loops.[7,12]

Angiogenesis and extracellular matrix (ECM) remodeling constitute additional pathways linking stress biology to cancer progression.[9,13] Catecholamines released during chronic stress stimulate tumor and endothelial cells via β-adrenergic receptors, increasing vascular endothelial growth factor (VEGF) expression and other pro-angiogenic mediators.[13,17] Enhanced angiogenesis improves tumor vascularization, supports metabolic demands, and facilitates metastatic dissemination.[17] Simultaneously, stress-mediated activation of matrix metalloproteinases contributes to ECM degradation, tissue destabilization, and increased tumor invasiveness.[10,13] These processes collectively reduce structural barriers to metastasis, the principal cause of cancer-related mortality.[17]

Importantly, mechanistic studies demonstrate that stress-related neuroendocrine signaling interacts with core molecular pathways regulating cell cycle control, apoptosis, and DNA repair.[6,18] Chronic glucocorticoid exposure can disrupt p53 signaling, reduce apoptotic sensitivity, and permit survival of genetically damaged cells.[18,19] β-adrenergic signaling activates downstream cascades such as cyclic AMP–protein kinase A pathways, influencing tumor cell proliferation, migration, and resistance to therapy.[17,20]

These findings underscore that stress is not merely a psychosocial correlate but may directly modulate fundamental biological processes central to carcinogenesis.[18] Taken together, the mechanistic evidence strongly supports the biological plausibility of chronic severe stress as a contributory factor in cancer development and progression.[5,8,15] However, stress alone is unlikely to be sufficient to initiate malignancy.[7] Rather, chronic stress appears to function as a modifier or amplifier of genetic susceptibility, environmental carcinogen exposure, and lifestyle-related risk factors.[14,15] This interpretation aligns with multifactorial models of carcinogenesis in which cancer arises from cumulative and interacting biological, behavioral, and environmental influences over time.[7,20]

Limitations and challenges in epidemiological evidence

Despite the compelling and coherent mechanistic framework described above, epidemiological studies in human populations have produced mixed and often inconclusive findings regarding the association between chronic stress and cancer incidence, progression, or survival. Several methodological and conceptual challenges contribute to this inconsistency and limit the ability to draw firm causal inferences.

A primary challenge lies in the heterogeneity of stress measurement across studies. Many epidemiological investigations rely on self-reported perceived stress, single-point assessments, or checklists of stressful life events. While these tools capture subjective experiences, they often fail to adequately represent the chronicity, severity, and cumulative biological burden of stress exposure. Psychological stress is inherently dynamic, fluctuating over time and influenced by individual coping capacity, social support, and contextual factors. Single assessments may therefore misclassify exposure and dilute true associations. Moreover, subjective stress measures do not necessarily correspond to physiological stress responses, such as sustained cortisol dysregulation or sympathetic activation, which are central to the proposed biological mechanisms.

Confounding represents another substantial obstacle in observational research on stress and cancer. Chronic stress is closely intertwined with a wide range of behavioral and socioeconomic factors known to influence cancer risk, including smoking, alcohol consumption, dietary patterns, physical inactivity, sleep disturbances, and healthcare access. Socioeconomic disadvantage, in particular, is associated with both higher stress exposure and increased cancer risk through multiple pathways. Although many studies attempt statistical adjustment for these factors, residual confounding remains difficult to eliminate. Even large individual-participant meta-analyses, such as those conducted within consortia examining psychosocial factors and cancer outcomes, have found no consistent interactions between stress-related variables and established behavioral risk factors, highlighting the complexity of disentangling these relationships.

Reverse causality further complicates interpretation of epidemiological findings. Psychological distress, depression, and anxiety may arise as early manifestations of undiagnosed cancer or as responses to subtle physiological changes preceding clinical diagnosis. In such cases, observed associations between stress and cancer outcomes may reflect the psychological consequences of emerging disease rather than a causal role of stress in cancer development. Although prospective study designs with long follow-up periods can reduce this bias, few studies are able to completely exclude reverse causation, particularly for cancers with long latency periods. Publication bias and methodological variability also contribute to inconsistent results across studies and meta-analyses. Studies reporting positive associations between stress and cancer outcomes may be more likely to be published, while null findings

remain underreported. Additionally, variations in study populations, cancer types, follow-up duration, exposure definitions, and outcome measures introduce heterogeneity that limits comparability. Systematic reviews and meta-analyses have repeatedly highlighted substantial between-study variability and moderate-to-low overall quality of evidence, underscoring the need for more standardized and rigorous approaches.

Given these limitations, the current epidemiological evidence does not provide sufficient support to establish a causal relationship between chronic severe stress and cancer incidence or progression in humans. Rather than refuting the mechanistic evidence, these inconsistencies highlight the inherent challenges of translating complex biological processes observed under controlled experimental conditions into population-level associations influenced by numerous interacting factors.

Integration of mechanistic and epidemiological perspectives

The apparent discrepancy between strong mechanistic evidence and inconclusive epidemiological findings should not be interpreted as a contradiction but rather as an indication of the limitations of existing research paradigms. Mechanistic studies demonstrate what is biologically possible under conditions of sustained stress exposure, while epidemiological studies attempt to detect these effects within heterogeneous human populations where stress exposure is variable, multifaceted, and difficult to quantify.

One plausible explanation is that the impact of chronic stress on cancer risk may be modest in magnitude and context-dependent, becoming detectable only in specific subgroups or in interaction with other vulnerabilities, such as genetic predisposition, immunosuppression, or high environmental exposure to carcinogens. Additionally, stress may exert a stronger influence on cancer progression, metastasis, and survival rather than on initial cancer incidence, outcomes that are less frequently and less precisely assessed in large population studies.

Furthermore, stress-related biological effects may be most relevant during specific windows of susceptibility, such as early tumor development or periods of immune compromise. Epidemiological studies that do not account for timing, duration, and biological embedding of stress may therefore fail to capture these nuanced effects. Bridging this gap requires integrative research designs that combine rigorous psychosocial assessment with objective biological markers and long-term clinical follow-up.

Implications for research

Advancing understanding of the role of chronic severe stress in carcinogenesis and cancer progression will require methodological innovations and interdisciplinary collaboration. Future research should prioritize prospective longitudinal designs that incorporate repeated assessments of psychological stress alongside biological measures, such as cortisol rhythms, catecholamine levels, inflammatory markers, and indicators of immune function. Such approaches would allow investigators to capture cumulative stress exposure and its physiological correlates more accurately.

Incorporating biomarker endpoints into epidemiological studies is particularly critical. Linking stress exposure to intermediate biological outcomes, such as immune dysregulation or chronic inflammation, may provide stronger evidence for causal pathways even in the absence of large effects on cancer incidence. Additionally, comprehensive control of confounding variables, including lifestyle behaviors, socioeconomic status, and comorbid conditions, is essential to improve internal validity.

Interventional studies represent another important avenue for future research. Trials evaluating stress-management interventions, psychosocial support, behavioral modification, or pharmacological modulation of stress pathways (e.g., β-adrenergic blockade) can provide experimental evidence regarding the reversibility and clinical relevance of stress-related biological effects. Although ethical and practical considerations limit the feasibility of cancer prevention trials, studies focusing on cancer progression, treatment response, and survivorship outcomes may yield valuable insights.

Implications for nursing and clinical practice

From a nursing and clinical perspective, the findings of this review have important implications even in the absence of definitive epidemiological proof of causality. The mechanistic evidence underscores that chronic stress can adversely affect immune function, inflammation, and overall physiological resilience—factors that are highly relevant to cancer prevention, treatment tolerance, and quality of life. Screening for chronic stress, depression, and anxiety, and integrating stress-management strategies into routine care, align with holistic and patient-centered models of nursing practice.

Nurses play a critical role in identifying psychosocial stressors, facilitating access to support services, and delivering interventions that promote coping, resilience, and emotional well-being. While stress reduction should not be presented as a standalone cancer prevention strategy, it may represent a valuable adjunct to established medical and public health interventions, with potential benefits extending beyond oncology to overall health and well-being.

Conclusion

A substantial body of preclinical and translational research provides compelling evidence that persistent severe psychological stress can biologically influence carcinogenesis and tumor progression through multiple interconnected pathways. Experimental studies consistently demonstrate that chronic stress activates key neuroendocrine systems, particularly the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), leading to sustained elevations in glucocorticoids and catecholamines. These hormonal changes exert profound effects on immune regulation, cellular signaling, and tissue homeostasis, thereby creating biological conditions that may favor tumor initiation, growth, angiogenesis, invasion, and metastasis.

Mechanistically, chronic stress has been shown to suppress antitumor immune surveillance by impairing the function of cytotoxic T lymphocytes, natural killer cells, and antigen-presenting cells. Simultaneously, stress-related neuroendocrine signaling promotes a pro-inflammatory milieu characterized by increased production of cytokines, chemokines, and growth factors. This inflammatory environment can enhance DNA damage, inhibit apoptosis, stimulate angiogenesis, and facilitate extracellular matrix remodeling, all of which are recognized hallmarks of cancer development and progression. Furthermore, emerging evidence indicates that stress-induced molecular changes within the tumor microenvironment may enhance tumor cell plasticity, epithelial–mesenchymal transition, and resistance to immune-mediated destruction, thereby accelerating disease progression in established malignancies.

Despite the strong biological plausibility supported by preclinical models, evidence from human epidemiological studies remains inconsistent and insufficient to establish a definitive causal relationship between chronic psychological stress and cancer risk or outcomes. While some large-scale observational studies and meta-analyses

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suggest modest associations between psychosocial stressors—such as depression, anxiety, or major life stress—and increased cancer incidence, progression, or mortality, other well-conducted studies fail to confirm these findings. The heterogeneity of results likely reflects substantial methodological challenges, including variability in stress definitions, reliance on self-reported measures, differences in exposure duration and timing, and inadequate control for confounding factors such as smoking, physical inactivity, diet, and socioeconomic status.

Moreover, the long latency period of many cancers complicates the assessment of temporal relationships between stress exposure and disease onset, making causal inference particularly challenging. Reverse causation and residual confounding further limit the interpretability of existing findings. Consequently, at present, chronic severe stress should be regarded as a biologically plausible but not yet definitively established contributing factor in cancer etiology or progression, rather than a direct or independent cause.

To advance the field, there is a critical need for well-designed prospective cohort studies that employ validated, standardized measures of chronic stress and integrate objective biological markers of neuroendocrine and immune function. Additionally, randomized interventional studies targeting stress-related pathways—such as psychosocial interventions, behavioral stress management, or pharmacological modulation—may provide valuable insight into causal mechanisms and potential clinical benefits. Clarifying the magnitude and clinical relevance of stress-related effects on cancer risk and outcomes will be essential for informing prevention strategies and integrating psychosocial care into comprehensive oncology and nursing practice.

Implications for nursing practice

1. **Psychosocial assessment and screening:** Nurses should routinely assess chronic stress, depression, anxiety, and history of severe life events among patients — not only those with cancer, but the general population — to identify individuals at risk.
2. **Integration of stress-management interventions:** Incorporating stress-reduction strategies (e.g., relaxation training, mindfulness, counseling, social support) into care plans could help mitigate biological stress responses.
3. **Multidisciplinary collaboration:** Nurses should work with mental health professionals, oncologists, and other care providers to address the psychosocial dimension of cancer prevention and care.
4. **Patient education:** Educate patients and families about potential links between chronic stress, immune function, and general health, promoting healthy coping strategies and lifestyle behaviors.
5. **Support for research and monitoring:** In clinical settings or research contexts, nurses can assist in biomarker monitoring (stress hormones, immune and inflammatory markers), and implement stress-reduction programs to evaluate their effects on health outcomes.

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