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Review Article

Trauma, Chronic Stress, and Breast Cancer Risk in Women: A Review of Potential Biological Pathways

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ABSTRACT

Breast cancer remains the most commonly diagnosed cancer among women worldwide and continues to represent a major challenge for healthcare systems despite significant advances in screening, diagnosis, and treatment. While established risk factors such as age, genetic susceptibility, hormonal influences, reproductive history, lifestyle factors, and environmental exposures explain a substantial proportion of breast cancer cases, they do not fully account for the variability in disease occurrence. Increasing attention has therefore been directed toward psychosocial determinants of health, particularly the long-term biological consequences of trauma and chronic stress. This review critically examines current evidence regarding the relationship between trauma, chronic stress, and breast cancer risk in women. Drawing upon literature from psychoneuroimmunology, endocrinology, oncology, neuroscience, and women's health, the review explores the biological pathways through which traumatic experiences may become biologically embedded across the life course. Particular attention is given to dysregulation of the hypothalamic-pituitary-adrenal axis, chronic inflammation, immune dysfunction, oxidative stress, epigenetic modifications, and behavioural adaptations that may collectively influence the physiological environment associated with breast cancer susceptibility. The review also considers women's unique exposure to traumatic experiences, including adverse childhood experiences, intimate partner violence, caregiving burden, financial adversity, and gender-based violence, all of which may contribute to cumulative physiological stress. Importantly, the available evidence does not support a direct causal relationship between trauma and breast cancer. Rather, it suggests that chronic stress associated with traumatic experiences may interact with established genetic, hormonal, environmental, and behavioural risk factors through complex and interconnected biological mechanisms. By integrating evidence across multiple disciplines, this review highlights the importance of adopting a life course perspective when examining breast cancer risk in women. It identifies important gaps in the current literature and outlines priorities for future research, including longitudinal investigations, mechanistic studies, and the integration of trauma-informed approaches within women's health and cancer prevention. A deeper understanding of these pathways has the potential to inform more comprehensive models of disease prevention, early intervention, and patient-centred care.

Keywords: Breast cancer; Trauma; Chronic stress; Adverse childhood experiences; Allostatic load; Inflammation; Immune dysregulation; Neuroendocrine function; Women's health;

INTRODUCTION

Breast cancer continues to be the most frequently diagnosed malignancy among women and remains one of the leading causes of cancer-related mortality worldwide. Although advances in screening programmes, early detection, molecular diagnostics, and targeted therapies have contributed to improved survival rates, the global burden of breast cancer remains substantial. The disease affects women across diverse geographical, socioeconomic, and cultural settings, underscoring the need to better understand not only the biological mechanisms of tumour development but also the broader factors that shape disease susceptibility over the life course. Current understanding of breast cancer risk has largely been informed by research examining genetic predisposition, hormonal influences, reproductive history, age, lifestyle behaviours, and environmental exposures. Mutations in high-penetrance genes such as BRCA1 and BRCA2, prolonged lifetime exposure to oestrogen, obesity after menopause, alcohol consumption, physical inactivity, and increasing age are among the most consistently recognised risk factors. While these factors explain a significant proportion of breast cancer incidence, they do not fully account for why some women develop the disease in the absence of recognised risk

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factors, while others with multiple established risk factors never do. This observation has encouraged researchers to explore additional biological, psychological, and social influences that may contribute to cancer susceptibility. Over the past three decades, growing attention has been directed towards the health consequences of trauma and chronic psychological stress. Traumatic experiences, whether occurring during childhood or adulthood, have been associated with an increased risk of numerous adverse health outcomes, including cardiovascular disease, metabolic disorders, autoimmune conditions, depression, and premature mortality. Rather than representing isolated psychological events, trauma is increasingly understood as an experience capable of producing long-lasting physiological adaptations involving the nervous, endocrine, immune, and metabolic systems. These adaptations, while initially protective, may become maladaptive when stress is persistent or repeatedly activated, resulting in cumulative physiological burden over time. Women experience certain forms of trauma disproportionately throughout the life course. Adverse childhood experiences, sexual violence, intimate partner violence, reproductive trauma, caregiving responsibilities, financial hardship, and chronic gender-based discrimination represent 2 significant sources of psychological stress that may persist for years or even decades. Such exposures rarely occur in isolation. Instead, they often accumulate, interact, and influence multiple aspects of physical and mental health. This cumulative burden has prompted increasing interest in the concept of biological embedding, whereby repeated exposure to adversity becomes reflected in measurable alterations in physiological functioning that extend well beyond the original traumatic event. Several biological pathways have been proposed through which chronic stress may influence processes relevant to carcinogenesis. Dysregulation of the hypothalamic-pituitary-adrenal axis, sustained activation of the sympathetic nervous system, chronic low-grade inflammation, impaired immune surveillance, oxidative stress, and epigenetic modifications have each been implicated in both the physiological response to trauma and the development or progression of malignancy [1]. At the same time, trauma may influence behavioural factors known to affect cancer risk, including smoking, alcohol use, dietary patterns, physical activity, sleep quality, healthcare utilisation, and adherence to preventive screening. Together, these biological and behavioural mechanisms suggest that the relationship between trauma and breast cancer is likely to be complex, multidimensional, and mediated through interacting pathways rather than a single causal process. Despite growing interest in this field, important questions remain unresolved. Existing studies have reported inconsistent findings, reflecting differences in study design, definitions of trauma, methods of measuring psychological stress, follow-up periods, and the consideration of potential confounding variables. Furthermore, much of the literature has examined individual biological mechanisms in isolation, with relatively few reviews integrating evidence across psychoneuroimmunology, endocrinology, oncology, behavioural medicine, and women's health. A comprehensive synthesis of these interconnected pathways is therefore warranted. This review critically examines current evidence regarding the relationship between trauma, chronic stress, and breast cancer risk in women. It explores the biological and behavioural mechanisms through which traumatic experiences may become biologically embedded across the lifespan while recognising that breast cancer is a multifactorial disease arising from the interaction of genetic, hormonal, environmental, behavioural, and psychosocial influences. By integrating evidence from multiple disciplines, this review aims to provide a balanced evaluation of current knowledge, identify important gaps in the literature, and highlight priorities for future research that may advance both scientific understanding and trauma-informed approaches to women's health [2].

METHODS

Review Design This review was conducted as a critical narrative review to examine current evidence regarding the relationship between trauma, chronic stress, and breast cancer risk in women. A narrative approach was selected because of the complexity of the subject, the diversity of study designs within the available literature, and the need to integrate findings from multiple scientific disciplines, including oncology, psychoneuroimmunology, neuroscience, endocrinology, behavioural medicine, and women's health. Rather than providing a quantitative synthesis, this review critically evaluates existing evidence, identifies areas of consensus and disagreement, and discusses potential biological mechanisms that may explain observed associations. Literature Search Strategy A comprehensive search of the published literature was undertaken using major biomedical and multidisciplinary electronic databases. Searches included studies indexed in PubMed/MEDLINE, Scopus, Web of Science, PsycINFO, Embase, and GoogleScholar to ensure broad coverage of medical, psychological, and public health research. Reference lists of relevant review articles and original studies were also examined to identify additional publications that may not have been captured through the initial database search. Search terms were developed to reflect three principal concepts: trauma, chronic stress, and breast cancer. Keywords and Medical Subject Headings (MeSH), where appropriate, included combinations of terms such as "breast cancer," "breast neoplasm," "trauma," "psychological trauma," "adverse childhood experiences," "ACEs," "childhood adversity," "chronic stress," "toxic stress," "allostatic load," "psychoneuroimmunology," "inflammation," "immune function," "epigenetics," and "women's health." Boolean operators were used to combine search terms, and database-specific search strategies were adapted where necessary [3]. Eligibility Criteria Studies were considered eligible if they examined trauma, chronic psychological stress, or adverse childhood experiences in relation to breast cancer risk, biological mechanisms relevant to carcinogenesis, or physiological responses associated with chronic stress in women. Original observational studies, prospective cohort studies, case-control studies, systematic reviews, 4 meta-analyses, and foundational mechanistic studies were included where they contributed to understanding the proposed biological pathways. Studies focusing exclusively on acute stress responses, animal models without clear relevance to human physiology, or cancer types unrelated to breast cancer were considered outside the primary scope of this review, although selected foundational studies were included where they provided important mechanistic insights applicable to breast cancer biology. Data

Synthesis Given the heterogeneity of the available literature, findings were synthesised narratively rather than statistically. Particular attention was given to recurring biological mechanisms identified across studies, including neuroendocrine dysregulation, chronic inflammation, immune dysfunction, oxidative stress, epigenetic modification, and behavioural pathways associated with chronic stress. Evidence was interpreted within the broader context of women's health and life course epidemiology, recognising that trauma frequently occurs alongside social, environmental, and behavioural factors that may independently influence breast cancer risk. Critical Appraisal Throughout the review, emphasis was placed on evaluating the strength, consistency, and limitations of the available evidence. Consideration was given to study design, sample characteristics, methods used to assess trauma exposure, duration of follow-up, measurement of biological outcomes, and the extent to which studies accounted for potential confounding variables. Particular attention was paid to distinguishing established evidence from emerging hypotheses, thereby ensuring that interpretations remained consistent with the current state of scientific knowledge [4].

UNDERSTANDING TRAUMA AND CHRONIC STRESS

Trauma has traditionally been conceptualised as a psychological response to an overwhelming event that exceeds an individual's capacity to cope. Contemporary research, however, increasingly recognises trauma as a multidimensional experience with enduring biological, psychological, and social consequences. Although many individuals recover following exposure to adversity, traumatic experiences may, in some cases, initiate long-term physiological adaptations that extend far beyond the resolution of the original event. These adaptations are now recognised as important contributors to health across the lifespan and have become a 5 growing focus of research within psychoneuroimmunology, neuroscience, and behavioural medicine. The experience of trauma is inherently subjective. Events that result in profound and persistent distress for one individual may be experienced differently by another, reflecting the complex interaction of genetic susceptibility, developmental stage, previous life experiences, social support, and individual coping resources. Consequently, trauma is not defined solely by the objective characteristics of an event but also by its lasting impact on emotional regulation, physiological functioning, and overall wellbeing. This understanding has shifted research away from viewing trauma as an isolated psychological phenomenon towards recognising it as a potential determinant of long-term physical health. Traumatic experiences occur across a broad spectrum of circumstances. Acute trauma may arise from natural disasters, serious accidents, or life-threatening medical events, whereas chronic trauma often reflects repeated or prolonged exposure to adversity. Examples include childhood abuse, neglect, intimate partner violence, sexual violence, emotional abuse, discrimination, chronic financial hardship, forced displacement, and exposure to armed conflict. Complex trauma describes repeated interpersonal trauma, frequently occurring during childhood, in which the individual experiences ongoing threat within relationships that would ordinarily provide safety and protection. Such experiences have consistently been associated with long-term alterations in emotional functioning, stress regulation, and physical health. Among the most influential developments in trauma research has been the recognition of adverse childhood experiences as predictors of adult health. The landmark Adverse Childhood Experiences study demonstrated a graded relationship between childhood adversity and numerous chronic diseases later in life. Individuals exposed to multiple forms of adversity during childhood were found to have substantially higher risks of cardiovascular disease, diabetes, depression, substance use disorders, and premature mortality. Subsequent research conducted across diverse populations has largely supported these observations, suggesting that early adversity may become biologically embedded through cumulative alterations in physiological stress systems. The concept of chronic stress is closely related to trauma but should not be regarded as synonymous. Trauma refers to exposure to events or circumstances that overwhelm an individual's capacity to cope, whereas chronic stress reflects the sustained activation of physiological stress responses over extended periods. Although trauma frequently gives rise to chronic stress, persistent stress may also emerge in the absence of a single identifiable traumatic event. Long-term caregiving responsibilities, financial insecurity, occupational strain, chronic illness, discrimination, and social isolation represent examples of prolonged stressors capable of 6 maintaining continuous activation of neuroendocrine and immune pathways. From a biological perspective, it is often the persistence of this stress response, rather than the initiating event itself, that is believed to influence long-term health. Women experience several forms of trauma and chronic stress at disproportionately higher rates than men, reflecting both biological and social determinants of health [5]. Gender-based violence, sexual assault, intimate partner violence, reproductive loss, infertility, caregiving responsibilities, workplace inequity, and economic disadvantage represent significant sources of cumulative psychological burden. These experiences frequently overlap throughout the life course, resulting in repeated activation of physiological stress systems during critical developmental and reproductive periods. Such cumulative exposure has prompted growing interest in understanding how women's lived experiences may influence long-term disease susceptibility through mechanisms extending beyond traditional behavioural risk factors. Not all women exposed to trauma develop chronic disease, nor do all women diagnosed with breast cancer report significant traumatic experiences. Breast cancer remains a multifactorial disease influenced by complex interactions among genetic, hormonal, reproductive, environmental, behavioural, and psychosocial factors. Nevertheless, the possibility that trauma and chronic stress may modify biological processes relevant to carcinogenesis has generated increasing scientific interest. Rather than proposing a direct causal relationship, current research increasingly seeks to understand whether chronic activation of stress-responsive physiological systems creates conditions that may contribute to cancer development in susceptible individuals. Understanding this distinction is essential. The question is no longer whether trauma affects the body, as this has been convincingly demonstrated across multiple physiological systems. Instead, the more challenging and scientifically important question concerns how these biological changes interact with established mechanisms of breast carcinogenesis and whether they meaningfully influence cancer

susceptibility over the course of a woman's life. Addressing this question requires careful examination of the interconnected biological pathways linking chronic stress to immune regulation, endocrine function, inflammation, and cellular homeostasis [6].

BIOLOGICAL MECHANISMS LINKING TRAUMA AND BREAST CANCER RISK

Chronic Stress as a Biological Process

The relationship between trauma and disease is increasingly understood through the lens of biological adaptation rather than psychological distress alone. From an evolutionary perspective, 7 the human stress response developed as a highly efficient survival mechanism, enabling rapid physiological adjustments in the presence of danger. During periods of acute threat, activation of stress-responsive systems promotes immediate survival by mobilising energy reserves, increasing cardiovascular output, sharpening attention, and temporarily suppressing physiological processes that are not essential for immediate survival. Under normal circumstances, these responses are tightly regulated and resolve once the threat has passed [7]. Trauma has the potential to alter this adaptive process. Repeated or prolonged exposure to adversity may result in persistent activation of the body's stress response, even in the absence of an immediate external threat. Rather than returning to physiological baseline, stress-responsive systems may remain chronically engaged, producing subtle but sustained alterations across multiple organ systems. These changes are not confined to the brain or psychological functioning. They extend to endocrine regulation, immune activity, metabolic processes, cardiovascular function, and cellular homeostasis, creating widespread physiological effects that may accumulate over many years. Central to this process is the coordinated interaction between the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Together, these systems regulate the body's response to physical and psychological stress through the release of glucocorticoids, particularly cortisol, and catecholamines, including adrenaline and noradrenaline. Acute activation of these pathways is essential for survival and generally produces beneficial short-term effects. Difficulties arise, however, when activation becomes prolonged or repeatedly triggered without sufficient opportunity for recovery. Sustained exposure to stress hormones may gradually disrupt normal physiological regulation. Chronic alterations in cortisol secretion have been associated with impaired immune function, metabolic dysregulation, disrupted circadian rhythms, sleep disturbance, and changes in inflammatory signalling [8]. Although these responses initially serve protective functions, prolonged activation may contribute to a state of physiological wear and tear that affects multiple biological systems simultaneously. This cumulative burden is commonly described as allostatic load, a concept that has become central to understanding how chronic stress contributes to long-term health outcomes. Allostatic load refers to the biological cost of repeatedly adapting to stress over time. Rather than reflecting a single disease process, it represents the gradual accumulation of physiological changes across interconnected systems, including the neuroendocrine, cardiovascular, metabolic, and immune systems. Individuals exposed to persistent adversity often demonstrate higher levels of biological markers associated with chronic stress, suggesting that repeated activation of stress pathways may leave measurable physiological consequences. Importantly, 8 allostatic load is influenced not only by the severity of stress exposure but also by its duration, timing across the life course, and the availability of protective factors such as social support, psychological resilience, and access to healthcare. Emerging evidence suggests that chronic activation of stress-responsive systems may also influence biological processes relevant to cancer development. Experimental and observational studies have reported associations between prolonged stress exposure and alterations in immune surveillance, inflammatory regulation, angiogenesis, cellular proliferation, and apoptosis. While these findings do not establish trauma as a direct cause of breast cancer, they support the hypothesis that chronic stress may contribute to a biological environment in which malignant processes are more likely to develop or progress in susceptible individuals. The pathways involved are highly interconnected and should not be interpreted in isolation, as neuroendocrine, immune, inflammatory, metabolic, and behavioural responses continuously influence one another throughout the lifespan. The transition from psychological experience to biological consequence is one of the defining concepts within contemporary stress research. Trauma is increasingly recognised not simply for its emotional impact but for its capacity to shape physiological regulation across multiple systems for years after the original exposure. Understanding these adaptations provides an essential foundation for examining the individual biological mechanisms through which chronic stress may influence breast cancer susceptibility. The sections that follow explore these mechanisms in greater detail, beginning with dysregulation of the hypothalamic-pituitary-adrenal axis, the body's principal neuroendocrine stress response system [9].

HPA-Axis Dysregulation and Altered Stress Recovery

The hypothalamic-pituitary-adrenal (HPA) axis is one component of a broader neuroendocrine network through which the brain interprets and responds to environmental demands. Following exposure to a perceived threat, hypothalamic corticotropin-releasing hormone stimulates pituitary adrenocorticotropic hormone release, which subsequently promotes glucocorticoid secretion from the adrenal cortex. Cortisol then participates in the regulation of energy availability, cardiovascular activity, immune signalling, metabolism, and inflammatory responses. Under conditions of acute stress, this response is adaptive because it prioritises immediate survival and facilitates recovery once the stressor has resolved.

The biological significance of chronic trauma may therefore lie less in the simple presence of elevated cortisol than in altered regulation and recovery of the stress-response system. Prolonged adversity can modify the timing, amplitude, feedback sensitivity, and circadian organisation of HPA-axis activity. Importantly, chronic stress does not produce a uniform endocrine phenotype. Some individuals exhibit increased cortisol exposure, whereas others demonstrate lower basal concentrations, altered diurnal rhythms, or impaired responses to subsequent stressors. These differences may reflect variation in the timing and duration of adversity, developmental stage, biological sex, social

environment, coping resources, and opportunities for recovery [10].

This distinction is important when considering breast cancer because a biologically plausible stress pathway should not be reduced to the proposition that "high cortisol causes cancer." Rather, repeated activation of stress-responsive systems may modify the regulatory environment in which other biological processes operate. Altered glucocorticoid signalling can influence immune-cell activity, inflammatory regulation, cellular metabolism, apoptosis, and communication between systemic physiology and the tissue microenvironment. Experimental and translational research has increasingly demonstrated that neuroendocrine signals can influence tumour-associated processes, although the strength and direction of these effects depend on tumour type, disease stage, and biological context.

One potentially important mechanism is altered glucocorticoid sensitivity. Cortisol ordinarily contributes to the resolution of inflammatory responses. Persistent stress exposure, however, may produce changes in cellular responsiveness to glucocorticoids, allowing inflammatory signalling to persist despite continued hormonal feedback. This provides a possible biological bridge between chronic stress and the inflammatory state observed in several chronic diseases. It also demonstrates why endocrine and immune mechanisms should not be conceptualised as independent pathways.

The HPA axis should consequently be understood as an upstream regulatory component within a larger stress-response network rather than as a direct carcinogenic mechanism. Its relevance to breast cancer may arise through interactions with immune surveillance, inflammatory signalling, metabolic regulation, sleep, reproductive physiology, and behavioural adaptation. Recent reviews of breast cancer biology similarly emphasise interactions between chronic stress, neuroendocrine signalling, immune function, and the tumour microenvironment rather than a single linear pathway.

The distinction between biological plausibility and demonstrated causality is particularly important. Although altered HPA-axis activity has been associated with chronic adversity and has been implicated in cancer-related processes, current human evidence does not establish that trauma-induced HPA-axis dysregulation independently initiates breast cancer [11]. The most defensible interpretation is therefore that persistent alteration of stress-response regulation may constitute one component of a biological susceptibility environment in which established genetic, hormonal, reproductive, environmental, metabolic, and behavioural determinants operate.

Inflammatory Signalling as a Point of Biological Convergence

Inflammation represents a second major component of the proposed pathway, but its role requires careful qualification. Inflammation is not intrinsically pathological. Acute inflammatory responses are essential for host defence, tissue repair, and restoration of physiological integrity. The potential relevance to chronic disease arises when inflammatory signalling becomes persistent, poorly resolved, or inappropriately regulated.

Chronic psychological stress has been associated with alterations in inflammatory activity, including changes in circulating cytokines and acute-phase proteins. Interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) have received particular attention in psychoneuroimmunology. However, these biomarkers are nonspecific and can be influenced by obesity, infection, sleep disturbance, physical inactivity, socioeconomic conditions, medication use, ageing, and numerous other factors. Consequently, an elevated inflammatory marker cannot be interpreted as evidence of trauma-induced carcinogenesis.

The more useful question is how persistent stress-related signalling might interact with inflammatory processes already recognised as relevant to cancer biology. Chronic inflammatory activity can influence cellular proliferation, tissue remodelling, angiogenesis, apoptosis, and communication within the tumour microenvironment. In breast cancer, inflammatory signalling interacts with tumour-associated immune cells, stromal cells, vascular processes, and malignant cells, potentially affecting tumour growth and progression.

A potentially important connection between stress and inflammation is the loss of normal regulatory coordination between endocrine and immune systems. Under acute conditions, glucocorticoid signalling helps constrain excessive inflammation. Persistent stress may alter this regulatory relationship through changes in glucocorticoid sensitivity and immune-cell responsiveness. The resulting state should not be understood as a simple increase in inflammation, but as a disturbance in inflammatory regulation.

This distinction introduces a systems-level interpretation. HPA-axis activity may influence immune signalling; immune-derived cytokines can influence neuroendocrine function; inflammatory processes can increase oxidative activity; and oxidative stress can further amplify inflammatory signalling. Behavioural changes associated with chronic adversity—including sleep disruption, reduced physical activity, altered dietary patterns, and substance use—may simultaneously influence these systems. Thus, the potential contribution of trauma is more appropriately conceptualised as a network of reciprocal interactions than as a single inflammatory pathway [12].

Recent cancer research supports the broader concept that chronic stress can remodel neuroendocrine and immune interactions relevant to tumour biology. However, much of this evidence concerns tumour progression, immune function, or biological markers rather than the initial development of breast cancer in previously healthy women.

Accordingly, inflammation should be positioned within this review as a potential mediator of biological vulnerability rather than a demonstrated mediator of trauma-related breast cancer incidence. This distinction is essential because inflammation is simultaneously a consequence of numerous exposures and a component of many disease processes. The evidence therefore supports investigation of inflammatory dysregulation as one

component of cumulative biological embedding, while causal attribution to trauma remains premature.

Immune Regulation, Surveillance, and Tumour Microenvironment

The immune system provides another potential interface between chronic stress and cancer biology. Immune surveillance involves continuous recognition and elimination of abnormal cells through coordinated innate and adaptive immune responses. Natural killer (NK) cells, cytotoxic T lymphocytes, dendritic cells, macrophages, and other immune populations contribute to this process. In cancer, however, the relationship between immunity and tumour development is dynamic rather than simply protective [13].

The contemporary concept of cancer immunoediting describes a process involving elimination, equilibrium, and escape. Emerging malignant cells may initially be recognised and destroyed by immune mechanisms. Some cells may subsequently persist in a state of equilibrium, allowing additional molecular changes to accumulate. Tumour populations that acquire mechanisms for immune evasion can eventually escape effective immune control and establish clinically detectable disease.

Chronic stress may potentially influence this process by altering the communication between neuroendocrine and immune systems. Experimental and observational research has reported changes in NK-cell activity, T-cell function, cytokine signalling, leukocyte distribution, and other immune processes following prolonged psychological stress. Breast-cancer research has further suggested that stress-related neuroendocrine signalling can influence immune and tumour-associated pathways.

However, an important distinction must be maintained between altered immune function and failure of immune surveillance sufficient to initiate breast cancer. The former is supported by a substantial body of psychoneuroimmunological research; the latter has not been demonstrated convincingly in humans. Most studies measure intermediate biological outcomes rather than prospectively establishing that trauma-related immune changes precede tumour initiation.

The tumour microenvironment provides an additional level of complexity. Tumours do not develop in isolation from surrounding tissues. Cancer cells interact with immune cells, fibroblasts, endothelial cells, extracellular matrix components, and signalling molecules. Stress-related neuroendocrine signals may influence some of these interactions, particularly through sympathetic signalling and glucocorticoid pathways. Recent reviews describe potential effects on cytotoxic lymphocytes, immunosuppressive populations, inflammatory signalling, angiogenesis, and tumour-associated immune environments [14].

This evidence suggests that the immune system may function as an important interface between systemic stress physiology and local tumour biology. Such an interpretation differs from a simple model in which trauma directly suppresses immunity and therefore produces cancer. Instead, chronic adversity may alter the regulatory conditions under which immune surveillance occurs, while genetic susceptibility, hormonal exposure, ageing, metabolic health, environmental factors, and tumour characteristics simultaneously determine the biological outcome.

This distinction is particularly important for breast cancer because the disease is molecularly and immunologically heterogeneous. Different breast-cancer subtypes possess different tumour microenvironments and immune profiles, meaning that the biological consequences of stress cannot reasonably be assumed to be uniform across all women.

The evidence therefore supports immune dysregulation as a candidate component of cumulative biological embedding, particularly in relation to tumour progression and immune–tumour interactions. Whether such alterations materially increase the probability of breast-cancer initiation following trauma remains unresolved and should be examined through prospective studies incorporating repeated measures of stress exposure, immune function, tumour biomarkers, and established cancer-risk determinants [14].

Oxidative Stress as a Convergence Mechanism

Oxidative stress represents a further mechanism through which multiple physiological systems may converge. Reactive oxygen species (ROS) are continuously generated during normal cellular metabolism and perform important functions in signalling, host defence, and cellular regulation. Under physiological conditions, antioxidant systems maintain an appropriate balance between oxidant production and neutralisation. Oxidative stress occurs when this balance is disrupted sufficiently to produce cellular damage.

The relevance of oxidative stress to cancer biology arises from its potential effects on DNA, proteins, lipids, mitochondrial function, and cellular signalling. Persistent oxidative imbalance can increase molecular damage and interfere with genomic maintenance and repair. Because genomic stability is central to preventing malignant transformation, oxidative stress has become an important area of investigation within cancer biology [15].

The relationship between psychological stress and oxidative biology is more complex. Chronic activation of stress-responsive systems may influence metabolic activity, mitochondrial function, inflammatory signalling, and antioxidant capacity. At the same time, inflammatory processes themselves can generate reactive oxygen species. Consequently, oxidative stress may represent a downstream convergence point through which endocrine, inflammatory, metabolic, and behavioural processes interact rather than an isolated consequence of psychological trauma.

This distinction is important because oxidative stress is influenced by a wide range of established and non-psychological exposures. Ageing, obesity, tobacco exposure, alcohol consumption, physical inactivity, nutritional status, environmental pollutants, infection, metabolic disease, and medication use can all alter oxidative balance. Any attempt to attribute oxidative damage specifically to trauma must therefore account for these competing influences.

Within breast cancer, oxidative processes have been implicated in genomic instability, altered cellular signalling, proliferation, apoptosis, angiogenesis, and interactions within the tumour microenvironment. These observations establish the biological

importance of oxidative stress to carcinogenesis, but they do not establish that trauma-induced oxidative stress causes breast cancer. Current evidence linking psychological stress to cancer remains substantially stronger for certain biological and tumour-progression mechanisms than for a direct pathway from trauma exposure to cancer initiation.

The more useful contribution of oxidative biology to the present framework is therefore conceptual. Oxidative stress may provide a cellular-level convergence point linking prolonged neuroendocrine activation, inflammatory activity, metabolic disturbance, sleep disruption, and health behaviours. This possibility warrants further investigation because it may help explain how relatively modest disturbances across several physiological systems could accumulate over time [16].

Rather than proposing oxidative stress as another independent pathway from trauma to breast cancer, this review positions it as one component of an interconnected biological network. Such a model is consistent with the broader concept of biological embedding, in which repeated environmental experiences are incorporated into physiological regulation through interacting rather than isolated processes.

Epigenetic Regulation and the Biological Embedding of Adversity

Epigenetic regulation provides a particularly important theoretical bridge between lived experience and long-term biological function. Unlike genetic mutations, epigenetic processes can modify gene expression without changing the underlying DNA sequence. DNA methylation, histone modification, chromatin remodelling, and non-coding RNA regulation contribute to the regulation of gene accessibility and transcription.

Interest in epigenetic mechanisms within trauma research has emerged partly because they offer a potential explanation for how environmental experiences may become biologically persistent. Studies of childhood adversity and chronic stress have identified alterations in DNA methylation and other regulatory processes involving genes associated with stress regulation, immune function, inflammation, and neurobiological development. Evidence for biological embedding is therefore increasingly plausible, particularly in relation to early-life adversity.

The glucocorticoid receptor system has received particular attention because changes in the regulation of glucocorticoid-related genes may influence subsequent stress responsiveness. However, findings across human studies are heterogeneous. Differences in tissue sampled, developmental stage, timing and type of adversity, age, sex, ancestry, environmental exposure, health status, and analytical methods make it difficult to identify a single epigenetic signature of trauma [17].

Epigenetic mechanisms are also central to breast-cancer biology. Aberrant DNA methylation, histone modification, chromatin regulation, and non-coding RNA activity can influence genes involved in cell proliferation, apoptosis, DNA repair, differentiation, and tumour suppression. Consequently, the intersection between stress-related epigenetic regulation and breast-cancer biology is biologically plausible.

Nevertheless, the critical scientific gap lies between these two bodies of evidence. Demonstrating that trauma is associated with epigenetic changes does not demonstrate that those changes subsequently produce breast cancer. Similarly, identifying epigenetic alterations within breast tumours does not demonstrate that psychological adversity caused those alterations. Tissue specificity and temporal ordering are particularly important problems because epigenetic profiles differ across tissues and can change throughout the lifespan.

The strongest interpretation is therefore that epigenetic regulation represents a candidate mechanism of biological memory rather than a demonstrated molecular pathway from trauma to breast cancer. Recent work examining stress and breast cancer has similarly characterised epigenetic findings as hypothesis-generating while emphasising that direct causal evidence remains insufficient.

This distinction also prevents an overly deterministic interpretation of epigenetics. Epigenetic regulation is dynamic and responsive to developmental, environmental, metabolic, behavioural, and therapeutic influences [18]. The presence of a stress-associated epigenetic alteration should therefore not be interpreted as an irreversible biological imprint or as evidence that an individual is destined to develop disease.

Within the present framework, epigenetic regulation is best understood as one possible component of biological embedding, through which repeated experiences may influence the regulation of physiological systems over time. Its importance lies not in providing a single explanation for trauma-related disease, but in potentially linking environmental exposure with changes in neuroendocrine regulation, immune function, inflammation, metabolism, and cellular maintenance.

Integrating the Biological Pathways: From Isolated Mechanisms to Cumulative Biological Embedding

The mechanisms described above should not be interpreted as independent pathways operating sequentially from trauma to breast cancer. A more appropriate interpretation is that chronic adversity may influence several regulatory systems simultaneously, with changes in one system feeding back into others.

For example, prolonged stress exposure may alter HPA-axis and sympathetic activity. These neuroendocrine changes may influence immune regulation and inflammatory signalling. Inflammatory and metabolic changes may increase oxidative activity, while oxidative processes may further modify inflammatory signalling and cellular stress responses. Epigenetic regulation may influence the persistence or adaptation of some of these responses. At the same time, trauma-related changes in sleep, physical activity, nutrition, substance use, social relationships, and healthcare engagement may modify the same biological systems.

The resulting model is therefore better represented as a network of interacting adaptations than as a linear causal chain.

This distinction provides an important conceptual contribution to the literature. Existing research has frequently examined stress biology, inflammation, immune function, oxidative stress,

epigenetic regulation, or behavioural pathways separately. The present review instead proposes that their potential relevance to breast cancer should be considered within a common life-course framework of cumulative biological embedding. The framework does not claim that trauma independently causes malignancy. Rather, it proposes that repeated adversity may alter the physiological context in which established determinants of breast cancer operate.

These established determinants remain central. Genetic susceptibility, reproductive and hormonal factors, age, metabolic health, environmental exposures, lifestyle, and access to healthcare can influence breast-cancer risk independently of trauma. The proposed model therefore represents trauma and chronic stress as contextual modifiers of biological regulation, rather than replacements for conventional models of breast-cancer risk.

This distinction is particularly important given the current epidemiological evidence. A recent umbrella review incorporating more than four million participants found no statistically significant association between psychological stress and breast-cancer incidence overall, highlighting the gap between mechanistic plausibility and demonstrated population-level causation. The absence of a definitive epidemiological association does not invalidate mechanistic investigation; instead, it indicates that any effect is likely to be heterogeneous, context-dependent, mediated by multiple factors, or difficult to detect using conventional exposure measures.

Individual differences may therefore be central to understanding the relationship. The biological consequences of adversity are likely to depend on timing, duration, repetition, severity, developmental stage, social context, biological susceptibility, recovery opportunities, and protective resources. Two women exposed to apparently similar traumatic circumstances may consequently develop very different physiological adaptations and health trajectories.

The concept of biological embedding provides a useful framework for this heterogeneity. It allows trauma to be considered neither purely psychological nor independently carcinogenic, but as a form of lived experience capable of interacting with multiple biological regulatory systems across the life course [19]. Importantly, biological embedding should be understood as a process rather than a fixed biological state. Physiological systems remain responsive to environmental change, social support, health behaviours, treatment, and recovery.

The resulting hypothesis is therefore more precise than the proposition that "trauma causes breast cancer." The hypothesis is that cumulative adversity may contribute to a state of altered biological regulation in some women, and that this altered regulatory environment may interact with established breast-cancer determinants to influence susceptibility or disease trajectory. Whether, when, and in whom these interactions become clinically meaningful remains an empirical question.

Future research should consequently move beyond single biomarkers and isolated pathways. Prospective longitudinal studies should measure trauma exposure, stress appraisal, recovery, HPA-axis activity, autonomic regulation, inflammatory and immune markers, oxidative balance, metabolic indicators, epigenetic profiles, health behaviours, and established breast-cancer risk factors repeatedly across the life course. Such designs would allow investigators to determine whether biological changes precede disease, emerge as consequences of disease, or reflect common underlying exposures.

This systems-oriented approach may ultimately provide greater explanatory value than attempts to identify a single "trauma pathway" to breast cancer. It also creates opportunities for research into resilience and recovery by asking not only how adversity becomes biologically embedded, but also why many women exposed to substantial adversity do not develop breast cancer or other stress-related diseases [20].

DISCUSSION

The relationship between trauma, chronic stress, and breast cancer has generated increasing scientific interest over recent decades, reflecting a broader shift in health research towards understanding how psychosocial experiences become biologically embedded across the lifespan. The evidence reviewed in this paper suggests that trauma should not be conceptualised as an isolated psychological event, nor should breast cancer be interpreted through a purely biomedical lens. Rather, both exist within a complex network of interacting biological, behavioural, environmental, and social influences that collectively shape health over time. A consistent theme emerging from the literature is that no single biological mechanism adequately explains the potential relationship between trauma and breast cancer susceptibility. Instead, chronic adversity appears capable of influencing multiple physiological systems simultaneously. Persistent activation of the stress response affects neuroendocrine regulation, 21 immune function, inflammatory signalling, oxidative balance, metabolic processes, and patterns of gene regulation. These biological responses do not occur independently. They interact continuously throughout life, influencing one another through complex feedback mechanisms that are only beginning to be understood. This systems perspective offers an important conceptual shift. Traditional approaches to disease often seek individual causes that operate in relatively linear ways. The evidence reviewed here instead supports a network model in which cumulative physiological adaptation may gradually influence disease susceptibility. Within this framework, trauma is not regarded as a direct cause of breast cancer. Rather, repeated exposure to adversity may contribute to a biological environment characterised by persistent physiological dysregulation that interacts with established determinants of disease, including inherited genetic susceptibility, hormonal influences, reproductive history, ageing, environmental exposures, and lifestyle factors [21]. The concept of biological embedding provides a useful lens through which these observations may be interpreted. Experiences occurring throughout life, particularly during sensitive developmental periods, appear capable of producing lasting physiological adaptations that extend well beyond the immediate psychological response to adversity. These adaptations reflect the remarkable capacity of human biology to respond to

environmental conditions. Although such changes are often protective in the context of survival, prolonged activation of these adaptive processes may carry unintended consequences for long-term health. This perspective reframes trauma not as an event confined to memory but as an experience that may influence biological regulation across multiple organ systems for years or even decades. Importantly, the available evidence remains insufficient to support causal conclusions. While numerous studies have demonstrated associations between trauma, chronic stress, physiological dysregulation, and chronic disease, the pathway linking these observations to breast cancer development remains incompletely understood. Human populations experience trauma in highly diverse ways, making standardisation difficult across epidemiological studies. Definitions of trauma differ considerably, biological responses vary between individuals, and many investigations rely on retrospective self-report measures that are vulnerable to recall bias. Furthermore, breast cancer itself represents a heterogeneous group of diseases with distinct molecular characteristics, suggesting that psychosocial influences may differ across tumour subtypes. Several methodological limitations continue to challenge this field. Many existing studies are cross-sectional, preventing conclusions regarding temporal relationships between trauma exposure and biological change. Sample sizes are frequently modest, follow-up periods vary considerably, and biological markers are often measured at a single point in time despite the 22 dynamic nature of stress physiology. Confounding variables, including socioeconomic disadvantage, obesity, physical activity, reproductive history, healthcare access, and comorbid medical conditions, further complicate interpretation. Future research will benefit from prospective longitudinal studies capable of examining cumulative trauma exposure alongside repeated biological measurements across extended periods. The findings of this review also have important implications for women's healthcare. Trauma-informed care has become increasingly recognised within mental health, primary care, and obstetric services, yet its integration within cancer prevention and oncology remains relatively limited. Recognising the potential influence of chronic stress on health does not imply that every woman with a history of trauma is at increased risk of breast cancer, nor does it suggest that psychosocial interventions can prevent malignancy in isolation. Rather, it supports a more holistic understanding of health in which emotional wellbeing, social context, physiological regulation, and preventive healthcare are viewed as interconnected components of comprehensive patient care. From a public health perspective, these findings reinforce the importance of prevention across the life course. Reducing childhood adversity, preventing gender-based violence, improving access to mental health services, addressing financial insecurity, and promoting trauma-informed healthcare may produce health benefits that extend far beyond psychological wellbeing alone. Although direct effects on breast cancer incidence remain to be established, such interventions have well-documented benefits for numerous chronic diseases and represent important investments in population health. Taken together, the current evidence supports neither dismissal nor exaggeration of the relationship between trauma and breast cancer. Instead, it encourages a more nuanced understanding of disease that acknowledges the complex interplay between biological susceptibility and lived experience. Future advances will likely emerge not from attempts to identify a single causal pathway but from increasingly sophisticated models capable of integrating genetics, endocrinology, immunology, neuroscience, behavioural science, and the social determinants of health into a unified understanding of women's health across the life course.

PROPOSED CONCEPTUAL FRAMEWORK

The evidence examined throughout this review suggests that the relationship between trauma, chronic stress, and breast cancer cannot be explained by a single biological mechanism. Instead, current research supports a multidimensional model in which prolonged exposure to adversity influences several interconnected physiological systems that collectively shape health over time. 23 While each pathway has been investigated independently, fewer attempts have been made to integrate these mechanisms into a single explanatory framework. Figure 1 presents a conceptual synthesis of the evidence reviewed in this paper. Rather than proposing a causal model, the framework illustrates how traumatic experiences may contribute to cumulative physiological adaptation through interacting neuroendocrine, immunological, inflammatory, oxidative, epigenetic, and behavioural pathways. These processes are presented as dynamic and reciprocal, recognising that alterations within one biological system frequently influence multiple others. The framework also acknowledges that these pathways operate alongside established determinants of breast cancer, including inherited genetic susceptibility, reproductive history, hormonal influences, ageing, environmental exposures, and lifestyle factors. At the centre of the model is the concept of biological embedding. Repeated exposure to adversity may result in persistent activation of stress-responsive systems, leading to long-term physiological adaptations that extend beyond the original traumatic experience. Dysregulation of the hypothalamic-pituitary-adrenal axis, chronic low-grade inflammation, altered immune surveillance, oxidative stress, and epigenetic regulation are not viewed as isolated mechanisms but as components of an integrated biological response to prolonged stress. Behavioural adaptations, including changes in sleep, physical activity, nutrition, healthcare engagement, and substance use, may further influence these biological processes through continuous feedback loops. Importantly, the proposed framework does not suggest that trauma independently causes breast cancer. Rather, it illustrates how trauma-related physiological adaptations may contribute to a broader biological environment that interacts with recognised genetic, hormonal, environmental, and behavioural determinants of disease. Individual susceptibility is likely to differ considerably according to the timing, duration, and severity of trauma exposure, together with protective factors such as social support, resilience, healthcare access, and opportunities for recovery. The framework is intended to serve as a guide for future research rather than as a definitive model of disease development [22]. It highlights opportunities for interdisciplinary investigation by bringing together evidence from oncology, psychoneuroimmunology, neuroscience, endocrinology, behavioural medicine, and women's health. Future longitudinal

studies incorporating repeated biological measurements, psychosocial assessments, and molecular biomarkers will be essential to evaluate the relationships proposed within this framework and to determine how these pathways contribute to breast cancer susceptibility across the life course.

STRENGTH OF THE CURRENT EVIDENCE

The body of literature examining the relationship between trauma, chronic stress, and breast cancer has expanded considerably over the past three decades. Collectively, the evidence supports the conclusion that trauma is associated with measurable alterations across multiple biological systems, including neuroendocrine regulation, immune function, inflammatory signalling, oxidative balance, and behavioural health [23]. These physiological changes are well documented and have been replicated across numerous populations and study designs. Consequently, there is strong evidence that chronic adversity has important implications for long-term biological functioning. The evidence becomes more nuanced when examining breast cancer specifically. Individual biological pathways such as chronic inflammation, immune dysregulation, and epigenetic modification are recognised contributors to carcinogenesis and tumour progression. Similarly, substantial evidence supports associations between chronic stress and many of these physiological processes. However, demonstrating that trauma-related biological alterations directly increase breast cancer risk has proven considerably more challenging. Most available studies report associations rather than causal relationships, and relatively few investigations have followed women prospectively from trauma exposure through to cancer diagnosis while simultaneously measuring biological changes over time. Current evidence therefore supports biological plausibility rather than biological certainty. The mechanisms reviewed throughout this paper provide credible explanations for how trauma may contribute to disease susceptibility, yet the precise contribution of each pathway remains difficult to quantify. The interaction of genetic predisposition, reproductive history, hormonal influences, ageing, environmental exposures, lifestyle factors, and psychosocial experiences makes it unlikely that any single mechanism will fully explain breast cancer development. An additional challenge lies in the heterogeneity of trauma itself. Childhood adversity, interpersonal violence, bereavement, financial hardship, discrimination, and chronic caregiving each differ in duration, severity, developmental timing, and psychological impact. It should not be assumed that all traumatic experiences produce equivalent biological responses. Greater precision in trauma measurement will therefore be essential for advancing future research. Overall, the available literature provides compelling justification for continued investigation while also emphasising the importance of scientific caution. The evidence is sufficiently robust to support further interdisciplinary research but not sufficiently definitive to support causal conclusions.

CHALLENGES IN ESTABLISHING CAUSALITY

Determining whether trauma contributes directly to breast cancer risk remains methodologically complex. Unlike many traditional biomedical risk factors, trauma cannot be experimentally assigned, and researchers must rely primarily on observational study designs. Although such studies provide valuable insights, they are inherently limited in their ability to establish causation. One of the principal challenges is the extended latency period associated with breast cancer. Tumour development may occur over several decades, making it difficult to identify the precise contribution of exposures experienced during childhood, adolescence, or early adulthood. Biological adaptations occurring across the lifespan are themselves dynamic and may change considerably before disease becomes clinically apparent. Measurement of trauma presents an additional source of uncertainty. Studies vary widely in their definitions of trauma, methods of assessment, and thresholds for determining exposure. Some rely upon retrospective self-report questionnaires, whereas others use structured clinical interviews or documented adverse experiences. These methodological differences contribute to inconsistencies across studies and complicate direct comparisons between findings. Residual confounding also remains an important consideration. Trauma frequently coexists with socioeconomic disadvantage, limited healthcare access, reduced educational opportunity, chronic illness, environmental exposures, and behavioural risk factors that independently influence breast cancer risk. Although many studies attempt to adjust for these variables statistically, complete separation of these interacting influences is rarely possible. Publication bias represents another potential limitation. Studies reporting significant associations are generally more likely to be published than studies reporting null findings, potentially influencing perceptions of the overall evidence base. Equally important is the growing recognition that resilience, protective relationships, and supportive environments may modify biological responses to trauma. Failure to account for these protective factors risks oversimplifying the relationship between adversity and disease. These challenges do not diminish the importance of the existing evidence. Rather, they highlight the need for increasingly sophisticated research designs capable of capturing the complexity of biological adaptation across the life course.

TRAUMA, RESILIENCE, AND BIOLOGICAL RECOVERY

An exclusive focus on trauma risks overlooking an equally important aspect of human biology: the capacity for recovery. Although prolonged adversity may influence physiological regulation, biological adaptation is not synonymous with irreversible damage [24]. Considerable evidence demonstrates that many individuals exposed to significant trauma maintain good physical health throughout life, while others experience meaningful biological recovery following improvements in safety, social connection, and psychological wellbeing. Resilience should not be viewed as a fixed personality trait possessed by only a minority of individuals. Rather, it emerges through dynamic interactions between biological, psychological, social, and environmental factors. Secure interpersonal relationships, community support, stable housing, financial security, regular physical activity, restorative sleep, balanced nutrition, access to healthcare, and effective psychological interventions each contribute to resilience by reducing chronic activation of stress-responsive systems. Emerging evidence suggests that several

biological processes discussed throughout this review may retain considerable plasticity. Improvements in inflammatory regulation, neuroendocrine function, immune activity, and even selected epigenetic markers have been reported following interventions that reduce chronic stress or improve overall health. Although further research is required to determine the durability and clinical significance of these changes, such findings challenge deterministic interpretations of trauma biology and reinforce the importance of prevention and early intervention. Recognition of resilience also carries important implications for women's health. Many women experience adversity while simultaneously demonstrating extraordinary adaptive capacity through supportive relationships, caregiving, education, community engagement, and personal growth. Understanding why some individuals remain biologically resilient despite substantial adversity may ultimately prove as informative as understanding why others become more vulnerable to disease [25].

GLOBAL PERSPECTIVES AND RESEARCH GAPS

The majority of research examining trauma, chronic stress, and breast cancer has been conducted in high-income countries, particularly North America, Western Europe, and Australia. While these studies have contributed substantially to current understanding, they do not fully capture the diversity of women's lived experiences across different cultural, economic, and healthcare settings. 27 Women living in low- and middle-income countries frequently experience unique combinations of adversity, including poverty, food insecurity, political instability, limited access to healthcare, environmental hazards, forced migration, infectious disease burdens, and gender-based violence. These exposures may interact in ways that differ substantially from populations represented in existing research. Despite this, women from these regions remain markedly underrepresented in mechanistic studies investigating trauma-related biological pathways. African populations deserve particular attention. The continent experiences a growing burden of breast cancer alongside persistent social inequalities, yet relatively little research has explored how chronic adversity, structural inequity, and cumulative stress influence women's biological health within African contexts. Addressing this gap is essential for ensuring that future scientific understanding reflects global rather than predominantly Western experiences. Future research should also prioritise greater diversity with respect to ethnicity, socioeconomic status, geographical location, and life course experiences. Expanding participation across diverse populations will strengthen external validity and improve understanding of how trauma-related biological adaptations may differ according to cultural, environmental, and structural contexts [26].

FUTURE RESEARCH PRIORITIES

The complexity of the relationship between trauma and breast cancer demands equally sophisticated approaches to future investigation. Several priorities emerge from the current evidence. First, large prospective longitudinal studies are needed to examine trauma exposure before disease onset while incorporating repeated assessment of neuroendocrine, inflammatory, immune, metabolic, and epigenetic biomarkers. Such designs would strengthen understanding of temporal relationships that cannot be established through cross-sectional research. Second, greater consistency in measuring trauma is essential. The adoption of standardised and validated assessment instruments would improve comparability across studies and facilitate future evidence synthesis. Third, interdisciplinary collaboration should become the norm rather than the exception. Progress in this field will require expertise spanning oncology, neuroscience, endocrinology, immunology, psychology, epidemiology, behavioural science, and public health. 28 Fourth, greater attention should be given to resilience and recovery. Understanding the biological mechanisms that protect against long-term disease despite adversity may identify novel opportunities for prevention and intervention. Finally, future studies should investigate whether incorporating trauma history into women's preventive healthcare improves risk assessment, patient engagement, or health outcomes [27]. Such work should be undertaken cautiously and ethically, recognising that trauma history represents one component of a much broader clinical picture rather than an independent predictor of disease

TOWARDS A TRAUMA-INFORMED WOMEN'S HEALTH RESEARCH AGENDA

The evidence reviewed throughout this manuscript reflects a broader transformation occurring across biomedical science. Increasingly, health is understood not solely as the product of genetics or isolated environmental exposures, but as the consequence of continuous interactions between biology and lived experience. Trauma occupies an important place within this evolving perspective because it provides a model through which psychological, social, and environmental adversity may become biologically embedded over time. The next generation of women's health research should move beyond asking whether trauma influences disease. The more scientifically valuable question concerns how traumatic experiences interact with established biological determinants across different stages of life, within different populations, and under different environmental conditions [28]. Addressing this question will require research frameworks that integrate molecular biology, neuroscience, immunology, endocrinology, behavioural science, epidemiology, and the social determinants of health rather than considering these disciplines inperson-centred healthcare for women across the lifespan

CONCLUSION

The relationship between trauma, chronic stress, and breast cancer represents an evolving area of interdisciplinary research that challenges traditional distinctions between psychological experience and biological disease. Although breast cancer remains fundamentally influenced by 29 established genetic, hormonal, reproductive, environmental, and lifestyle determinants, growing evidence suggests that prolonged exposure to adversity may also contribute to biological processes relevant to carcinogenesis. Rather than acting through a single mechanism, trauma appears to influence multiple interconnected physiological systems, including neuroendocrine

regulation, immune surveillance, inflammatory signalling, oxidative stress, epigenetic regulation, and health-related behaviours. Together, these adaptations provide biologically plausible pathways through which chronic stress may influence disease susceptibility across the life course. At the same time, the available evidence requires careful interpretation. While substantial research demonstrates associations between trauma and dysregulation of stress-responsive biological systems, current evidence does not establish trauma as an independent cause of breast cancer. The complexity of breast cancer biology, the heterogeneity of traumatic experiences, methodological variation across studies, and the influence of numerous confounding factors all limit causal inference. These limitations should not be viewed as weaknesses of the field, but rather as reflections of the complexity of studying human health across biological, psychological, and social domains. This review contributes to the literature by integrating evidence from neuroscience, psychoneuroimmunology, oncology, endocrinology, behavioural science, and public health into a unified conceptual perspective. By synthesising these disciplines, it highlights how biological embedding may provide an important framework for understanding the long-term physiological consequences of adversity while recognising that these adaptations occur alongside, rather than in place of, established biomedical risk factors. The findings also reinforce the importance of adopting a life course approach to women's health. Experiences occurring during childhood, adolescence, and adulthood should be understood not only for their psychological significance but also for their potential influence on long-term physiological regulation. Such a perspective supports greater integration of trauma-informed principles within research, clinical practice, and public health without implying deterministic relationships between adversity and disease. Future progress will depend upon rigorous prospective longitudinal research incorporating standardised measures of trauma, repeated biological assessments, molecular biomarkers, and diverse populations that have historically been underrepresented in this field. Equally important will be interdisciplinary collaboration capable of integrating advances in molecular biology, neuroscience, epidemiology, immunology, behavioural medicine, and women's health. Ultimately, understanding how lived experience becomes biologically embedded represents one of the most important challenges in contemporary health science. Addressing this challenge has 30 the potential not only to deepen understanding of breast cancer susceptibility but also to reshape broader approaches to disease prevention, personalised medicine, and women's health across the lifespan.

CONFLICT of INTREST STATEMENT

Conflict of Interest: The author declares that there are no conflicts of interest associated with this manuscript.

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