

Research Article

Open Access, Volume 6

Chronic Stress in Epithelial Ovarian Cancer: Mechanisms and Impact

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Abstract

Objective: Review aimed to synthesize current evidence on the association between chronic psychophysiological stress and Epithelial Ovarian Cancer (EOC), with emphasis on neuroendocrine signaling, molecular mechanisms, immune modulation, tumor progression, and potential clinical implications.

Methods: A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. PubMed, Scopus, and Google Scholar were searched for English-language studies published from January 2014 through January 2025 using terms related to stress, epithelial ovarian cancer, catecholamines, β -adrenergic signaling, and the hypothalamic-pituitary-adrenal axis. Relevant studies were identified by screening reference lists of eligible publications; earlier landmark studies identified through this supplementary process were retained for mechanistic and historical context. Preclinical, cohort, case-control, systematic review, and pharmaco-epidemiological studies were considered.

Results: Evidence suggests that chronic stress-related activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis increases catecholamine and glucocorticoid signaling. In preclinical ovarian cancer models, these pathways have been associated with angiogenesis, extracellular matrix remodeling, invasion, metastatic dissemination, inflammatory signaling, and impaired anti-tumor immune responses. Human studies reported associations between psychological distress and adverse biological - clinical outcomes, although findings are heterogeneous and predominantly observational. β -blockers and psychosocial interventions are potential therapeutic approaches, but clinical evidence remains insufficient.

Conclusion: Chronic psycho-physiological stress may contribute to EOC progression through interconnected neuroendocrine, β -adrenergic, inflammatory, and immune pathways. The biological evidence is compelling, but causal inference in humans remains limited. Prospective studies integrating validated stress measures, molecular biomarkers, immune profiling, and oncologic outcomes are needed to clarify clinical relevance.

Keywords: Epithelial ovarian cancer; Chronic stress; β -adrenergic signaling neuroendocrine pathways; Hypothalamic-pituitary-adrenal axis; Angiogenesis; Psychosocial oncology.

Manuscript Information: Received: Sep 08, 2026; Accepted: Oct 01, 2026; Published: Oct 08, 2026

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Citation: Kumar Jaggi V, Agarwal P, Chandra Das B. Chronic Stress in Epithelial Ovarian Cancer: Mechanisms and Impact. J Oncology. 2026; 6(2): 1216.

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Introduction

Epithelial Ovarian Cancer (EOC) a major cause of cancer-related mortality among women worldwide. Although substantial progress has been made in cytoreductive surgery, platinum-based chemotherapy, targeted therapies, and immunotherapeutic strategies, long-term survival remains limited because many patients present with advanced-stage disease and may subsequently develop treatment resistance and recurrence.

In addition to the biological complexity of EOC, increasing attention has been directed toward the influence of psychosocial and physiological factors on tumor progression and clinical outcomes. Cancer diagnosis, intensive treatment, fear of recurrence, treatment-related toxicities, and social disruption can impose a substantial psychological burden on patients. Chronic psychological stress has therefore emerged as a potential modifier of tumor behavior, treatment response, survivorship, and quality of life.

Experimental and translational studies have demonstrated that chronic stress activates sympathetic nervous system (SNS) and the Hypothalamic-Pituitary-Adrenal (HPA) axis, leading to the sustained release of catecholamines and glucocorticoids. These stress mediators may influence multiple biological processes associated with cancer progression, including angiogenesis, inflammation, extracellular matrix remodeling, tumor cell invasion, metastasis, and suppression of anti-tumor immune surveillance. Recent advances in psychoneuroimmunology and tumor microenvironment research have increased interest in understanding how stress-related signaling pathways interact with ovarian cancer biology. Several preclinical studies have identified β -adrenergic signaling as an important mediator of ovarian tumor progression, whereas epidemiological investigations have explored the associations between psychological distress and ovarian cancer outcomes. Evidence from clinical and epidemiological studies has also examined whether chronic stress is associated with ovarian cancer risk and outcomes. However, the principal focus of this review is the potential influence of chronic psycho-physiological stress on established epithelial ovarian cancer biology and progression [1].

Given the growing body of evidence in this area, a structured synthesis of mechanistic, translational, and clinical findings is warranted. This review aimed to synthesize the current evidence regarding chronic psycho-physiological stress and epithelial ovarian cancer, summarize relevant molecular and clinical pathways, and discuss potential therapeutic and psychosocial implications.

Methods

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. PubMed, Scopus, and Google Scholar were searched for English-language studies published from January 2014 through January 2025 using terms related to stress, epithelial ovarian cancer, catecholamines, β adrenergic signaling, and the hypothalamic-pituitary-adrenal axis. Additional relevant studies were identified by screening reference lists of eligible publications; earlier landmark studies identified through this supplementary process were retained for mechanistic

and historical context. Preclinical, cohort, case-control, systematic review, and pharmaco-epidemiological studies were considered.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [2].

Search strategy: A literature search was performed using PubMed, Scopus, and Google Scholar to identify studies evaluating associations between psycho-physiological stress and epithelial ovarian cancer. The primary database search included studies published in English between January 2014 and January 2025. Earlier landmark studies were considered only when identified through manual screening of reference lists and were used to provide essential mechanistic and historical context.

Medical Subject Headings (MESH) terms and keywords were combined using Boolean operators.

The primary search strategy was followed:

- “stress” OR “psychological stress” OR “chronic stress”
- AND “ovarian cancer” OR “epithelial ovarian cancer”
- AND “catecholamines” OR “ β -adrenergic signaling” OR “ADRB2” OR “cortisol” OR “HPA axis”

Additional relevant studies were identified through manual screening of reference lists from relevant articles. Earlier landmark studies identified through this process were retained when they provided essential mechanistic or historical context for the review.

Eligibility criteria

The inclusion criteria were as follows:

1. EOC was evaluated epithelial ovarian cancer in relation to psychological, physiological, or chronic stress.
2. Investigated neuroendocrine, immune, inflammatory, or β -adrenergic signaling mechanisms.
3. Preclinical experiments, cohort studies, case-control studies, systematic reviews, and pharmaco-epidemiologic analyses related to stress and EOC.
4. Articles published in English literature.
5. Studies, have reported outcomes related to tumor progression, angiogenesis, metastasis, immune modulation, survival, treatment response, and quality of life.

The exclusion criteria were as follows:

1. Studies focusing on non-epithelial ovarian tumors,
2. Those lacking relevance to stress-related mechanisms,
3. Conference abstracts without sufficient data,
4. Duplicate publications.

Study selection: Titles and abstracts identified through database searches were independently screened for relevance. Full-text articles were subsequently assessed for eligibility using the predefined inclusion and exclusion criteria. Discrepancies regarding study eligibility were resolved through discussion

among the authors.

Data extraction

Data extracted from eligible studies included:

- study design,
- sample characteristics,
- stress-related variables,
- molecular pathways evaluated,
- oncologic outcomes,
- and principal findings.

Data synthesis

Because of substantial heterogeneity in study designs, methodologies, stress measures, and reported outcomes, a quantitative meta-analysis was not performed. The findings were synthesized and organized into thematic sections addressing molecular mechanisms, neuroendocrine signaling, immune modulation, epidemiological evidence, and therapeutic implications.

Results

Available evidence suggests that chronic stress-related activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis increases catecholamine and glucocorticoid signaling. In preclinical ovarian cancer models, these pathways have been associated with angiogenesis, extracellular matrix remodeling, invasion, metastatic dissemination, inflammatory signaling, and impaired anti-tumor immune responses. Human studies have reported associations between psychological distress and adverse biological or clinical outcomes, although findings are heterogeneous and predominantly observational. β -blockers and psychosocial interventions are potential therapeutic approaches, but clinical evidence remains insufficient to establish routine oncologic use. Experimental studies suggest that chronic

behavioral stress can alter the ovarian tumor microenvironment. Activation of sympathetic nervous system pathways can increase intratumorally catecholamine signaling, particularly through norepinephrine and epinephrine, with subsequent activation of tumor-associated signaling cascades.

β -adrenergic receptor activation has been implicated in cyclic AMP-protein kinase A signaling, with downstream effects that may increase angiogenesis, tumor growth, and metastatic potential. Increased expression of vascular endothelial growth factor, matrix metalloproteinases, and inflammatory cytokines has been observed in ovarian cancer models exposed to stress-related signaling. These findings suggest that inhibition of β -adrenergic signaling may have therapeutic potential in ovarian cancer, although clinical translation remains to be established [3].

Catecholamine exposure has also been associated with enhanced tumor cell invasion through extracellular matrix remodeling. Nor epinephrine and epinephrine significantly enhance ovarian tumor cells invasion of the basement membrane, mediated via β -adrenergic receptors on cancer cells, and matrix metalloproteinase-2 and matrix metalloproteinase-9 expression appear to play important roles in facilitating tumor cell migration and invasion. These effects appear to involve β -adrenergic signaling and matrix metalloproteinase expression [4].

Additional evidence suggests that adrenergic signaling may protect ovarian cancer cells from anoikis, thereby supporting the survival of disseminating tumor cells. Focal adhesion kinase signaling has emerged as an important mediator of this process and could be a potential new therapeutic target for cancer management [5]. Elevated catecholamine levels have been observed in individuals with low social support, chronic stress, and depression and even in EOC patients poor social support has been linked to higher levels of angiogenic cytokines including VEGF and IL-6, both in peripheral blood and in the tumor microenvironment, thus enhancing cancer progression [6].

Table 1: Summary of key preclinical studies evaluating stress signaling in ovarian cancer.

Author year	Experimental model	Stress mediator/pathway	Major findings	Clinical relevance
Thaker et al., 2006 [3]	Orthotopic mouse ovarian cancer model	Norepinephrine, β -adrenergic signaling	Chronic stress increased tumor burden and angiogenesis progression through VEGF upregulation	Demonstrated mechanistic link between stress and ovarian cancer
Sood et al 2010 [5]	Ovarian cancer cell lines and xenografts	Catecholamine signaling	Enhanced invasion and metastasis via MMP activation	Suggested β -blockers as potential therapeutic agents
Lutgendorf et al., 2011 [6]	Tumor micro environment studies	SNS activation	Increased IL-6 production and inflammatory signaling	Supported role of stress in tumor-promoting inflammation
Cole and Nagaraja et al., 2015	Preclinical translational models	β 2-adrenergic receptor pathway	Activation promoted EMT and metastatic potential	Highlighted importance of adrenergic signaling pathways
Armaiz-Pena et al., 2013	In vivo murine ovarian cancer models	Chronic restraint stress	Increased angiogenesis and tumor dissemination	Confirmed stress-related enhancement of metastasis
Moreno-Smith et al., 2010	Ovarian carcinoma xenografts	Dopamine and catecholamine regulation	Dopamine inhibited stress-mediated angiogenesis	Proposed dopaminergic modulation as therapeutic strategy
Shahzad et al., 2016	Cell culture and mouse models	Glucocorticoid receptor signaling	Cortisol exposure promoted chemoresistance and anti-apoptotic signaling	Suggested caution with glucocorticoid exposure during chemotherapy
Hassan et al., 2020	Ovarian cancer cell lines	STAT3 and NF- κ B activation	Stress signaling enhanced inflammatory cytokine expression and proliferation	Supported inflammatory mechanisms in disease progression

Neuroendocrine, immune, and tumor microenvironment effects

Persistent activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis during chronic stress results in prolonged glucocorticoid release, particularly cortisol. Elevated cortisol levels may suppress an -tumor immunity by reducing of natural killer cell activity, impairing cytotoxic T-cell responses, and altering cytokine production.

Stress-related neuroendocrine signaling also influences the tumor microenvironment by promoting inflammatory and pro-angiogenic pathways. Increased concentrations of interleukin6 and Vascular Endothelial Growth Factor (VEGF) have been reported in patients experiencing greater psychosocial distress and reduced social support.

Recent studies have identified neural innervation within ovarian tumors, further supporting the interaction between nervous system signaling and cancer progression. Neurotransmitters released by the activation of the sympathetic nervous system promote the proliferation and metastasis of tumor cells and regulate immune cells in the tumor microenvironment, with the potential for the use of blockers and dopamine agonists in the treatment of gynecological cancers [7,8].

Adrenergic receptors (1, 2, 3) are a group of G protein-coupled receptors that mediate SNS signal transduction and activate downstream signaling pathways to prepare the body for “fight or flight.” 2-Adrenergic receptor (ADRB2) is overexpressed in ovarian

cancer and is positively correlated with poor prognosis [9].

Chronic stress can reduce natural killer cell cyto-toxicity, through the suppression of type 1 helper T cells (Th1) and cytotoxic T cells (CTL)-mediated cellular immunity as well as interferon production. This weakens immune surveillance, alters macrophage polarization, and increases regulatory T cells, thereby increasing the risk of cancer invasion and metastasis and reducing the effectiveness of an -tumor therapy. Cortisol released through HPA-axis activation may inhibit apoptosis and an equate responses to chemotherapy. Thus, ovarian cancer patients with high glucocorticoid receptor expression may have shorter progression-free and overall survival [10,12].

Epidemiological evidence: Clinical and epidemiological studies investigating stress and ovarian cancer outcomes have reported mixed but suggestive findings. Meta-analytical evidence indicates modest associations between psychological stress and ovarian cancer risk, although heterogeneity and confounding factors limit definitive conclusions. Evidence relating stress specifically to outcomes among women with established ovarian cancer is also limited and heterogeneous. Pooled overall response was reported as an Odds Ratio (OR) of 1.18 (95 % CI 1.04-1.34) [13].

Longitudinal studies have also reported possible associations between Post-Traumatic Stress Disorder (PTSD) symptoms and ovarian cancer incidence [14]. However, the variability in stress assessment methods and psychosocial measurements remains a major limitation (Table 2).

Table 2: Clinical and epidemiological studies evaluating psychological stress and ovarian cancer outcomes.

Author year	Study design	Population	Stress related variable	Key findings	Limitations
Lutgendorf et al., 2008	Prospective observational study	Patients with epithelial ovarian cancer	Psychological distress and social support	Higher distress associated with elevated IL-6 and poorer immune response	Small sample size
Costanzo et al., 2005	Cohort study	Women with ovarian cancer	Chronic stress and depressive symptoms	Psychological distress correlated with reduced quality of life and impaired survival trends	Observational design
Lutgendorf et al., 2012	Translational clinical study	Advanced ovarian cancer patients	Stress hormone levels	Elevated norepinephrine associated with tumor progression markers	Limited longitudinal follow-up
Antoni et al., 2013	Behavioral intervention study	Gynecologic cancer patients	Stress management intervention	Improved psychological well-being and reduced inflammatory biomarkers	Mixed cancer populations
Schrepf et al., 2015	Clinical psychosocial study	Ovarian cancer survivors	Depression and fatigue	Persistent stress symptoms associated with poorer functional outcomes	Self-reported measures
Chida et al., 2008	Meta-analysis	Multiple cancer populations	Psychological stress factors	Chronic stress associated with worse cancer survival outcomes	Heterogeneous cancer types
Hamer et al., 2009	Epidemiological analysis	Female cancer patients	Psychosocial stress	Increased stress linked to adverse health outcomes and inflammation	Limited ovarian specific data
Lutgendorf and	Review and clinical synthesis	Ovarian cancer literature	Biobehavioral influences	Strong evidence for stress related	Need for larger prospective trials
Andersen, 2015				neuroendocrine modulation in ovarian cancer	

Pharmacologic implications: Interest has increased in the potential a tumor effects of β -blockers because they inhibit adrenergic signaling pathways. Observational and preclinical studies suggest that non-selective β -blockers, particularly propranolol, may influence tumor progression and survival in selected ovarian cancer populations [15-19]. Meta-analysis of epidemiological and perioperative clinical studies showed no

association with cancer recurrence, while Disease-Free Survival (DFS), and Overall Survival (OS) showed beneficial effects of beta-blockers however this was variable, tumor-specific, and of low-level evidence at present [20]. Moreover, preclinical evidence suggests that sustained adrenergic activation can promote ovarian cancer growth and metastasis [21].

Stimuli that disrupts homeostasis acts through the hypothalamus, which becomes the command center and communicates with the whole body for initiation of the stress response, aimed to attenuate further tissue damage, through multiple effects caused by activation of the Sympathetic-Adreno-Medullary (SAM) axis, Hypothalamic-Pituitary-Adrenal (HPA) axis, and the immune system [22].

Table 3: Potential therapeutic implications of stress-modulating interventions in epithelial ovarian cancer.

Intervention	Proposed mechanism	Potential benefits	Current evidence	Limitations/Future directions
β -blockers (e.g., propranolol)	Inhibition of β adrenergic signaling	Reduced angiogenesis, invasion, and metastasis	Preclinical studies and retrospective clinical analyses suggest survival benefit	Need randomized controlled trials
Stress management therapy	Reduction of psychological distress and cortisol levels	Improved quality of life and immune function	Behavioral intervention studies show reduced inflammatory biomarkers	Long-term oncologic outcomes unclear
Cognitive behavioral therapy (CBT)	Modulation of stress perception and coping	Reduction in anxiety, depression, and fatigue	Beneficial psychosocial outcomes reported	Limited ovarian cancer-specific trials
Mindfulness based interventions	Regulation of autonomic stress responses	Improved emotional wellbeing and sleep quality	Small clinical studies demonstrate feasibility	Requires larger prospective studies
Exercise interventions	Reduction of systemic inflammation and stress hormones	Improved physical function and fatigue reduction	Increasing evidence in cancer survivorship programs	Optimal intensity and duration uncertain
Dopaminergic agents	Counteraction of catecholamine-induced angiogenesis	Potential suppression of VEGF-mediated tumor growth	Supported by preclinical evidence	Minimal clinical translation to date
Anti-inflammatory agents	Targeting IL-6, NF- κ B, and inflammatory signaling	Reduction of tumor promoting inflammation	Early translational evidence promising	Requires biomarker-guided studies
Integrative supportive care	Combined psychosocial and pharmacologic management	Enhanced treatment tolerance and patient centered outcomes	Increasing incorporation into oncology care models	Standardization of protocols required

Based on the dura on, source, and response, stress is categorized into the following types

Acute stress: Short-term challenging situation, causing body's fight-or-flight response with temporary physiological changes such as increased heart rate and adrenaline release.

Chronic stress: Prolonged persistent exposure to stressors leads to cumulative physiological and psychological effects, increasing the risk of cardiovascular diseases, anxiety, and depression.

Episodic acute stress: These are frequent episodes of acute stress, characteristic of individuals who lead disorganized lifestyles, face deadlines, commitments, or interpersonal conflicts.

Traumatic stress: Traumatic events, such as natural disasters, accidents, or violent acts, lead to post traumatic stress disorder (PTSD), including intrusive memories, avoidance behaviors, and hyper-arousal.

Environmental stress: Adverse or unsafe living conditions in one's surroundings, for example, noise pollution and, overcrowding, contribute to a sense of discomfort.

Psychological stress: Cognitive or emotional factors, such as perceived threats, worries, or negative thoughts, due to work-related pressures, academic expectations, social comparisons, or self-imposed demands, causing anxiety, rumination, or perfectionism.

Stressors may be intense or respective, resulting in repeated acute responses or prolonged chronic stress and potentially leading to maladaptive physiological responses. Exposure to chronic stressors can cause maladaptive reactions, such as, depression, anxiety, cognitive impairment, and heart disease, adversely affect the body and mind and cause distress [23,24].

In contrast, positive stressors, termed as eustress, are enjoyable, stimulating, and inspiring, and serve to replenish energy, enhance cardiovascular health, boost endurance, and sharpen cognitive function, mental acuity, and motivation [24] (Table 3).

Physiological stress: This refers to the body's response to internal or external stressors that disrupt homeostasis, such as illness, injury, sleep deprivation, and nutritional deficiencies. These activate physiological stress pathways.

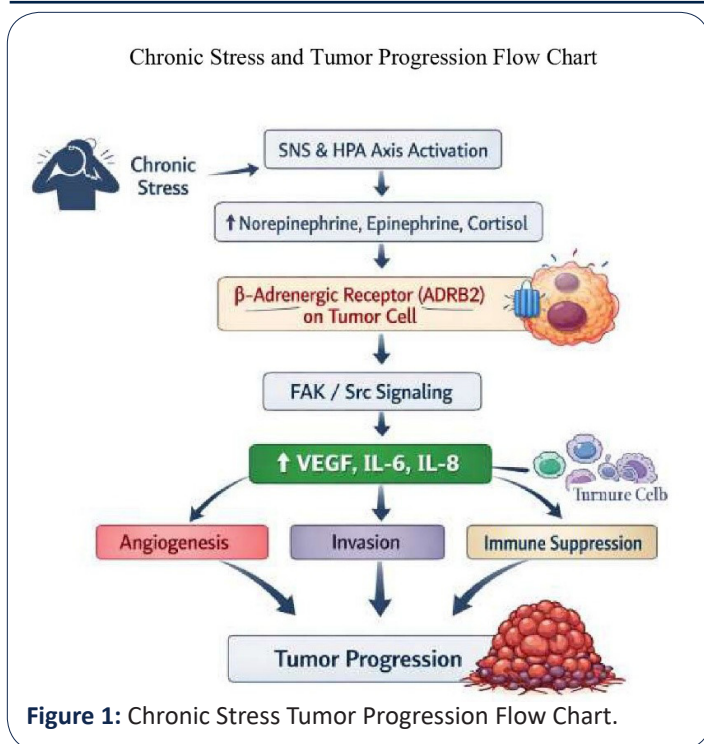
Physiological stress response could be fast mediated by the Sympathetic-Adreno-Medullary System (SAM axis), or slow mediated by the HPA axis [25-27].

Discussion

This review summarizes emerging evidence linking psychophysiological stress with epithelial ovarian cancer progression through neuroendocrine, inflammatory, and immune-mediated mechanisms (Figure 1).

Current data support the concept that chronic stress may influence tumor biology by activating the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. The data suggests that psychological intervention can influence neuroendocrine (e.g., cortisol) and immune function indicators, especially lymphocyte proliferation and TH1 cytokine production [28].

Preclinical investigations provide substantial mechanistic evidence that stress-related signaling can enhance pathways associated with ovarian cancer progression. Catecholamine-mediated β adrenergic signaling promotes angiogenesis, extracellular matrix remodeling, tumor cell survival, and metastatic dissemination [3-5]. In parallel, chronic glucocorticoid exposure



may impair anti-tumor immunity through the suppression of natural killer cell activity and altered T cell responses.

Clinical evidence in humans remains less definitive because of the variability in psychosocial assessment methods, confounding lifestyle factors, and differences in study design.

Nevertheless, observational studies have suggested that chronic psychological distress, depression, social isolation, and post-traumatic stress symptoms may adversely influence ovarian cancer outcomes.

An important translational implication of these findings is the potential value of stress modulating interventions as adjuncts to cancer care.

Psychosocial support programs, cognitive behavioral therapy, structured exercise interventions, and stress management strategies may improve the quality of life and potentially influence biological pathways associated with disease progression [29].

Similarly, increasing interest has been focused on repurposing β -blockers as adjunctive cancer therapies because of their effects on adrenergic signaling.

Although preliminary findings are encouraging, prospective randomized trials are required before these agents can be incorporated into routine ovarian cancer management.

This review has several limitations. The included studies demonstrated substantial methodological heterogeneity, particularly regarding the stress assessment tools, study populations, and measured outcomes. Most human studies are observational in nature, which limits their causal interpretation. In addition, publication bias and variability in biological markers may influence the interpretation of current evidence. Future prospective trials incorporating validated stress measures and biomarker monitoring (e.g., cortisol and catecholamines) are needed to determine their clinical relevance.

Future research should focus on large prospective studies integrating psychological assessment with molecular biomarkers, immune profiling, and long-term oncologic outcomes with the integration of β -blockers. A better understanding of stress-related tumor biology may contribute to the development of personalized supportive therapeutic strategies in epithelial ovarian cancer.

Conclusion

Chronic psycho-physiological stress may contribute to EOC progression through interconnected neuroendocrine, β -adrenergic, inflammatory, and immune pathways. The biological evidence is compelling, but causal inference in humans remains limited. Prospective studies integrating validated stress measures, molecular biomarkers, immune profiling, and oncologic outcomes are needed to clarify clinical relevance.

Although direct causal relationships in humans remain incompletely established, substantial biological plausibility has been demonstrated through experimental and translational studies.

Integration of psychosocial assessment, supportive-care interventions, behavioral therapies, and further investigation of stress-targeted pharmacological approaches may represent valuable directions for comprehensive ovarian cancer care.

Limitation: Current clinical evidence remains predominantly observational, limiting conclusions regarding a direct causal relationship between chronic stress and ovarian cancer progression.

PRISMA Flow Diagram

Identification

Records identified through database searching:

- PubMed: n=142
- Scopus: n=178
- Google Scholar: n=96

Total records identified: n=416

Additional records identified through reference screening: n=18

Total records before duplicate removal: n=434

Duplicates removed: n=102

Records screened: n=332

Screening

Records excluded on title and abstract screening: n=221

Full-text articles assessed for eligibility: n=111

Eligibility

Full-text articles excluded:

- Not relevant to stress pathways: n=38
- Non-EOC studies: n=16
- Insufficient data: n=12

• Non-English publications: n=5

Total excluded after full-text review: n=71

Included: Studies included in qualitative synthesis: n=40

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