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# Post-Mastectomy Pain Syndrome Following Breast Cancer Treatment: A Neuroimmune Disorder from an Integrative Oncology Perspective

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## Abstract

Post-mastectomy pain syndrome (PMPS) is a common and often disabling complication of breast cancer treatment that may persist long after surgical recovery and substantially impair quality of life among survivors. Recent estimates suggest that PMPS affects approximately 20–68% of women following breast surgery, with significant long-term consequences for physical functioning, sleep quality, emotional well-being, and participation in daily activities [1-3]. Historically, PMPS has been conceptualized primarily as a localized postsurgical neuropathic condition resulting from peripheral nerve injury sustained during breast surgery [4].

However, growing evidence indicates that persistent pain following mastectomy reflects a more complex and enduring condition that extends beyond peripheral nerve damage alone. Sustained immune activation, chronic neuroinflammation, microglial dysregulation, central sensitization, and altered neuroendocrine stress-response signaling appear to play central roles in pain persistence, consistent with mechanisms described in chronic postsurgical and cancer-related pain states [5-7].

From an integrative oncology perspective, PMPS may be more accurately understood as a neuroimmune disorder arising from the convergence of peripheral nerve injury, persistent inflammatory signaling, disruption of the local tissue microenvironment following surgery or radiation therapy, and maladaptive central nervous system plasticity [2,3,8]. Drawing on contemporary literature from pain neuroscience, immunology, neuroendocrinology, and cancer survivorship research, this article synthesizes key biological mechanisms implicated in persistent post-mastectomy pain. These include cytokine-mediated nociceptor sensitization, microglial activation and glial–neuronal crosstalk, impaired neural repair processes, autonomic nervous system dysregulation, and sleep disturbance, all of which contribute to pain chronification [5,8-10].

By integrating these mechanisms within a unified neuroimmune framework, this review provides a clinically relevant conceptual foundation for mechanism-informed, multimodal, and opioid-sparing approaches to PMPS management [6,11]. Reframing PMPS in this manner may help guide future research priorities, inform clinical innovation, and support the development of individualized, integrative strategies that more fully address the multidimensional biological and psychosocial burden of chronic pain in breast cancer survivorship [3,12].

**Keywords: Post-mastectomy pain syndrome; Breast cancer survivorship; Neuroimmune dysregulation; Central sensitization; Integrative oncology; Multimodal pain management; Opioid-sparing strategies**

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## Introduction

post-mastectomy pain syndrome (PMPS) is a common and often debilitating complication of breast cancer treatment, affecting a substantial proportion of survivors long after the completion of surgery, radiation therapy, and systemic therapies. Contemporary studies estimate that PMPS occurs in approximately 20–68% of women following breast cancer surgery, with many patients reporting persistent symptoms months to years after initial treatment [1-3]. As breast cancer survival continues to improve, PMPS has emerged as a major contributor to long-term morbidity within survivorship populations, aligning with guidelines that increasingly emphasize the enduring

burden of chronic symptoms and quality-of-life impairment among long-term breast cancer survivors [13].

Persistent post-mastectomy pain is associated with substantial impairments in physical functioning, sleep quality, emotional well-being, and participation in daily activities [14,15]. Many survivors' report difficulty returning to work, maintaining physical activity, and fully engaging in social and family roles, underscoring the profound functional and psychosocial consequences of this condition. Despite advances in surgical techniques, perioperative pain management, and adjuvant oncologic therapies, PMPS remains a largely unmet challenge in survivorship care, with many patients experiencing incomplete or unstained pain relief using conventional treatment approaches [3,16]. This persistent gap in effective long-term pain control has contributed to growing interest in integrative and multimodal approaches to cancer pain management that extend beyond isolated pharmacologic or procedural interventions [17].

Historically, PMPS has been conceptualized primarily as a localized neuropathic pain condition attributed to intraoperative nerve injury, scar formation, or mechanical irritation of peripheral nerves during breast surgery [4]. While peripheral nerve trauma clearly contributes to symptom onset, this nerve-centric framework does not adequately explain the marked clinical heterogeneity of PMPS, the frequent mismatch between symptom severity and structural findings, or the persistence of pain long after apparent tissue healing. Increasing evidence from chronic postsurgical pain research suggests that ongoing pain may reflect failures of resolution and maladaptive neuroplasticity rather than continued peripheral nerve damage alone [7,8]. Continued reliance on narrowly peripheral explanations may therefore limit both clinical understanding and therapeutic effectiveness, particularly in patients with complex or treatment-refractory symptoms.

Emerging literature supports a broader conceptualization of PMPS as a dynamic and evolving sustained inflammatory signaling, immune dysregulation, maladaptive central nervous system plasticity, and altered neuroendocrine stress-response pathways. Neuroimmune mechanisms—including central sensitization, glial activation, and cytokine-mediated amplification of nociceptive signaling—have been implicated across diverse chronic pain states and are increasingly recognized as relevant to cancer-related and postsurgical pain syndromes [5,18]. Dysregulation of hypothalamic–pituitary–adrenal axis signaling and autonomic stress responses may further contribute to pain persistence by impairing endogenous pain modulation, prolonging immune activation, and delaying resolution of inflammatory processes [14]. In cancer populations, chronic stress has been linked to biologically meaningful alterations in neuroendocrine and immune signaling that influence treatment outcomes and long-term recovery trajectories, underscoring the clinical relevance of stress-mediated neuroimmune dysregulation in survivorship contexts [19].

Clinical observations further reinforce this expanded view. Breast cancer survivors who experience postoperative complications—including surgical site infection, delayed wound healing, radiation-induced tissue injury, lymphedema, or reconstructive complications—appear to be at heightened risk for the development and persistence of chronic post-mastectomy pain [1,2,20]. These clinical contexts are characterized by prolonged immune activation, disruption of the local tissue microenvironment, and sustained nociceptive input, which may promote maladaptive neuroimmune signaling, glial activation, and central sensitization, thereby facilitating pain chronification and treatment resistance [8,16].

Importantly, the present work does not introduce new primary clinical or experimental data. Rather, its contribution lies in the integrative synthesis of existing evidence across pain neuroscience, immunology, neuroendocrinology, and cancer survivorship research to advance a unified neuroimmune conceptual framework for PMPS. By explicitly integrating these domains, this review seeks to clarify mechanisms of pain chronification, account for clinical heterogeneity and treatment resistance, and provide a biologically grounded foundation for mechanism-informed, multimodal, and integrative approaches to PMPS management.

Taken together, these findings support growing recognition that PMPS may be more accurately conceptualized as a neuroimmune disorder rather than purely peripheral neuropathy. From an integrative oncology perspective, PMPS can be understood as a condition driven by dynamic interactions among peripheral nerve injury, immune and glial activation, neuroendocrine stress responses, and central pain amplification mechanisms [5,6]. This framework is particularly well suited to survivorship care, where patients are often presented with overlapping biological, psychological, and treatment-related vulnerabilities that are not readily addressed by single-mechanism interventions. Reframing PMPS in this way carries important implications for research design, risk stratification, and clinical management, supporting the development of mechanism-based, multimodal, and compassionate care strategies that better reflect the complexity of breast cancer survivorship [12].

## Conceptual Framework: A Neuroimmune Model of Post-Mastectomy Pain Syndrome

Building on the limitations of peripheral nerve–centric models outlined above, this article proposes a unifying conceptual framework that reframes post-mastectomy pain syndrome (PMPS) as a neuroimmune disorder rather than a purely localized neuropathy. This framework is intended as a hypothesis-generating synthesis that integrates established findings from pain neuroscience, immunology, neuroendocrinology, and cancer survivorship research to explain the persistence of pain, marked clinical heterogeneity, and limited durability of conventional treatment approaches observed in many breast cancer survivors. Contemporary pain science increasingly characterizes chronic pain as a disorder of maladaptive system-level regulation rather than a consequence of ongoing structural injury alone, particularly in postsurgical and cancer-related contexts [5,6,8]. Survivorship research further emphasizes that persistent pain after cancer treatment often reflects intertwined biological, psychological, and social processes that extend beyond traditional biomedical definitions of pain [21].

Central to this framework is a shift in clinical reasoning away from isolated tissue or nerve damage and toward dynamic interactions among four interrelated domains: persistent immune activation, maladaptive central nervous system plasticity, dysregulation of autonomic and neuroendocrine stress-response systems, and sustained nociceptive input from the peripheral and local tissue environment. Neuroimmune processes such as prolonged inflammatory signaling, glial activation, and central sensitization have been implicated across diverse chronic pain conditions and provide a biologically plausible explanation for pain persistence following mastectomy, even in the absence of ongoing peripheral

pathology [5,7,18]. Advances in neuroplasticity research further support the concept that chronic pain reflects enduring alterations in neural networks governing sensory processing, affective regulation, and threat appraisal, reinforcing pain states long after apparent tissue healing has occurred [22].

Within this model, dysregulation of neuroendocrine stress systems—including hypothalamic–pituitary–adrenal axis signaling and autonomic tone—plays a modulatory role by impairing endogenous pain inhibition, amplifying immune activation, and delaying resolution of inflammatory processes [14]. These mechanisms are particularly relevant in breast cancer populations, where cumulative treatment exposures, psychosocial stressors, and survivorship-related uncertainty may contribute to sustained stress-system activation. In this context, neuroimmune and neuroendocrine dysregulation may act synergistically to reinforce central sensitization and promote pain chronification.

Importantly, this framework is tailored to the clinical realities of PMPS. Breast cancer survivors frequently encounter postoperative and treatment-related complications—such as surgical site infection, delayed wound healing, radiation-induced tissue injury, lymphedema, and reconstructive complications—that are characterized by prolonged immune activation and disruption of the local tissue microenvironment. These peripheral processes can serve as ongoing sources of nociceptive and inflammatory signaling, which, when coupled with central and stress-system vulnerability, may accelerate maladaptive neuroimmune signaling and increase the likelihood of persistent pain [8,16]. This convergence of peripheral insult, immune dysregulation, and central plasticity distinguishes PMPS from many other chronic pain syndromes and underscores the need for a condition-specific neuroimmune model.

By conceptualizing PMPS as a neuroimmune disorder, this framework supports mechanism-informed, multimodal, and opioid-sparing approaches to pain management that are aligned with survivorship priorities and whole-person oncology care. Rather than focusing exclusively on symptom suppression, the model emphasizes restoration of functional capacity, sleep regulation, emotional well-being, and system-level resilience as meaningful therapeutic targets. This orientation is consistent with contemporary integrative oncology guidelines and survivorship-focused pain care models that advocate coordinated, evidence-based strategies for managing cancer- and treatment-related pain [12,23].

While not intended as a definitive explanatory model, the framework presented here provides a structured foundation for future research and clinical innovation. By explicitly integrating neuroimmune, neuroendocrine, and survivorship perspectives, it aims to guide more nuanced clinical assessment, inform individualized treatment strategies, and support more compassionate and durable approaches to care for individuals living with persistent pain after breast cancer treatment.

## Proposed Neuroimmune Pathophysiology of Post-Mastectomy Pain Syndrome

Post-mastectomy pain syndrome (PMPS) emerges from the convergence of multiple biological processes that extend beyond isolated peripheral nerve injury. Surgical trauma initiates nociceptive signaling through direct nerve damage accompanied by local inflammation, cytokine release, oxidative stress, and immune-cell recruitment within the surgical field [2,3]. While this inflammatory response typically resolves with tissue healing, a clinically meaningful subset of patients—particularly those who experience postoperative complications such as infection, delayed wound healing, radiation-induced tissue injury, or lymphedema—develop persistent inflammatory signaling that fails to resolve appropriately. This prolonged inflammatory state sustains nociceptive input and promotes peripheral sensitization, facilitating the transition from acute postoperative pain to chronic pain states. Increasingly, this process is understood as pain chronification rather than a marker of ongoing tissue pathology [7,8,24].

At the peripheral level, sustained release of pro-inflammatory mediators—including tumor necrosis factor-α, interleukins, prostaglandins, and reactive oxygen species—lowers nociceptor activation thresholds and may induce spontaneous or ectopic neural firing. These molecular changes increase the excitability of primary afferent neurons and amplify nociceptive signaling from the surgical site [5,25]. Experimental and translational models further demonstrate that persistent immune–neuronal interactions can induce hyperalgesic priming, a state in which prior inflammatory or injury-related insults sensitize nociceptive pathways and predispose individuals to exaggerated and prolonged pain responses following subsequent stimuli [26]. Sustained afferent input from sensitized peripheral nerves thus serves as a critical driver of downstream central nervous system adaptations, promoting the progression from acute postoperative pain to chronic neuropathic pain phenotypes [24,26].

Within the central nervous system, ongoing nociceptive input promotes activation of microglia and astrocytes within the spinal dorsal horn and higher-order pain-processing regions. Activated glial cells release pro-inflammatory cytokines, chemokines, brain-derived neurotrophic factors, and excitatory neurotransmitters, which collectively enhance synaptic transmission, suppress inhibitory signaling, and reinforce central sensitization [5,27]. In parallel, network-level neuroplastic changes alter functional connectivity across cortical and subcortical regions involved in sensory discrimination, affective regulation, and cognitive appraisal of pain [28]. Clinically, these central adaptations manifest as allodynia, hyperalgesia, expansion of pain fields, and persistence of pain in the absence of ongoing tissue injury—features characteristic of centrally mediated pain amplification rather than unresolved peripheral pathology [18].

Neuroimmune signaling in PMPS is further shaped by dysregulation of neuroendocrine and autonomic stress-response pathways. Chronic pain, cancer treatment exposures, and psychosocial stressors can disrupt hypothalamic–pituitary–adrenal axis function and autonomic balance, leading to altered cortisol signaling and impaired immune regulation. These changes weaken endogenous pain-modulating systems and interfere with physiologic mechanisms that normally constrain inflammation and support recovery [14,18]. Emerging evidence suggests that pain and autonomic regulation share overlapping central compensatory pathways, reflected in consistent alterations in heart rate variability across chronic pain conditions [29]. Sleep disturbance—highly prevalent among breast cancer survivors—further exacerbates pain persistence by amplifying pain perception and impairing restorative neurophysiologic processes [10]. Preclinical models demonstrate that spontaneous nociceptor activity can directly fragment non–rapid eye movement sleep, thereby reinforcing neuroimmune dysregulation and sustaining chronic pain states [30].

Importantly, PMPS is also shaped by abnormalities within the local tissue microenvironment. Conditions such as lymphedema, fibrosis, radiation-induced injury, and impaired wound healing perpetuate mechanical stress and inflammatory signaling around vulnerable neural structures, reinforcing peripheral nociceptive input [2,3]. These peripheral factors interact bidirectionally with central neuroimmune and stress-related mechanisms, sustaining maladaptive pain circuits and contributing to the marked clinical heterogeneity and treatment resistance observed among breast cancer survivors with PMPS.

Taken together, these observations support a unifying pathophysiologic model in which PMPS arises from sustained neuroimmune dysregulation across peripheral, central, and systemic domains rather than from isolated nerve injury alone [5,8]. Conceptualizing PMPS through this lens provides a biologically coherent rationale for therapeutic strategies that extend beyond single-target symptom suppression and instead address immune signaling, glial activation, neural plasticity, autonomic balance, sleep regulation, and psychosocial contributors to pain. This approach aligns with contemporary calls for mechanism-based, multimodal, and integrative strategies for managing chronic neuropathic pain in cancer survivorship [12,23].

## Neuroimmune Mechanisms Contributing to Persistent Post-Mastectomy Pain

While the preceding section outlined the broader neuroimmune pathophysiologic trajectory of post-mastectomy pain syndrome (PMPS), the present section focuses on specific neuroimmune mechanisms that actively sustain pain persistence once chronification has occurred. Rather than reiterating the full peripheral-to-central cascade, this section highlights discrete immune, glial, and neural network processes that help explain why pain becomes self-perpetuating, clinically heterogeneous, and resistant to conventional interventions in a subset of breast cancer survivors.

PMPS has historically been attributed to peripheral nerve injury incurred during breast cancer surgery, particularly involving the intercostobrachial and adjacent sensory nerves [2,3]. Surgical evidence demonstrates that operative handling of these nerves—including preservation, dissection, or reconstruction—can significantly influence postoperative pain outcomes, underscoring nerve injury as an important initiating factor rather than the sole determinant of chronic pain [31,32]. Increasing evidence from chronic postsurgical pain research indicates that long-term pain persistence reflects maladaptive neuroimmune signaling and central nervous system adaptations rather than unresolved structural injury alone [7,24].

At the peripheral neuroimmune interface, dysregulated inflammatory signaling plays a key role in maintaining nociceptive drive. Pro-inflammatory mediators—including tumor necrosis factor-α, interleukins, prostaglandins, and reactive oxygen species—lower nociceptor activation thresholds and promote spontaneous or ectopic neural firing, thereby amplifying peripheral nociceptive input [5,25]. Failure of endogenous resolution pathways, including specialized pro-resolving mediator signaling, may further sustain inflammatory activity and prolong neuroimmune activation in chronic pain states [33]. Experimental and translational studies demonstrate that persistent immune–neuronal interactions can induce hyperalgesic priming, a state in which prior inflammatory or injury-related insults sensitize nociceptive pathways and predispose individuals to exaggerated and prolonged pain responses following subsequent stimuli [26]. These mechanisms are particularly relevant in PMPS patients with ongoing tissue stressors such as radiation injury, lymphedema, or delayed wound healing [3,20].

Within the central nervous system, sustained peripheral input facilitates activation of microglia and astrocytes within the spinal dorsal horn and higher-order pain-processing regions. Activated glial cells release pro-inflammatory cytokines, chemokines, brain-derived neurotrophic factors, and excitatory neurotransmitters, which enhance excitatory synaptic transmission, suppress inhibitory signaling, and reinforce maladaptive synaptic plasticity [5,27]. These processes contribute to central sensitization, a core neuroimmune mechanism underlying persistent pain amplification. Importantly, emerging human studies demonstrate that chronic pain states can be predicted using intracranial neural biomarkers, supporting the concept that persistent pain reflects a stable and identifiable brain network state rather than ongoing peripheral pathology [34]. Complementary work has linked chronic pain to increased neural entropy within prefrontal cortical networks, suggesting disorganized information processing and impaired top-down modulation in regions critical for pain regulation and affective integration [35].

Clinical expression of these central neuroimmune changes includes allodynia, hyperalgesia, expansion of pain fields, and pain intensity disproportionate to peripheral finding features commonly reported in refractory PMPS. Increasingly, such features are identifiable through structured diagnostic frameworks and quantitative sensory testing approaches applied to cancer-related pain populations [18,36]. These findings further support the view that persistent PMPS reflects centrally mediated pain amplification rather than ongoing tissue injury.

Neuroimmune mechanisms in PMPS are further modulated by psychosocial and survivorship-related factors. Psychological stress, mood disturbances, and trauma-related experiences—highly prevalent among breast cancer survivors—interact bidirectionally with immune regulation and pain-processing systems through shared neuroimmune pathways [37,38]. In parallel, treatment-related factors such as radiation exposure, infection, delayed wound healing, lymphedema, and reconstructive complications can prolong inflammatory signaling and disrupt the local tissue microenvironment, reinforcing maladaptive peripheral–central feedback loops [2,3,20]. Together, these interacting biological and psychosocial influences help explain the marked clinical heterogeneity and treatment resistance observed in PMPS populations [16].

Taken together, this mechanistic evidence supports recognition of PMPS as a multisystem pain disorder sustained by interacting immune, glial, neural network, endocrine, autonomic, and psychosocial mechanisms rather than a condition driven solely by peripheral nerve injury. By delineating specific neuroimmune processes that maintain pain persistence, this section complements the broader pathophysiologic framework and reinforces the rationale for mechanism-informed, multimodal approaches that address immune signaling, central sensitization, neuromodulatory pathways, and system-level dysregulation in parallel [5,7,8,39].

## Peripheral Immune Activation and Sustained Inflammatory Signaling

While earlier sections describe the initiation and central amplification of post-mastectomy pain syndrome (PMPS), this

section focuses specifically on peripheral immune mechanisms that maintain nociceptive signaling once pain has become persistent. In this maintenance phase, unresolved inflammatory activity within the local tissue microenvironment continues to reinforce nociceptor sensitization and provide ongoing input to central pain circuits, even in the absence of overt tissue pathology.

Following mastectomy, surgical injury initiates an acute inflammatory response characterized by the release of pro-inflammatory cytokines, chemokines, and danger-associated molecular patterns (DAMPs) that activate innate immune pathways and sensitize peripheral nociceptors [24,25]. DAMPs released from injured or stressed cells are recognized by pattern-recognition receptors, including toll-like receptors, thereby amplifying sterile inflammatory signaling in the postoperative setting [40,41]. Under normal healing conditions, this inflammatory response resolves as tissue repair progresses. However, postoperative complications—including infection, delayed wound healing, radiation exposure, and lymphatic disruption—may prolong immune activation and interfere with appropriate inflammatory resolution, sustaining nociceptive input well beyond the expected period of surgical recovery [3]. Persistent DAMP-mediated immune signaling has also been implicated in broader postoperative inflammatory sequelae, underscoring the clinical relevance of unresolved danger signaling following surgery [42].

Sustained elevations of inflammatory mediators such as tumor necrosis factor-α, interleukin-1β, interleukin-6, and interferon-γ lower nociceptor activation thresholds and promote spontaneous or ectopic neural firing, thereby contributing to peripheral sensitization [5,25]. In parallel, inflammatory signaling induces durable changes in ion channel expression, receptor density, and intracellular signaling pathways within primary afferent neurons, resulting in heightened neuronal excitability that may persist long after apparent tissue healing. Cytokines are increasingly recognized not only as peripheral mediators but also as active regulators of synaptic function and plasticity within the central nervous system, providing a mechanistic bridge between sustained peripheral inflammation and long-term alterations in pain processing [43]. Foundational work has established the critical role of voltage-gated sodium channels, particularly NaV1.7—in regulating nociceptor excitability and pain persistence [44,45], and more recent studies have identified pathological modulation of specific NaV1.7 domains as a driver of chronic pain maintenance in inflammatory contexts [46].

Failure of inflammatory resolution is further shaped by immune memory and priming mechanisms within the innate immune system. Emerging evidence indicates that macrophages can develop persistent, altered inflammatory responsiveness following tissue injury, a phenomenon described as innate immune memory or trained immunity, which may perpetuate low-grade inflammation even in the absence of ongoing tissue damage [47]. Experimental models also demonstrate that peripheral injury can induce long-lasting changes in neuroimmune signaling, supporting the concept that surgical tissue injury may leave a durable imprint on immune–neural communication that predisposes individuals to chronic pain states [48].

Lymphatic dysfunction represents an additional peripheral mechanism that sustains inflammatory signaling by impairing immune clearance and promoting inflammatory stasis within the postoperative tissue microenvironment. Lymphatic pain—manifesting as aching, soreness, or tenderness associated with fluid accumulation—is a recognized late effect among breast cancer survivors and contributes to ongoing symptom burden [49]. Breast cancer–related lymphedema has also been associated with long-term reductions in health-related quality of life extending up to a decade after treatment, reflecting chronic physical, functional, and psychosocial consequences that may interact with persistent nociceptive signaling [50]. Beyond the peripheral compartment, emerging evidence highlights the role of meningeal lymphatic drainage in regulating immune surveillance and inflammatory clearance within the central nervous system, suggesting a potential pathway by which impaired lymphatic function may contribute to sustained neuroimmune activation in chronic pain states [51].

Clinical observations from complex survivorship contexts further support the relevance of peripheral immune maintenance mechanisms in PMPS. Persistent inflammation, delayed wound healing, and refractory pain following mastectomy have been documented in patients requiring integrative therapeutic approaches, highlighting how unresolved peripheral immune activation and altered tissue microenvironments can continuously reinforce nociceptive input. In this setting, sustained peripheral immune dysregulation acts as a stabilizing force for chronic pain circuits, favoring the maintenance of neuropathic pain long after the initial surgical insult.

## Microglial Activation and Central Sensitization

Whereas preceding sections describe peripheral immune maintenance and neuroimmune mechanisms that initiate and sustain nociceptive input, this section focuses specifically on central glial-mediated amplification processes that stabilize and perpetuate pain once post-mastectomy pain syndrome (PMPS) has become established. In this phase, maladaptive interactions between microglia, astrocytes, and neurons within the central nervous system act as self-reinforcing drivers of pain persistence, largely independent of ongoing peripheral tissue pathology.

Persistent afferent signaling following mastectomy provides a critical trigger for glial activation within the spinal dorsal horn and higher-order pain-processing regions [5,25]. In the context of PMPS, this process unfolds within a uniquely sensitizing biological milieu shaped by surgical nerve injury, cancer-related inflammation, radiotherapy exposure, and survivorship-associated stress biology. Together, these factors increase the likelihood that glial activation will persist, amplify, and resist resolution compared with uncomplicated postsurgical pain states.

Although microglia have traditionally been emphasized as primary mediators of central sensitization, accumulating evidence indicates that astrocytes play a critical and complementary role in sustaining neuroimmune signaling and synaptic dysregulation during pain chronification [52,53]. Activated microglia and astrocytes release a broad array of pro-inflammatory mediators—including cytokines, nitric oxide, reactive oxygen species, and neurotrophic factors such as brain-derived neurotrophic factor (BDNF)—that enhance excitatory neurotransmission, suppress inhibitory control, and promote the persistent neuronal hyperexcitability characteristic of central sensitization [27,54]. Importantly, astrocytic signaling contributes to the maintenance of these maladaptive states by sustaining extracellular glutamate levels, altering synaptic homeostasis, and reinforcing long-term changes in network excitability.

At a molecular level, BDNF-mediated signaling represents a key pathway through which microglial activation alters spinal inhibitory tone. Experimental models demonstrate that microglial BDNF release activates TrkB receptors on dorsal horn neurons, leading to downregulation of the potassium–chloride cotransporter KCC2 and consequent impairment of GABAergic inhibition. This disinhibition facilitates dynamic allodynia and persistent pain amplification, providing a mechanistic link between immune activation and durable alterations in synaptic balance that extend well beyond the period of peripheral tissue injury [55].

Microglial priming is particularly relevant within cancer survivorship contexts. Chronic stressors associated with breast cancer treatment, including surgical trauma, systemic inflammation, radiotherapy, and psychological stress—can induce long-lasting reprogramming of microglial activation states, effectively lowering the threshold for subsequent neuroimmune responses and rendering central pain circuits disproportionately responsive to later nociceptive input [56,57]. Complementary evidence further demonstrates that chronic stress itself shapes microglial activation dynamics, reinforcing priming responses that persist over time and amplify vulnerability to central sensitization following additional insults [58]. In this setting, survivorship-related stress biology does not merely coexist with pain but actively modulates glial responsiveness and pain-processing capacity.

Clinically, these central glial-mediated processes manifest as allodynia, hyperalgesia, expansion of pain fields, and symptom fluctuations linked to stress and sleep disruption—features commonly reported among breast cancer survivors with refractory PMPS. Increasingly, validated clinical tools demonstrate convergent evidence of central sensitization in this population, supporting the translational relevance of glial-driven neuroimmune mechanisms for phenotyping, risk stratification, and treatment selection in survivorship care [59,60].

Taken together, this evidence positions glial-driven neuroimmune plasticity—particularly involving coordinated microglial and astrocytic signaling—as a central amplification module in persistent PMPS. By stabilizing maladaptive synaptic and network-level pain processing, these mechanisms help explain why pain remains resistant to single-target or peripherally focused interventions. Recognition of this central glial contribution reinforces the need for mechanism-informed, multimodal approaches that address central sensitization in parallel with peripheral immune maintenance and psychosocial contributors to pain.

## Neuroendocrine and Autonomic Dysregulation

Beyond peripheral immune maintenance and central glial amplification, persistent post-mastectomy pain syndrome (PMPS) is further shaped by neuroendocrine and autonomic dysregulation that modulates immune activity, neural excitability, and stress responsiveness over time. Rather than serving as primary initiators of pain, alterations in hypothalamic–pituitary–adrenal (HPA) axis function and autonomic balance act as systems-level regulators that stabilize and amplify existing pain circuits, particularly in the context of prolonged cancer-related stress and survivorship.

Repeated exposure to physiological and psychological stressors—including surgical injury, oncologic treatments, inflammatory burden, and ongoing nociceptive input—can progressively disrupt normal stress-response regulation, leading to maladaptive cortisol signaling and impaired homeostatic control [14,61]. Importantly, these alterations often persist beyond the completion of cancer treatment, reflecting a shift from adaptive stress responses toward dysregulated neuroendocrine states that increase vulnerability to pain chronification in survivorship.

Systematic analyses in oncology populations demonstrate that both sustained hypercortisolemia and blunted cortisol responsiveness are common manifestations of cancer-related stress physiology, indicating impaired HPA axis feedback sensitivity and reduced capacity for dynamic stress adaptation [62]. Such dysregulation compromises glucocorticoid-mediated restraint of inflammatory signaling, thereby facilitating immune activation and heightened nociceptive sensitivity. In breast cancer specifically, emerging evidence supports the presence of bidirectional brain–body feedback loops in which altered central stress-processing networks reinforce peripheral endocrine abnormalities, creating a self-perpetuating stress–pain cycle that increases susceptibility to persistent pain following mastectomy [63]. Consistent with this model, altered cortisol and cortisone profiles have been associated with disease course and survivorship outcomes, underscoring the clinical relevance of persistent neuroendocrine imbalance in this population [64].

Autonomic dysregulation further modulates pain persistence by shaping both peripheral inflammatory tone and central nociceptive processing. Heightened sympathetic nervous system activity promotes peripheral vasoconstriction, tissue ischemia, and neurogenic inflammation—processes that intensify nociceptive signaling and reinforce peripheral sensitization following surgical nerve injury [65]. In parallel, reduced parasympathetic tone weakens vagally mediated anti-inflammatory pathways that normally constrain immune activation and facilitate tissue recovery. The role of the vagus nerve in regulating inflammatory responses has been well established through the concept of the inflammatory reflex, providing a mechanistic framework linking autonomic imbalance to sustained immune and pain signaling [66]. In breast cancer populations, objective measures of autonomic function—including reduced heart rate variability—have been shown to correlate with inflammatory markers and anxiety-related symptom burden, further supporting the relevance of autonomic–immune coupling in cancer-related pain and distress [67].

Sleep disruption, anxiety, and affective distress—highly prevalent among individuals with PMPS—further interact with neuroendocrine and autonomic systems to modulate pain-processing circuits. Disturbed sleep has been shown to amplify inflammatory signaling, impair descending inhibitory pain pathways, and heighten pain perception, functioning as an active biological contributor to pain persistence rather than merely a secondary consequence of chronic pain [68]. Contemporary pain research increasingly conceptualizes sleep disturbance as a key driver of chronic pain vulnerability, reinforcing stress-related neuroimmune feedback loops that perpetuate nociceptive hypersensitivity [69]. In oncology populations, disruptions in stress-regulatory and neuroinflammatory pathways have been associated with more severe and persistent pain phenotypes, highlighting the clinical significance of stress-linked neuroimmune modulation in cancer-related pain states [70].

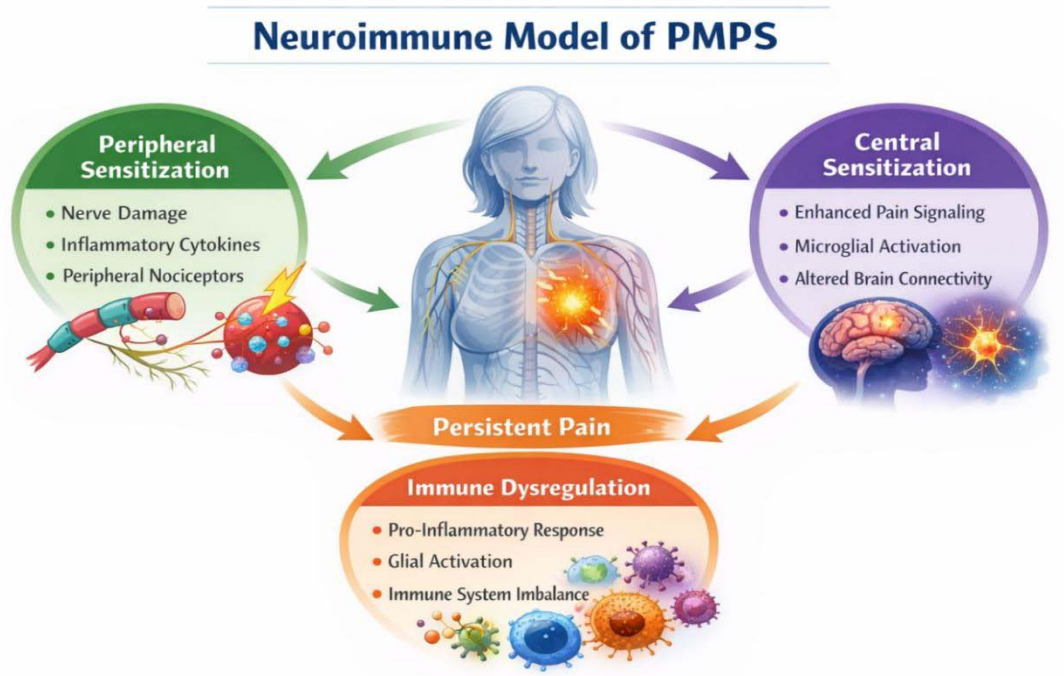


**Figure 1.** Schematic representation of the proposed neuroimmune model underlying post-mastectomy pain syndrome (PMPS). Surgical injury initiates peripheral sensitization, characterized by nerve damage, local inflammation, cytokine release, and heightened nociceptor excitability. Persistent peripheral nociceptive input promotes central sensitization through activation of spinal and supraspinal pain-processing networks, including microglial and astrocytic activation, enhanced excitatory neurotransmission, and altered central pain connectivity. Concurrent immune dysregulation, reflected by sustained pro-inflammatory signaling and glial–immune interactions, further amplifies pain processing. These peripheral, central, and immune mechanisms interact bidirectionally, contributing to persistent pain even in the absence of ongoing tissue injury. The model illustrates how neuroimmune integration, rather than isolated nerve damage, may drive the persistence of pain and treatment resistance in PMPS.

Collectively, these neuroendocrine, autonomic, and behavioral processes form a modulatory layer that shapes the intensity, persistence, and variability of post-mastectomy pain over time. By influencing immune regulation, central sensitization, and circadian stability, stress-system dysregulation helps stabilize maladaptive pain states and contributes to treatment resistance in breast cancer survivorship. Recognition of this modulatory role reinforces the importance of mechanism-informed, multimodal approaches that address stress physiology, autonomic balance, and sleep regulation alongside peripheral and central neuroimmune contributors to persistent PMPS.

## Integration of Peripheral, Central, and Systemic Mechanisms

Taken together, the mechanisms described above support conceptualizing post-mastectomy pain syndrome (PMPS) as a disorder of maladaptive neuroimmune integration rather than the direct consequence of isolated peripheral nerve injury. Contemporary pain science increasingly characterizes chronic pain as a system-level condition in which persistent immune activation, glial reactivity, and central nervous system plasticity interact dynamically to sustain pain beyond the expected period of tissue healing [5,71]. Within this framework, surgical nerve injury and oncologic treatments are best understood as initiating events, while long-term pain persistence reflects a failure of coordinated recovery across peripheral, central, and regulatory domains [72].

In PMPS, sustained peripheral nociceptive input engages spinal and supraspinal neuroimmune circuits, where microglial and astrocytic activation amplifies nociceptive transmission and promotes maladaptive synaptic plasticity. These central processes are further shaped by systemic stress-response dysregulation, including neuroendocrine and autonomic alterations that interfere with inflammatory resolution and descending pain inhibition. Conceptualizing cancer and its treatments as a prolonged homeostatic challenge provides a useful lens for understanding how immune, neural, endocrine, and autonomic systems become persistently dysregulated, reinforcing pain vulnerability during survivorship [73,24].

Central sensitization offers a unifying construct through which these peripheral, central, and systemic processes converge. Initially defined as an amplification of neural signaling within the central nervous system that leads to pain hypersensitivity [74], central sensitization is now understood as a heterogeneous, multifactorial phenomenon with important implications for phenotyping and mechanism-informed care [75]. In breast cancer survivors, recognition of central sensitization as a contributor to PMPS supports a shift away from uniform treatment approaches toward individualized, systems-informed models of pain management [59,76].

This integrated neuroimmune perspective provides the foundation for understanding why single-target interventions frequently yield incomplete or transient benefit in PMPS and underscores the need to consider coordinated, multimodal strategies that reflect the distributed nature of pain maintenance in survivorship contexts [12,17]. The sections that follow build on this framework to examine clinical implications for assessment, stratification, and mechanism-informed intervention in post-mastectomy pain.

## Post-Mastectomy Pain Syndrome as a Neuroimmune Condition

Building on the mechanistic pathways outlined above, post-mastectomy pain syndrome (PMPS) can be more precisely understood as a neuroimmune condition, in which persistent pain reflects dysregulated interactions among peripheral nerve injury, immune signaling, and central pain-processing networks rather than isolated structural pathology. Contemporary chronic pain research increasingly emphasizes immune–neural crosstalk as a core driver of pain persistence, reframing chronic pain as a disorder of maladaptive neuroimmune integration rather than a direct consequence of ongoing tissue damage alone [24,77].

Within this framework, peripheral nerve trauma associated with mastectomy represents an initiating event, while sustained inflammatory signaling, immune cell activation, and central nervous system plasticity act as maintaining and amplifying processes that can become partially autonomous from the original injury. Immune populations—including macrophages, T cells, and glial cells—actively shape nociceptive signaling through cytokine release and direct neuroimmune interactions, reinforcing pain chronification and relative resistance to conventional, peripherally focused treatments [24,78]. In PMPS, these mechanisms help explain why pain may persist despite apparent surgical healing and the absence of ongoing structural pathology.

Clinical and survivorship-focused research further supports the relevance of this neuroimmune conceptualization in breast cancer populations. Persistent pain following breast cancer treatment is increasingly recognized as a substantial survivorship burden characterized by sensory amplification, functional limitation, and frequent overlap with systemic symptoms such as fatigue, sleep disturbance, and emotional distress [79]. Systematic reviews of PMPS consistently highlight the multifactorial nature of the condition and the limited effectiveness of approaches that focus exclusively on localized nerve injury or anatomical pathology [80]. Contemporary phenotyping frameworks further underscore the heterogeneity of pain mechanisms among breast cancer survivors, reinforcing the need for systems-informed models that account for neuroimmune contributions to symptom persistence [76].

Postoperative and treatment-related factors may further shape neuroimmune vulnerability in susceptible individuals. Prolonged inflammatory responses, impaired immune resolution, and central sensitization processes have been associated with persistent postsurgical pain, particularly in contexts of repeated nociceptive input and sustained physiological stress [81]. In breast cancer survivors, radiation therapy represents an additional immune challenge, with emerging evidence linking radiation-induced tissue inflammation to subsequent development of PMPS [20]. Complementary findings suggest that baseline and treatment-induced systemic inflammatory indices may predict late radiation-related toxicity and long-term symptom burden, supporting a role for sustained immune activation in shaping pain trajectories after breast cancer treatment [82].

Viewed through this neuroimmune lens, PMPS reflects a failure of coordinated recovery across immune, neural, and regulatory systems following surgical and oncologic stressors. Integrative models of cancer-related symptomology increasingly recognize shared neuroimmune mechanisms underlying pain and other survivorship challenges, providing a biologically coherent framework for understanding symptom clustering, treatment resistance, and variability in recovery following breast cancer treatment [83,84]. This conceptualization sets the stage for more precise phenotyping and mechanism-informed approaches to assessment and management in breast cancer survivorship.

## Clinical Reframing of Post-Mastectomy Pain Syndrome: From Nerve Injury to Neuroimmune Dysfunction

Traditional clinical models have approached post-mastectomy pain syndrome (PMPS) primarily as a localized neuropathic condition arising from surgical nerve injury, often emphasizing nerve-directed procedures, regional interventions, or stepwise pharmacologic escalation. While these strategies may provide meaningful benefit for selected patients, clinical reviews consistently demonstrate that nerve-focused paradigms alone fail to fully account for the heterogeneity, chronicity, and treatment resistance commonly observed in real-world PMPS populations [2,80,84].

Reframing PMPS through a neuroimmune lens shifts clinical interpretation from a search for unresolved structural pathology toward recognition of dysregulated system-level pain maintenance. Within this framework, persistent pain is understood as the downstream consequence of altered immune signaling, central nervous system plasticity, autonomic imbalance, and stress-response dysregulation, rather than as evidence of incomplete surgical healing or ongoing nerve damage alone [24,72,77]. Importantly, this reframing does not negate the role of nerve injury as an initiating event but situates it within a broader biological process that governs pain persistence.

This shift has direct clinical implications. Survivorship research demonstrates that persistent pain following breast cancer treatment is frequently accompanied by altered pain processing, low-grade inflammation, sleep disturbance, fatigue, and psychological stress—features that extend beyond the boundaries of localized neuropathic injury and are increasingly recognized as characteristic of neuroimmune dysregulation and central sensitization [79,85,86]. Contemporary phenotyping frameworks further highlight substantial heterogeneity in underlying pain mechanisms among breast cancer survivors, reinforcing the limitations of uniform, nerve-centered treatment strategies [76].

Clinical studies also illustrate how this reframing clarifies patterns commonly encountered in practice. Breast cancer survivors with PMPS often engage in prolonged and diverse pain self-management behaviors months or years after completion of primary treatment, reflecting persistent symptom burden that is incompletely addressed by peripheral interventions alone [87]. State-of-the-art clinical models now identify central sensitization as a key mechanism underlying pain disproportionate to physical findings, symptom fluctuation with stress or sleep disruption, and incomplete or transient responses to procedural or pharmacologic escalation—patterns frequently observed in PMPS [59,75].

Viewed through a neuroimmune framework, features such as widespread sensitivity, autonomic symptoms, pain variability, and partial treatment response should not be interpreted as diagnostic ambiguity or treatment failure. Rather, they represent expected manifestations of sensitized pain networks operating within a dysregulated immune–neural environment. Recognizing this distinction may help reduce unnecessary diagnostic escalation, limit

**Table 1:** Clinical Patterns and Mechanistic Interpretation of Neuroimmune-Driven Post-Mastectomy Pain Syndrome.

| Clinical Pattern Observed in PMPS | Mechanistic Interpretation (Neuroimmune Framework) | Clinical Reasoning Implication |
|---|---|---|
| Persistent pain despite apparent surgical healing | Ongoing neuroimmune signaling and central nervous system plasticity maintain pain independent of tissue damage | Suggests pain persistence is not due to unresolved structural pathology |
| Pain that fluctuates with stress, sleep disruption, or systemic illness | Stress-responsive neuroendocrine and immune pathways modulating central pain processing | Indicates dynamic pain modulation rather than fixed neuropathic injury |
| Gradual expansion of pain beyond the original surgical distribution | Central sensitization and maladaptive cortical reorganization | Supports central amplification rather than localized nerve pathology |
| Widespread hypersensitivity, allodynia, or hyperalgesia | Enhanced excitability within central nociceptive networks and impaired inhibitory control | Points toward nociplastic and centrally mediated pain mechanisms |
| Autonomic symptoms (e.g., temperature dysregulation, palpitations, GI disturbance) | Dysregulated autonomic–immune interactions influencing nociception and inflammation | Suggests system-level dysregulation beyond peripheral nerve injury |
| Limited or transient response to nerve blocks or peripheral neuropathy–targeted therapies | Persistent immune activation and glial signaling sustaining pain despite local interventions | Explains treatment resistance to single-target or procedural approaches |
| History of radiation therapy, infection, delayed wound healing, or lymphedema | Prolonged inflammatory signaling and impaired immune resolution | Indicates sustained immune priming contributing to pain chronification |
| Co-occurrence of pain with fatigue, sleep disturbance, and emotional distress | Shared neuroimmune and stress-system pathways driving symptom clustering | Reinforces multisystem involvement rather than isolated pain pathology |

*This table summarizes clinical patterns observed in post-mastectomy pain syndrome (PMPS) and their mechanistic interpretation within a neuroimmune framework, presented as phenotypic indicators rather than diagnostic criteria.*

repeated invasive procedures with diminishing returns, and support more coherent, validating communication with patients living with persistent post-mastectomy pain.

Importantly, this clinical reframing redirects care away from isolated symptom suppression and toward restoration of system-level balance. Rather than asking only which nerve is injured, clinicians are encouraged to consider how immune activation, central sensitization, autonomic tone, sleep quality, emotional stress, and patient-driven behaviors interact to sustain pain over time. This perspective aligns with emerging survivorship care models and integrative oncology guidelines that emphasize coordinated, multimodal, and patient-centered approaches to cancer-related pain management [88,89]. The sections that follow build on this reframing to examine implications for assessment, phenotyping, and mechanism-informed intervention in post-mastectomy pain syndrome.

## Clinical Patterns Suggestive of Neuroimmune-Driven Post-Mastectomy Pain Syndrome

Clinical experience, supported by contemporary pain neuroscience, suggests that certain symptom patterns observed in post-mastectomy pain syndrome (PMPS) are more consistent with neuroimmune-driven pain mechanisms than with isolated peripheral nerve injury alone. Phenotype-based approaches to chronic pain increasingly emphasize that persistent pain may reflect maladaptive central and immune-mediated amplification rather than ongoing tissue damage, particularly when symptoms are disproportionate to physical findings or persist despite apparent surgical healing [90,91]. Recognizing these patterns can provide clinicians with a practical framework for identifying patients in whom neuroimmune mechanisms are likely contributing to pain persistence.

One commonly observed clinical pattern involves pain that fluctuates over time and is modulated by psychological stress, sleep disruption, systemic illness, or inflammatory stressors, rather than remaining fixed or anatomically stable. Longitudinal survivorship studies indicate that biopsychosocial phenotypes present during or shortly after cancer treatment may shape long-term pain trajectories, supporting a dynamic rather than static model of pain persistence [92]. Population-based data further demonstrate that sleep disturbance is independently associated with increased incidence of chronic and high-impact chronic pain, underscoring the bidirectional relationship between sleep dysregulation and pain chronification [93]. In clinical practice, stress- and sleep-sensitive pain variability often signals altered neuroendocrine and immune modulation of central pain processing rather than unresolved peripheral pathology.

Another pattern suggestive of neuroimmune-driven PMPS is the presence of widespread hypersensitivity, allodynia, hyperalgesia, or gradual expansion of pain beyond the original surgical distribution. Such features are commonly interpreted as manifestations of central sensitization or nociplastic pain processes. Although the precise causal role of central sensitization continues to be refined, recent critical reviews and clinical frameworks consistently highlight its association with persistent pain states and its relevance for clinical phenotyping and mechanism-informed reasoning [94,95]. Neuroimaging studies further support altered central pain network function in chronic pain conditions, reinforcing the contribution of central amplification to symptom persistence [96].

Autonomic features may provide additional phenotypic clues in patients with neuroimmune-driven PMPS. Symptoms such as temperature dysregulation, abnormal sweating, palpitations, gastrointestinal disturbance, or orthostatic intolerance suggest dysregulation of autonomic–immune interactions, which have been described across complex chronic pain conditions, including complex regional pain syndrome and cancer-related pain syndromes. Clinical and mechanistic studies demonstrate that autonomic nervous system activity can modulate both nociceptive signaling and immune responses, contributing to sustained pain and inflammation [97-100]. In breast cancer survivors, lymphatic dysfunction and associated pain further illustrate how immune and autonomic dysregulation may contribute to persistent symptom burden following treatment [101].

A further clinical signal supporting neuroimmune involvement is limited, incomplete, or transient response to nerve-directed interventions or single-mechanism pharmacologic therapies, such as regional nerve blocks or treatments targeting peripheral neuropathy alone. Contemporary neuroimmune models of chronic pain describe how immune cell activation, glial signaling, and persistent neuroinflammation within peripheral and central nervous systems can reinforce pain even in the absence of ongoing structural pathology, providing a biologically plausible explanation for treatment resistance frequently observed in PMPS [77].

Clinical history often provides additional context for neuroimmune interpretation. Postoperative infection, radiation exposure, delayed wound healing, lymphedema, or reconstructive complications may increase the likelihood that sustained immune activation has contributed to pain chronification. Updated reviews of

chronic postsurgical pain consistently identify inflammatory burden, surgical complications, and impaired recovery as key risk factors for long-term pain persistence [102]. Symptom cluster analyses in breast cancer populations similarly demonstrate that pain frequently co-occurs with fatigue, sleep disturbance, and psychological distress, reinforcing the value of a multisystem perspective when evaluating persistent post-mastectomy pain [103].

Although these clinical patterns are not diagnostic, their presence can serve as important phenotypic indicators supporting a neuroimmune formulation of PMPS. Framing such features within a neuroimmune context may reduce diagnostic uncertainty, validate patient experiences, and support more coherent, mechanism-informed clinical reasoning and management strategies for individuals living with persistent pain after breast cancer treatment [25,71,96].

## Neuroimmune Interactions and Pain Persistence in Cancer Contexts

Beyond general mechanisms of neuroimmune pain maintenance, cancer-related pain states—including post-mastectomy pain syndrome (PMPS)—exhibit distinct biological features shaped by tumor biology, oncologic treatments, and cancer-specific tissue remodeling. In this context, neuroimmune interactions are not merely downstream consequences of surgical injury but are actively influenced by immune activation associated with malignancy, tumor–nerve crosstalk, and treatment-induced alterations in neural and immune microenvironments.

Emerging evidence indicates that peripheral sensory neurons function as active participants in neuroimmune signaling within cancer contexts rather than passive conduits of nociceptive input. Integrative reviews describe bidirectional communication between sensory neurons, immune cells, and glial networks at tumor–nerve interfaces, highlighting how neural activity can shape local immune responses and sustain nociceptive signaling in cancer-related pain states [104]. In breast cancer–specific preclinical models, sensory neuron activation and neuroimmune pathways—including transient receptor potential vanilloid 1 (TRPV1)–mediated signaling—have been shown to modulate local inflammation and pain-related behaviors, supporting a role for persistent peripheral neuroimmune activation in pain maintenance following cancer treatment [105].

In addition to neuron–immune crosstalk, Schwann cells have emerged as important modulators of cancer-associated neuroimmune remodeling. Experimental studies demonstrate that interactions between Schwann cells and peripheral cancers can reshape both neural and immune microenvironments, influencing axonal structure, immune cell recruitment, and inflammatory signaling. These changes may contribute to sustained nociceptive input and relative resistance to conventional nerve-directed therapies in cancer survivors with persistent pain [106].

Cancer-related neuroimmune interactions also help explain why PMPS is frequently accompanied by systemic and non-sensory symptoms, including sleep disturbance, fatigue, anxiety, and autonomic dysfunction. Such features are difficult to reconcile with purely localized nerve injury models but are increasingly recognized as hallmarks of chronic pain states driven by sustained neuroimmune dysregulation. Longitudinal population-based data demonstrate that sleep deficiency significantly increases the risk of developing chronic and high-impact chronic pain, supporting a bidirectional relationship between sleep disruption and pain chronification in cancer populations [93,107]. In parallel, autonomic manifestations observed in PMPS align with evidence from chronic pain models demonstrating that autonomic nervous system activity modulates both nociceptive processing and immune responses, thereby contributing to persistent pain and inflammation [97,98].

Together, these oncology-specific neuroimmune processes suggest that PMPS arises within a biologically distinct pain environment shaped by tumor–nerve–immune interactions and treatment-related neuroimmune remodeling, rather than as a straightforward extension of postsurgical neuropathy. Recognizing these features adds important nuance to neuroimmune models of pain persistence and helps explain the complexity, symptom clustering, and treatment resistance observed in breast cancer survivorship.

Common clinical patterns suggestive of neuroimmune-driven post-mastectomy pain syndrome and their mechanistic interpretation are summarized in Table 2.

**Table 2:** Clinical Stratification of Post-Mastectomy Pain Syndrome Within a Neuroimmune Framework.

| Observed Clinical Pattern | Likely Dominant Mechanisms | Neuroimmune Interpretation | Clinical Reasoning Implication |
|---|---|---|---|
| Pain persists despite apparent surgical healing and absence of structural pathology | Central sensitization; glial activation; maladaptive synaptic plasticity | Pain is maintained by central neuroimmune amplification rather than ongoing tissue injury | Further nerve-targeted escalation alone is unlikely to provide a durable benefit |
| Pain fluctuates with stress, sleep disturbance, illness, or inflammation | Neuroendocrine dysregulation; autonomic imbalance; immune–stress interactions | Stress-responsive neuroimmune modulation of pain networks | Variability reflects system-level dysregulation rather than instability or nonadherence |
| Pain extends beyond original surgical or nerve distribution | Central sensitization; altered cortical pain network integration | Spatial generalization of pain due to central amplification | Supports nociplastic/neuroimmune phenotype over focal neuropathy |
| Widespread hypersensitivity, allodynia, or hyperalgesia | Glial-mediated disinhibition; impaired inhibitory control | Heightened central excitability driven by immune–glial signaling | Mechanism-informed phenotyping warranted |
| Limited or transient response to nerve blocks or peripheral neuropathy treatments | Persistent neuroimmune loops; central network stabilization | Treatment resistance reflects a mismatch between the mechanism and the intervention | Signals need for a multimodal, system-level approach |
| Co-occurring fatigue, sleep disruption, mood disturbance, or cognitive symptoms | Shared neuroimmune and stress-regulatory pathways | Symptom clustering reflects a common biological substrate | Pain should be assessed within a broader survivorship context |
| Autonomic symptoms (temperature dysregulation, palpitations, GI disturbance, orthostasis) | Autonomic–immune dysregulation; impaired vagal modulation | Pain embedded in dysregulated autonomic–immune network | Supports inclusion of autonomic and stress physiology in assessment |
| History of infection, radiation injury, delayed healing, lymphedema, or reconstruction complications | Sustained immune activation; impaired inflammatory resolution | Enhanced vulnerability to neuroimmune pain chronification | Identifies higher-risk survivorship subgroup |

This table summarizes common clinical patterns observed in post-mastectomy pain syndrome (PMPS) and their interpretation within a neuroimmune framework. The patterns described are not diagnostic but may assist clinicians in recognizing phenotypic features suggestive of immune–neural dysregulation, central sensitization, and system-level pain maintenance. The table is intended to support mechanism-informed clinical reasoning and to complement, rather than replace, individualized assessment in breast cancer survivorship care.

## Limitations of Existing PMPS Models and the Need for a Neuroimmune Framework

Post-mastectomy pain syndrome (PMPS) has traditionally been conceptualized as a neuropathic pain condition driven primarily by peripheral nerve injury, including intercostal nerve trauma, neuroma formation, and localized tissue damage during breast surgery. While peripheral nerve integrity is clearly relevant to pain initiation, accumulating clinical and experimental evidence indicates that nerve-centric models alone do not adequately account for the marked heterogeneity, chronicity, and treatment resistance observed in many breast cancer survivors with persistent pain [102].

Recent randomized surgical studies further highlight these limitations. Although intercostal nerve coaptation and other nerve-directed techniques may reduce postoperative pain in selected patients, they do not reliably prevent or resolve chronic pain syndromes, underscoring the limited explanatory and therapeutic reach of peripheral-focused interventions alone [32]. In clinical practice, many patients report pain that persists despite technically successful surgical repair, appears disproportionate to identifiable nerve damage, or fluctuates in response to systemic factors such as psychological stress, sleep disruption, infection, or inflammatory illness. Similar dissociations between tissue injury and pain severity have been described across nociplastic and centrally mediated pain conditions, challenging the sufficiency of strictly peripheral explanations for chronic pain persistence [108].

Limitations of nerve-centric models are further reflected in the modest and often transient efficacy of conventional PMPS treatments. Pharmacologic strategies such as gabapentinoids, antidepressants, opioids, and regional nerve blocks may provide partial symptom relief but are frequently associated with limited durability and cumulative adverse effects, particularly within long-term survivorship contexts [109,110]. Neuroablative procedures, including radiofrequency ablation, may benefit specific patient subsets but demonstrate variable outcomes and carry procedure-related risks, underscoring the shortcomings of destructive, single-target approaches in multifactorial chronic pain states [111].

Existing PMPS frameworks have also tended to underappreciate the contribution of systemic and contextual factors that shape pain persistence after breast cancer treatment. Postoperative complications such as infection, radiation-induced tissue injury, lymphedema, delayed wound healing, and systemic inflammatory insults introduce sustained immune and inflammatory stressors that extend beyond localized nerve damage and may amplify pain chronification [101,102,112,113]. Similarly, neuroendocrine and psychosocial factors—including stress reactivity, sleep fragmentation, anxiety, and trauma-related responses—are highly prevalent among breast cancer survivors and increasingly recognized as biologically active modulators of immune signaling and pain processing [93,107,114,115].

Together, these limitations highlight the need for a broader conceptual framework capable of integrating peripheral injury with immune activation, central nervous system plasticity, and systemic stress physiology. Reframing PMPS as a neuroimmune disorder provides a more coherent explanation for symptom variability, multisystem involvement, and treatment resistance, while aligning with emerging evidence that integrative, multimodal pain management strategies yield superior outcomes compared with unidimensional approaches in chronic pain and oncology populations [116-118].

## Clinical and Therapeutic Implications of a Neuroimmune Model of PMPS

Reframing post-mastectomy pain syndrome (PMPS) as a neuroimmune disorder shifts clinical reasoning away from a narrow focus on localized nerve injury and toward recognition of system-level pain maintenance involving immune activation, central sensitization, glial reactivity, and stress-response dysregulation [25,77,90]. In clinical practice, this perspective helps explain why many individuals with PMPS experience persistent pain despite technically successful surgery or nerve-directed interventions, and why single-mechanism approaches frequently provide limited or short-lived benefit [109,110].

Within a neuroimmune framework, therapeutic decision making in PMPS prioritizes mechanism alignment over escalation of isolated interventions. Rather than progressing sequentially through nerve-focused or pharmacologic options, clinicians are encouraged to consider how peripheral inflammation, central amplification, autonomic imbalance, and survivorship-related stressors interact to sustain pain over time. Contemporary pain models and oncology survivorship literature increasingly support coordinated, multimodal strategies as more appropriate for patients with refractory PMPS, particularly those with complex postoperative courses or prolonged inflammatory and psychosocial stress exposure [25,77,117,119,120].

This shift is especially relevant in breast cancer survivors whose clinical histories suggest sustained immune or inflammatory activation, including postoperative infection, radiation-induced tissue injury, delayed wound healing, or lymphedema. These conditions introduce persistent immune stressors that may maintain nociceptive signaling well beyond expected tissue recovery and are consistently associated with pain chronification and relative treatment resistance in PMPS [101,102,112,113]. Emerging perioperative evidence further suggests that anesthetic and analgesic strategies may influence long-term pain trajectories, underscoring the potential importance of early neuroimmune modulation in shaping PMPS outcomes [32,102,121].

Adopting a neuroimmune perspective also reframes therapeutic goals in PMPS. Rather than emphasizing pain intensity reduction alone, clinical priorities shift toward restoration of physical function, improvement in sleep quality, emotional regulation, and reduction of pain-related fear and hypervigilance—outcomes that more closely align with patient-reported priorities in breast cancer survivorship [90,101,110]. Oncology and survivorship research consistently demonstrate that meaningful improvements in function and quality of life may occur even in the presence of residual pain, highlighting the limitations of numeric pain scores as sole indicators of clinical success [103,117,118].

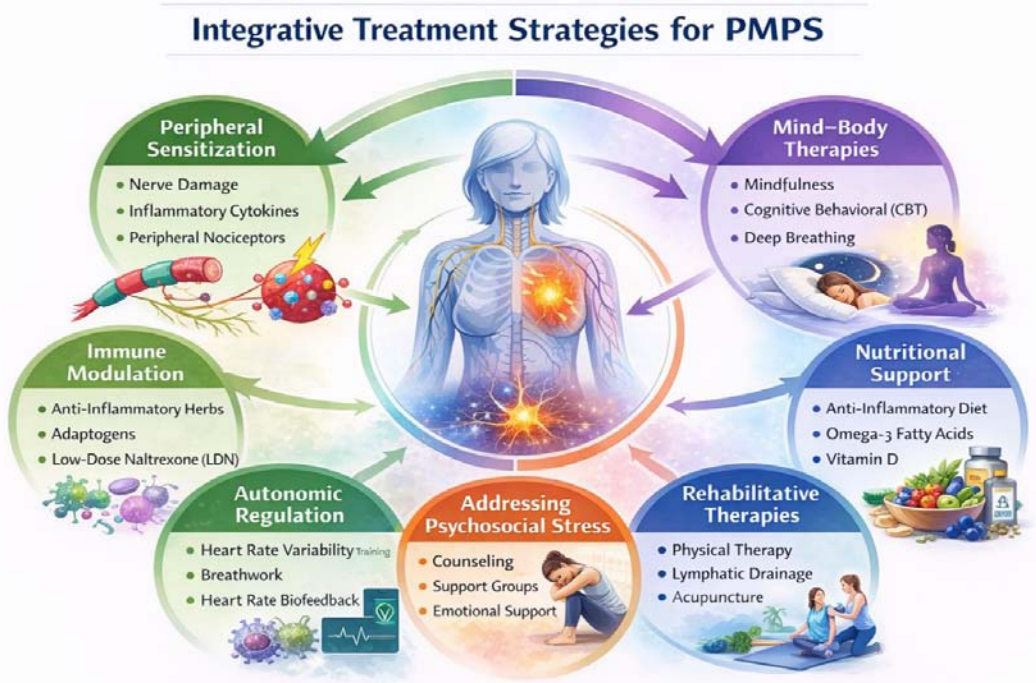


**Figure 2:** Integrative, Neuroimmune-Informed Approaches to the Management of Post-Mastectomy Pain Syndrome (PMPS)
Conceptual illustration of integrative, neuroimmune-informed strategies for the management of post-mastectomy pain syndrome (PMPS). The central figure represents the patient as an integrated neuroimmune system in which persistent pain arises from interactions between peripheral sensitization, central sensitization, immune dysregulation, and stress-response pathways. Surrounding domains depict complementary therapeutic targets that align with the neuroimmune model, including modulation of peripheral inflammation and nociceptor sensitization, immune and glial regulation, autonomic nervous system balance, psychosocial stress reduction, sleep optimization, nutritional support, mind–body therapies, and rehabilitative interventions. Together, these domains illustrate a coordinated, multimodal approach that emphasizes functional recovery, symptom resilience, and long-term survivorship rather than isolated symptom suppression.

A neuroimmune framework further provides a biologically grounded rationale for opioid-sparing approaches in PMPS. Pain driven by immune activation and central sensitization often responds incompletely to long-term opioid therapy and may be complicated by tolerance, opioid-induced hyperalgesia, and paradoxical pain amplification [5,25,122]. Neuroimmune mechanisms—including microglial activation and pro-inflammatory cytokine signaling—have been directly implicated in opioid-related pain dysregulation, supporting cautious use of opioids and consideration of alternative strategies that support endogenous pain modulation and system-level balance [5,77,90,117].

Finally, reframing PMPS as a neuroimmune condition emphasizes the importance of early identification and risk stratification across the perioperative and survivorship continuum. Patients exhibiting prolonged inflammatory states, complex surgical recoveries, or early features of central sensitization may benefit from proactive, coordinated care aimed at modulating immune–nervous system interactions before maladaptive pain circuits become entrenched [102,112]. Transitional pain service models that integrate perioperative and survivorship care have shown promise in reducing pain chronification and improving long-term functional outcomes following surgery, with emerging relevance for breast cancer populations at heightened risk for persistent pain [24,123,124].

## Implications for Integrative Oncology Practice

Integrative oncology provides a clinically appropriate and evidence-informed setting in which a neuroimmune model of post-mastectomy pain syndrome (PMPS) can be translated into routine care. By design, integrative oncology emphasizes coordinated approaches that address biological, psychological, and social dimensions of cancer-related symptoms alongside conventional oncologic treatment. Contemporary consensus documents and clinical guidelines jointly developed by the Society for Integrative Oncology and the American Society of Clinical Oncology explicitly endorse integrative therapies as complementary strategies for symptom management across the cancer care continuum, including survivorship [125]. Foundational definitions of integrative oncology similarly emphasize whole-person, systems-based care that augments—rather than replaces—standard oncologic treatment [126]. Conceptualizing PMPS through a neuroimmune lens aligns closely with this framework by framing persistent pain as an emergent property of interacting immune, neural, autonomic, and psychosocial systems rather than the consequence of a single localized lesion.

Within integrative oncology practice, a neuroimmune-informed perspective supports the thoughtful coordination of pharmacologic and non-pharmacologic strategies selected according to individual clinical context rather than applied in isolation. Survivorship-focused guidelines, including recent National Comprehensive Cancer Network Insights, increasingly emphasize individualized, multimodal symptom management for cancer survivors with persistent treatment-related sequelae [127]. Integrative survivorship models similarly advocate combining neuromodulatory and immune-modulating therapies with rehabilitation, movement-based interventions, mind–body approaches, and lifestyle-oriented strategies, sequenced according to each patient's treatment history, symptom burden, and functional priorities [90,117,128]. Evidence

from multidisciplinary cancer care further demonstrates that coordinated rehabilitation and supportive interventions can improve both physical and psychological outcomes, reinforcing the relevance of systems-based care in oncology populations [62].

Importantly, integrative oncology clinicians frequently care for breast cancer survivors who express a preference for conservative, non-invasive, or opioid-sparing approaches, often shaped by prior adverse effects, cumulative treatment fatigue, or personal values formed during the cancer experience. Surveys and preference-based studies consistently indicate that many cancer survivors seek integrative and complementary strategies for symptom management, particularly when conventional pharmacologic options provide limited benefit or unacceptable side effects [110,129]. A neuroimmune framework provides a biologically coherent rationale for contextualizing these preferences within evidence-informed care, particularly in chronic pain states where immune activation and central sensitization constrain the effectiveness of single-mechanism interventions.

This perspective also supports the inclusion of autonomic and stress-regulatory strategies as biologically relevant components of pain care rather than ancillary or purely supportive measures. Experimental and translational studies demonstrate that autonomic dysregulation and sustained sympathetic activation can amplify nociceptive and immune signaling, whereas interventions that enhance parasympathetic tone may attenuate neuroimmune activation [97,98]. Clinical evidence supports the role of mind–body interventions in reducing cancer-related pain and improving quality of life, with systematic reviews and meta-analyses demonstrating benefit across adult oncology populations [130]. Emerging breast cancer–specific research further suggests that targeted modulation of autonomic pathways, including transcutaneous vagus nerve stimulation, may influence symptom burden through neuroimmune mechanisms [131]. Within a neuroimmune framework, such approaches are understood as adjunctive strategies that influence pain-maintaining systems rather than as standalone treatments.

From a systems perspective, adopting a neuroimmune framework within integrative oncology practice may also help bridge longstanding gaps between oncology, pain medicine, rehabilitation, and supportive care disciplines. Policy statements and guideline-based survivorship models emphasize the importance of coordinated, multidisciplinary care planning to address the complex and long-term needs of cancer survivors [127,132]. This integration is particularly relevant for breast cancer survivors with complicated postoperative courses, in whom fragmented or siloed management may inadvertently contribute to prolonged symptom burden, delayed functional recovery, and escalation of treatment intensity.

Finally, incorporating neuroimmune concepts into integrative oncology practice encourages a shift away from narrow symptom suppression toward restorative, systems-oriented care that prioritizes long-term function, quality of life, and resilience. Evidence from contemporary multimodal pain management literature indicates that interdisciplinary approaches are associated with meaningful improvements in health-related quality of life and functional outcomes across chronic pain populations [117,133]. Within breast cancer survivorship, this approach aligns closely with patient-centered goals and supports a clinically coherent, compassionate, and durable response to persistent post-mastectomy pain.

## Emerging Clinical Evidence Supporting Neuroimmune-Informed Care in PMPS

While much of the neuroimmune framework for post-mastectomy pain syndrome (PMPS) has been derived from mechanistic and translational research, emerging clinical evidence increasingly supports its relevance for patient care. In breast cancer survivorship populations, persistent pain has been shown to correlate more closely with central pain processing, stress-related factors, and symptom network interactions than with peripheral pathology alone, reinforcing the clinical limitations of nerve-centric models [25,77,90,134].

Recent randomized clinical trial data provide particularly relevant support for mechanism-informed, non-invasive interventions aligned with a neuroimmune framework. In breast cancer survivors with chronic pain, integrative approaches combining pain neuroscience education with graded exposure to movement have demonstrated meaningful reductions in pain and improvements in physical function, highlighting the clinical value of addressing central sensitization, threat appraisal, and movement avoidance alongside nociceptive symptoms [135]. These findings underscore the importance of patient education and functional restoration as active components of pain care rather than adjunctive measures.

In parallel, growing evidence points to the role of autonomic and interoceptive regulation in shaping pain outcomes among breast cancer survivors. Measures of cardiac vagal control and emotional awareness have been shown to correlate with pain experience, supporting a contribution of parasympathetic function and interoceptive processing to neuroimmune pain modulation [136]. Such observations align with broader chronic pain literature demonstrating that autonomic imbalance and stress dysregulation can amplify immune signaling and central sensitization, thereby sustaining pain even in the absence of ongoing tissue injury.

Together, these emerging clinical findings complement mechanistic models by demonstrating that interventions targeting central processing, autonomic regulation, and functional recovery can meaningfully influence pain trajectories in PMPS. Rather than replacing conventional pain management strategies, these approaches support a neuroimmune-informed shift in clinical priorities—toward early identification of sensitization, restoration of movement confidence, and modulation of stress-responsive pain-maintaining systems within breast cancer survivorship care.

## Implications for Pain Assessment and Risk Stratification

A neuroimmune model of post-mastectomy pain syndrome (PMPS) refines clinical assessment and risk stratification by shifting attention toward earlier identification of individuals vulnerable to pain chronification following breast cancer surgery. Rather than relying predominantly on surgical variables or the presence of identifiable nerve injury, this framework emphasizes immune, inflammatory, autonomic, and systemic factors that shape long-term pain trajectories. Clinical and epidemiologic studies of chronic postsurgical pain consistently demonstrate that baseline inflammatory burden, postoperative complications, and broader survivorship context are critical determinants of persistent pain outcomes [102,137]. Survivorship-focused guidelines similarly emphasize that ongoing symptoms after cancer treatment frequently arise from

complex interactions among treatment exposures, host biology, and psychosocial stressors rather than isolated surgical pathology [127].

Within this framework, postoperative complications—including infection, delayed wound healing, radiation-induced tissue injury, lymphedema, and prolonged physiological stress responses—are best understood as **active contributors to sustained immune activation** rather than incidental comorbidities. Experimental and clinical evidence demonstrates that persistent inflammatory signaling following surgery can promote central sensitization and durable alterations in pain processing, particularly when immune activation is prolonged or compounded by radiation-related tissue injury [5,62,112]. In breast cancer survivors, these processes may interact with lymphatic dysfunction and tissue fibrosis, amplifying nociceptive input and delaying recovery, thereby increasing vulnerability to persistent pain beyond the expected period of surgical healing.

From a clinical assessment standpoint, a neuroimmune-informed approach supports **multidimensional evaluation** extending beyond pain intensity and anatomical distribution. Assessment may incorporate indicators of inflammatory burden, autonomic symptoms, sleep disruption, affective distress, and behavioral features of pain amplification, including allodynia, hyperalgesia, and widespread sensitivity. Contemporary pain neuroscience emphasizes that pain is shaped by interacting sensory, emotional, cognitive, and contextual factors, underscoring the limitations of assessment strategies that rely exclusively on numeric pain scores [138]. Clinical frameworks integrating these dimensions provide a more accurate reflection of the biological and psychosocial mechanisms underlying persistent pain states [90].

Identification of central sensitization is particularly relevant for phenotyping and risk stratification in PMPS. Clinical studies demonstrate that features such as pain disproportionate to tissue findings, expansion of pain beyond the original surgical site, and heightened sensitivity to normally non-painful stimuli are common in chronic pain conditions characterized by neuroimmune dysregulation [139]. Validated tools, including the Central Sensitization Inventory and its short form, have demonstrated utility in breast cancer survivorship populations and may support structured clinical assessment [60]. Complementary approaches such as quantitative sensory testing further allow objective characterization of altered sensory processing following breast cancer surgery [140]. Recent conceptual advances emphasizing nociplastic pain mechanisms in cancer survivors provide an additional framework for integrating these findings into routine clinical reasoning without attributing symptoms solely to ongoing peripheral pathology [90].

Sleep disturbance and autonomic dysregulation represent additional, clinically meaningful risk markers within a neuroimmune assessment framework. Longitudinal survivorship studies demonstrate that sleep disruption is highly prevalent among breast cancer survivors and may persist or worsen over time, contributing to pain chronification and impaired recovery [141]. Growing evidence further suggests that autonomic imbalance, reflected in altered heart rate variability, is associated with pain severity, fatigue, and neuropathic symptoms in cancer populations. Systematic reviews highlight the potential utility of heart rate variability as an accessible marker of autonomic and inflammatory dysregulation relevant to chronic pain states [142].

Taken together, these considerations illustrate how a neuroimmune framework refines pain assessment and risk stratification in PMPS by identifying biological and systemic markers of vulnerability before pain becomes entrenched. Early recognition of immune activation, central sensitization, sleep disruption, and autonomic imbalance may support more timely, mechanism-informed clinical decision-making and provide a foundation for improving long-term pain and functional outcomes in breast cancer survivorship.

## Implications for Therapeutic Strategy and Treatment Sequencing

If post-mastectomy pain syndrome (PMPS) is sustained by convergent neuroimmune mechanisms, therapeutic strategies based solely on sequential, single-target escalation are unlikely to provide durable relief in refractory cases. In conventional clinical practice, persistent pain is often managed through iterative trials of medications or procedures, frequently without systematic consideration of immune dysregulation, central sensitization, glial activation, or broader systemic contributors to pain persistence. Contemporary reviews of neuropathic and postsurgical pain management consistently demonstrate that such single-mechanism approaches commonly yield partial, transient, or inconsistent benefit, particularly in patients with centrally amplified or immune-mediated pain states [25,109]. Epidemiologic analyses of cancer-related pain further indicate that treatment-resistant pain represents a substantial and underrecognized clinical burden, highlighting persistent gaps between guideline recommendations and real-world outcomes [143].

Importantly, a neuroimmune-informed approach does not require abandonment of established pharmacologic or procedural therapies. Rather, it reframes their use within a coordinated, mechanism-informed strategy that integrates standard treatments with interventions targeting immune signaling, central nervous system sensitization, autonomic regulation, and functional recovery. Within this framework, treatment sequencing is guided not by symptom persistence alone, but by early identification of dominant pain-maintaining mechanisms, including sustained inflammation, central amplification, stress-related neuroregulatory imbalance, and behavioral contributors to pain persistence. Addressing these interacting processes in parallel is more consistent with the biology of chronic pain and may reduce the prolonged cycling of isolated therapies that characterizes refractory pain care [25,77,117].

Clinical observations of treatment resistance in chronic postsurgical and neuropathic pain underscore the limitations of trial-and-error escalation. Patients with persistent pain following surgery frequently cycle through multiple pharmacologic agents with diminishing returns, reflecting a mismatch between narrowly targeted interventions and the multisystem biology underlying pain chronification [102]. Survivorship studies in breast cancer populations further demonstrate that ongoing pain often leads patients to adopt self-management strategies months or years after completion of primary treatment, underscoring both the chronicity of symptoms and the perceived inadequacy of medication-centered approaches when applied in isolation [87]. Preference-based research similarly highlights that medication escalation is frequently constrained by limited efficacy, tolerability concerns, and cumulative treatment burden, reinforcing the need for more coherent, mechanism-aligned therapeutic strategies [110].

Within a neuroimmune framework, therapeutic sequencing emphasizes early integration rather than delayed escalation.

Pharmacologic treatments, physical rehabilitation, psychological and behavioral strategies, and educational interventions are viewed as complementary components of a unified care plan rather than as discrete steps applied sequentially. Mechanism-based pain treatment frameworks highlight that these modalities may exert synergistic effects when selected and sequenced according to the dominant drivers of pain in an individual patient, rather than introduced only after failure of prior interventions [77,90]. Authoritative oncology guidelines support this integrative, opioid-sparing approach, endorsing coordinated multimodal pain management strategies across the cancer care continuum [116].

Educational and rehabilitative interventions that explicitly address central sensitization and pain-related fear are particularly relevant within this sequencing model. Pain neuroscience education tailored to breast cancer survivorship has demonstrated promise in improving pain understanding, reducing threat perception, and supporting functional recovery when incorporated into broader multimodal care pathways [89]. Evidence from interdisciplinary pain programs further demonstrates that integrated approaches combining education, movement-based rehabilitation, and psychological support are associated with meaningful improvements in quality of life and functional outcomes across chronic pain populations, reinforcing their relevance for refractory PMPS [117,133].

Taken together, these considerations suggest that therapeutic strategy and treatment sequencing in PMPS may be optimized by shifting away from reactive, stepwise escalation toward early, mechanism-informed integration of complementary interventions. Aligning treatment selection and sequencing with underlying neuroimmune contributors to pain persistence has the potential to reduce ineffective cycling of therapies, limit cumulative treatment burden, and improve patient engagement, while supporting more durable recovery in breast cancer survivors living with chronic post-mastectomy pain.

## Implications for Opioid Use and Long-Term Safety

Conceptualizing post-mastectomy pain syndrome (PMPS) as a neuroimmune condition reframes the role of opioid therapy in long-term pain management. While opioids may provide short-term reductions in pain intensity, they do not directly target core drivers of pain persistence in PMPS, including immune activation, glial sensitization, altered cytokine signaling, and centrally mediated amplification of nociceptive processing. As a result, their effectiveness in chronic neuropathic and postsurgical pain states is frequently limited over time, particularly when pain is sustained by maladaptive neuroimmune interactions rather than unresolved tissue injury [109,144,145]. This limitation is especially relevant in PMPS, where persistent pain reflects dysregulated immune–nervous system signaling rather than continued peripheral pathology.

Beyond limited durability of analgesia, prolonged opioid exposure may further disrupt neuroimmune homeostasis and contribute to adverse pain outcomes. Experimental and translational studies demonstrate that opioids can activate neuroinflammatory pathways, including microglial signaling, altered cytokine release, and changes in central pain modulation, processes that may paradoxically increase pain sensitivity and promote opioid-induced hyperalgesia [5,25,146]. Emerging mechanistic evidence implicates central nervous system targets such as thalamic T-type calcium channels in opioid-related pain amplification, underscoring the complexity of opioid–neuroimmune interactions in chronic pain states [147].

In cancer-related neuropathic pain, these limitations are further shaped by treatment-induced vulnerability of immune and nervous system function. Neuroinflammatory alterations following surgery, chemotherapy, and radiation have been associated with persistent somatosensory dysfunction, cognitive and emotional symptoms, and heightened central pain sensitivity in breast cancer survivors [148,149]. Within this context, opioid-refractory neuropathic pain states are increasingly recognized in oncology populations, reflecting the limited capacity of opioids to modulate immune-driven and centrally maintained pain processes [150]. Viewed through a neuroimmune lens, diminishing opioid responsiveness may therefore serve as a clinical indicator of dominant central and immune-mediated pain mechanisms rather than as evidence of treatment nonadherence or failure.

Clinical evidence further indicates that long-term opioid therapy offers limited sustained benefit for chronic neuropathic pain and carries meaningful safety considerations, particularly in cancer survivorship populations with complex treatment histories. Patient-centered studies consistently highlight that tolerance, side-effect burden, functional impairment, and neurocognitive trade-offs frequently constrain the long-term utility of opioid-based strategies, even when initial analgesia is achieved [110,151,152]. In parallel, a growing body of literature has raised concern regarding potential associations between opioid exposure and adverse oncologic outcomes, including immune modulation and cancer recurrence. While causality remains incompletely defined, these observations reinforce the importance of judicious, risk-aware opioid use within survivorship care [153-155].

A neuroimmune-informed approach therefore supports opioid-sparing strategies that prioritize functional recovery, sleep restoration, emotional regulation, and stabilization of immune–nervous system signaling rather than short-term analgesia alone. Contemporary multimodal pain care models emphasize coordinated interventions acting across peripheral, central, and systemic levels, reducing reliance on opioids while addressing the biological complexity of chronic pain states [90,117,156,157]. Evidence from interdisciplinary pain programs and pain neuroscience–informed interventions further demonstrates that non-opioid-centered approaches are associated with meaningful improvements in quality of life, pain-related disability, and patient self-efficacy across chronic pain populations, including breast cancer survivors [81,133].

Within cancer survivorship care, this perspective aligns closely with guideline-based recommendations emphasizing long-term safety, symptom burden reduction, and quality of life rather than narrow analgesic targets. Procedure-specific and survivorship-focused guidelines consistently support individualized, multimodal pain management strategies designed to minimize cumulative harm while promoting durable recovery [127,158,159,160]. Viewed through a neuroimmune framework, opioid use in PMPS is best understood as a limited, adjunctive tool rather than a foundational long-term therapy, reinforcing the value of early, mechanism-aligned, and integrative approaches to pain management in breast cancer survivors.

## Implications for Survivorship and Long-Term Recovery

From a survivorship perspective, conceptualizing post-mastectomy pain syndrome (PMPS) as a neuroimmune condition provides an essential framework for understanding and validating persistent pain that continues long after surgical healing is complete. Population-level analyses and systematic reviews consistently demonstrate that pain remains a common and often under-recognized concern across the cancer continuum, including among long-term survivors, challenging assumptions that pain reliably resolves with the completion of treatment [161,162]. Longitudinal survivorship research further indicates that symptom burden often emerges early and may persist, fluctuate, or evolve over time rather than follow a linear trajectory toward resolution [163,164]. Within this context, persistent pain is best understood not as a failure of tissue healing, coping, or psychological resilience, but as the clinical expression of sustained biological and systemic dysregulation following cancer and its treatments.

Qualitative and patient-centered survivorship research reinforces this interpretation by highlighting the lived experience of individuals navigating persistent symptoms over extended periods. Long-term breast cancer survivors frequently describe the ongoing work of symptom self-management, uncertainty, and adaptation that extends well beyond active treatment, underscoring the disconnect that can arise when survivorship care models implicitly assume recovery has been achieved [165]. Additional qualitative studies document persistent unmet needs related to pain, functional limitation, and emotional well-being, alongside a clear desire for survivorship approaches that recognize survivorship as an active, evolving process rather than a static post-treatment phase [166,167]. Patient-reported outcome research further demonstrates that pain, fatigue, and functional limitations frequently persist across survivorship and are often best captured through patient-reported measures rather than objective clinical findings alone [168]. Together, these findings support reframing persistent pain as an expected and biologically grounded survivorship challenge rather than an anomalous or psychosomatic complaint.

Persistent pain also exerts a substantial influence on long-term recovery, functional reintegration, and quality of life among cancer survivors. Survivorship outcome studies consistently demonstrate associations between chronic pain and reduced physical functioning, impaired participation in daily activities, and diminished overall well-being [162,169]. Long-term follow-up research further shows that health-related quality of life may remain altered for years following breast cancer treatment, reflecting the enduring nature of survivorship challenges when pain and related symptoms are not adequately addressed [164]. Pain frequently co-occurs with fatigue, emotional distress, and disruption of social and occupational roles, compounding recovery challenges and contributing to prolonged functional impairment [170]. These data reinforce the importance of viewing pain as a central determinant of survivorship outcomes rather than a residual postoperative issue of secondary importance.

A neuroimmune perspective further supports the development of longitudinal survivorship care pathways that adapt over time in response to evolving biological, psychological, and social contexts. Expert consensus statements emphasize that high-quality survivorship care must move beyond episodic follow-up toward coordinated, proactive, and patient-centered management of chronic symptoms and late effects, including persistent pain [171]. Emerging survivorship models similarly highlight the value of proactive care pathways designed to anticipate changing needs, support self-efficacy, and promote sustained recovery across the survivorship continuum [172]. Clinical guidance on the management of persistent pain in cancer survivors underscores the need for individualized, flexible strategies that balance symptom control, safety, and functional goals over extended periods of survivorship [173]. Viewed through this lens, PMPS is not a static complication of surgery, but a dynamic condition requiring ongoing reassessment and adjustment as survivorship needs evolve.

Taken together, these perspectives highlight how integrating neuroimmune concepts into survivorship care reshapes understanding of long-term recovery in PMPS. Recognizing persistent pain as a biologically grounded, system-level condition can reduce stigma, validate patient experiences, and support survivorship care models that prioritize long-term function, participation, and quality of life. By aligning survivorship care with both the lived realities of patients and the underlying biology of chronic pain, a neuroimmune framework offers a more compassionate, coherent, and clinically meaningful foundation for supporting recovery well beyond the completion of breast cancer treatment.

## Discussion: Integrated Clinical and Survivorship Implications

Taken together, the preceding evidence supports the need for coordinated, systems-oriented approaches to refractory post-mastectomy pain syndrome (PMPS) that extends beyond isolated symptom suppression. Contemporary pain theory increasingly recognizes persistent pain as an emergent property of interacting biological and psychosocial processes rather than the consequence of a single dominant lesion, challenging linear and reductionist treatment models that remain common in clinical practice [90,174]. In breast cancer populations, real-world clinical studies further demonstrate that conventional pain management strategies frequently fail to accommodate the complexity, variability, and persistence of post-treatment pain, underscoring the need for more adaptive and comprehensive models of care [130,175].

An integrative, neuroimmune-informed perspective provides a coherent framework for aligning emerging biological insights with the realities of long-term cancer survivorship. Survivorship-specific guidance increasingly emphasizes minimizing cumulative treatment-related harm while prioritizing functional recovery, symptom burden reduction, and quality of life over prolonged pharmacologic escalation alone [17,127]. Neuroimmune-informed care models support the intentional coordination of pharmacologic, rehabilitative, behavioral, and supportive strategies within a unified clinical plan that remains responsive to changing survivorship needs and patient priorities [17,176]. From a systems perspective, these models acknowledge that persistent pain reflects ongoing interactions among immune activation, neural plasticity, stress physiology, and behavioral adaptation rather than a single pathological pathway [177-179].

Functional recovery and quality-of-life outcomes are increasingly recognized as central indicators of successful survivorship care in breast cancer populations. Persistent pain has been consistently associated with limitations in physical functioning, reduced participation in daily activities, and diminished overall well-being, highlighting the

inadequacy of care strategies focused narrowly on pain intensity reduction alone [169,170]. Expert consensus statements emphasize that high-quality survivorship care should be longitudinal, adaptive, and multidisciplinary, explicitly addressing chronic symptoms such as pain as integral components of comprehensive survivorship planning rather than residual or secondary concerns [171]. Integrative survivorship frameworks further emphasize that sustained recovery is best supported when care models proactively address biological vulnerability, psychosocial stressors, and functional goals over time, rather than relying on episodic or reactive interventions [120,175].

Viewed through this integrative lens, PMPS is most coherently understood not as a static postoperative complication, but as an evolving survivorship condition shaped by neuroimmune dysregulation across biological, psychological, and social domains. Emphasizing coordinated, systems-based care that prioritizes function, safety, participation, and quality of life offers a more durable and compassionate response to persistent post-treatment pain than models centered exclusively on localized nerve injury or symptom suppression. In this way, a neuroimmune framework aligns clinical management of PMPS with the long-term realities of cancer survivorship, supporting care strategies that honor both biological complexity and lived experience.

## Clinical Take-Home Concepts for Integrative Oncology Practice

### Post-mastectomy pain syndrome is not solely a nerve injury disorder

Persistent PMPS is best understood as a neuroimmune condition involving sustained immune activation, central sensitization, autonomic imbalance, and maladaptive stress responses that may persist long after apparent tissue healing. Contemporary pain frameworks increasingly emphasize system-level dysregulation rather than isolated peripheral pathology, providing a more coherent explanation for chronic pain persistence following cancer treatment [27,174]. Clinically, this perspective supports reframing conversations away from "what went wrong surgically" toward understanding how cancer and its treatments can leave lasting imprints on immune–nervous system regulation.

### Pain persistence does not imply ongoing structural damage

Continued pain following mastectomy often reflects a failure of neuroimmune and central nervous system resolution rather than unresolved surgical pathology. Advances in neuroimaging and network neuroscience demonstrate that chronic pain is associated with enduring alterations in brain network organization, complexity, and information processing—even in the absence of ongoing tissue injury—helping explain why symptoms may persist despite normal imaging or healed surgical sites [28,35]. Recognizing this distinction may reduce unnecessary diagnostic escalation and help validate patient experiences when conventional testing appears reassuring, but symptoms remain severe.

### Clinical heterogeneity reflects system-level dysregulation

Marked variability in pain severity, distribution, and treatment response among breast cancer survivors is more consistent with differences in immune activation, central nervous system plasticity, autonomic tone, sleep disruption, and psychosocial stress exposure than with differences in nerve injury alone. Reviews of central sensitization highlight that pain phenotypes emerge from dynamic interactions among multiple neural and immune processes, accounting for the heterogeneity commonly observed in chronic pain populations [94,139]. Emerging evidence linking stress physiology and hypothalamic–pituitary–adrenal axis dysregulation to persistent symptoms further underscores the relevance of brain–body feedback loops in refractory PMPS [63].

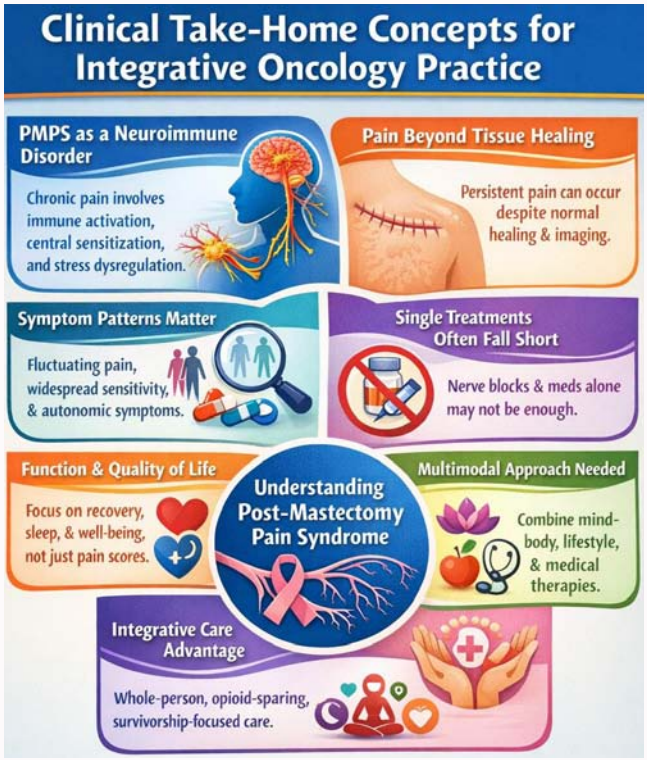


**Figure 3:** Clinical take-home concepts for neuroimmune-informed management of post-mastectomy pain syndrome**.** This figure summarizes key clinical insights derived from a neuroimmune framework of PMPS, highlighting system-level contributors to pain persistence, limitations of single-mechanism interventions, and the rationale for integrative, multimodal survivorship care. That single sentence makes the figure *journal-appropriate*.

### Single-mechanism interventions frequently provide limited or transient benefit

Therapies targeting isolated pathways—such as regional nerve blocks or monotherapy pharmacologic approaches—often fail to address the interacting biological processes that sustain pain in refractory PMPS. Clinical and translational pain literature consistently demonstrates that reductionist treatment strategies are poorly matched to the multisystem nature of chronic pain and are therefore unlikely to yield durable benefit when neuroimmune amplification is present [109, 71]

### Symptom patterns can guide mechanism-informed care

Pain that is disproportionate to physical findings, fluctuates with stress or sleep disturbance, extends beyond the original surgical distribution, or is accompanied by autonomic symptoms and limited response to nerve-directed interventions is more consistent with neuroimmune or centrally mediated pain states than with purely peripheral neuropathy. Clinical phenotyping approaches grounded in pain neuroscience emphasize recognition of these patterns to support more appropriate, mechanism-aligned management [90,97].

Survivorship research further indicates that a subset of breast cancer survivors carries a disproportionately high symptom burden across multiple domains, highlighting the importance of early identification and tailored intervention [180].

### Treatment goals should extend beyond pain scores alone

For many breast cancer survivors, improvements in physical function, sleep quality, emotional regulation, and overall quality of life represent more meaningful indicators of recovery than reductions in pain intensity alone. Patient-reported outcome research underscores the importance of aligning pain management with survivor-defined goals and functional priorities rather than narrowly focusing on analgesia [168,169].

### Integrative oncology is well suited to operationalize neuroimmune-informed care

Because integrative oncology emphasizes systems-based, multimodal, and opioid-sparing approaches, it is uniquely positioned to translate neuroimmune concepts into longitudinal survivorship care for PMPS. Integrative frameworks that combine pharmacologic, rehabilitative, behavioral, educational, and supportive strategies align closely with emerging pain science and survivorship guidance, offering a practical pathway for addressing the complexity of persistent cancer-related pain [88,117,125]. Educational strategies such as pain neuroscience education may further support patient engagement and self-efficacy by helping individuals reconceptualize pain in a non-threatening, biologically grounded manner [181].

## Future Directions

Further research is needed to refine the conceptualization of post-mastectomy pain syndrome (PMPS) as a neuroimmune disorder and to translate emerging mechanistic insights into clinically actionable survivorship care pathways. Prospective, longitudinal investigations integrating immune, neurophysiological, and psychosocial domains represent a critical next step for delineating patient subgroups at heightened risk for pain chronification and clarifying the relative contributions of immune activation, central sensitization, and autonomic dysregulation over time [90,174]. In parallel, growing interest in inflammatory and immune biomarkers as predictors of persistent symptoms underscores the potential value of incorporating peripheral blood markers and immune profiling into survivorship research, particularly as tools for early risk stratification and mechanism-informed intervention planning [182,183]. Advances in predictive analytics, including machine learning models applied to postoperative breast cancer pain, further suggest that data-driven approaches may augment—rather than replace—clinical phenotyping and improve early identification of individuals at risk for persistent pain [167].

Future studies should also prioritize multidimensional outcome measures that extend beyond pain intensity alone. Functional capacity, sleep quality, emotional regulation, fatigue, and patient-reported quality of life are increasingly recognized as central indicators of recovery in cancer survivorship and may more accurately reflect meaningful neuroimmune resolution than numeric pain scores in isolation [168,169,171]. Mixed-methods research incorporating patient-reported outcomes alongside qualitative data can further illuminate how individuals adapt to persistent symptoms over time, providing essential context for interpreting clinical trajectories and treatment responses [87]. Longitudinal designs that integrate quantitative and experiential dimensions may therefore be particularly well suited to capturing the evolving course of recovery following breast cancer treatment.

Translational and clinical research evaluating multimodal, opioid-sparing strategies remains a high priority within this framework. Neuroimmune-informed interventions that combine pharmacologic, rehabilitative, behavioral, and lifestyle-oriented components warrant systematic investigation to determine optimal sequencing, duration, and patient selection across the survivorship continuum [125,173]. Pragmatic trials embedded within real-world survivorship care settings may be especially valuable for assessing feasibility, safety, and effectiveness, while minimizing barriers to implementation. Emerging work in implementation science and pragmatic oncology provides a methodological foundation for bridging efficacy and effectiveness, helping ensure that promising neuroimmune-informed strategies can be successfully integrated into routine clinical practice [184-186]. Notably, breast cancer–specific pragmatic trial protocols evaluating pain education and activity-based coaching illustrate how mechanism-informed approaches can be operationalized within survivorship care pathways [175].

Beyond intervention development, continued investigation of the evolving interface between immune modulation and pain biology in cancer populations represents an important translational frontier. Emerging evidence linking immune cell activity to cancer-related neuropathic pain, as well as exploratory associations between immunotherapy pathways and pain mechanisms, highlights opportunities for advancing both risk assessment and therapeutic targeting [187,78]. While much of this work remains early-stage, it underscores the need for sustained cross-disciplinary collaboration among pain scientists, immunologists, oncologists, rehabilitation specialists, and data scientists.

Finally, well-documented case series and mixed-methods investigations can play a valuable role in bridging mechanistic models and clinical practice, particularly in complex or refractory presentations that are underrepresented in randomized trials. Integrative case reports describing whole-person approaches to persistent post-mastectomy pain and wound-healing complications have begun to illustrate the potential clinical relevance of neuroimmune-informed care in survivorship settings [188,189]. Importantly, such reports should be viewed as hypothesis-generating and complementary to larger prospective studies, highlighting the need for broader validation across diverse populations and care contexts. Collectively, these research directions can inform the development of more coherent, compassionate, and evidence-informed strategies for managing persistent pain in breast cancer survivorship and advance the field toward more personalized and sustainable models of care.

## Conclusion

Post-mastectomy pain syndrome (PMPS) represents a complex and often persistent condition that cannot be adequately explained by peripheral nerve injury alone. Accumulating evidence from pain neuroscience and cancer survivorship research increasingly supports a neuroimmune framework in which sustained immune activation, central sensitization, autonomic dysregulation, and maladaptive stress responses interact dynamically to drive pain persistence long after apparent tissue healing has occurred [90,174]. Continued reliance on narrow, structurally focused models may therefore limit both clinical understanding and therapeutic effectiveness, particularly in patients

whose symptom burden remains disproportionate to identifiable tissue pathology. By contrast, a neuroimmune model offers a more coherent explanation for the clinical heterogeneity of PMPS, the frequent mismatch between pain severity and imaging findings, and the limited durability of single-mechanism interventions.

Viewed through this neuroimmune lens, persistent post-mastectomy pain is best understood as a system-level disorder with important implications for assessment, risk stratification, and treatment strategy. Neuroimaging and clinical pain research increasingly demonstrate that chronic pain states are associated with enduring alterations in central neural networks, immune signaling, and autonomic regulation rather than ongoing peripheral injury, reinforcing the need for multimodal, mechanism-informed approaches to care [94]. Within breast cancer survivorship, such approaches align closely with contemporary guidance emphasizing opioid-sparing strategies, restoration of function, sleep regulation, emotional resilience, and quality-of-life outcomes over pain intensity reduction alone [171,173]. Importantly, qualitative survivorship research underscores that persistent symptoms are frequently experienced as invalidating or minimized, highlighting the clinical importance of frameworks that explicitly acknowledge chronic pain as biologically real, multifactorial, and deserving of sustained, compassionate care [166].

Emerging integrative and case-based literature further illustrates how whole-person, neuroimmune-informed strategies may offer clinically meaningful benefit for select breast cancer survivors with refractory post-mastectomy pain and related complications [188,189]. While such observations remain preliminary, they provide valuable translational insight into how multimodal, patient-centered approaches can be operationalized in real-world survivorship settings characterized by biological complexity and clinical heterogeneity. In this context, well-documented case series and mixed-methods investigations serve as important hypothesis-generating complements to mechanistic and trial-based research. Consistent with this perspective, evidence from supported self-management pathways suggests that when survivorship care explicitly incorporates patient priorities, education, and longitudinal support, meaningful improvements in quality of life and healthcare utilization may occur even in the presence of persistent symptoms [190,191].

Looking forward, advancing care for patients with PMPS will require not only continued mechanistic and clinical investigation, but also deliberate attention to implementation, dissemination, and sustainability. Implementation science frameworks offer practical tools for translating neuroimmune-informed survivorship models into routine oncology practice, helping bridge the gap between emerging evidence and durable clinical impact across diverse care settings [184]. Collectively, these insights support a more compassionate, biologically grounded, and survivorship-focused approach to post-mastectomy pain—one that validates patient experience, reframes chronic pain as a system-level condition, prioritizes long-term function and quality of life, and aligns scientific understanding with the lived realities of breast cancer survivorship.

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## References

1. Gong Y, Tan Q, Qin Q, Wei C. Prevalence of postmastectomy pain syndrome and associated risk factors. Medicine.2020;99(20):19834.
2. Calapai M, Esposito E, Puzzo L, Vecchio DA, Blandino R, Bova G, et al. Post-mastectomy pain: An updated overview on risk factors, predictors, and markers. Life. 2021;11(10):1026.
3. Salati SA, Alsulaim L, Alharbi MH, Alharbi NH, AlsenaidTM, Alaodah SA, et al. Postmastectomy Pain Syndrome: A narrative review. Cureus. 2023;15(10):47384.
4. Andersen KG, Kehlet H.Persistent pain after breast cancer treatment: A critical review of risk factors and strategies for prevention. J Pain. 2011;12(7):725-746.
5. Ji R.-R, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018;129(2):343366.
6. Bennett MI, Kaasa S, Barke A, Korwisi B, Rief W, Treede RD, et al.The IASP classification of chronic pain for ICD-11: Chronic cancer-related pain. Pain. 2019;160(1):38-44.
7. TassouA, RichebeP, Rivat, C. Mechanisms of chronic postsurgical pain. Reg Anesth Pain Med. 2025;50(2):7-85.
8. Zhang S, Ning Y, Yang Y, Mu G, Yang Y, Ren C, et al.Decoding pain chronification: Mechanisms of the acute-to-chronic transition. Fron MolNeurosci. 2025;18:1596367.
9. Xiong HY, Hendrix J, Schabrun S, Wyns A, Campenhout JV, Nijs J, et al. The role of the brain-derived neurotrophic factor in chronic pain: Links to central sensitization and Neuroinflammation. Biomolecules. 2024;14(1):71.
10. Finan PH, Goodin, BR, Smith MT.The Association of Sleep and pain: An update and a path forward. JPain. 2013;14(12);1539-52.
11. Sluka KA, WagerTD, Sutherland SP, Labosky PA, Balach T, Bayman EO, et al. Predicting chronic postsurgical pain: Current evidence and a novel program to develop predictive biomarker signatures. Pain. 2023;164(9):1912-1926.
12. Mao J,Ismaila N,Bao T,Barton D, Ben-Arye E, Garland EL, et al. Integrative medicine for pain management in oncology: Sio-ASCO guideline. ASCO Podcast DO Group.J Clin Oncol. 2022;40(34):3998-4024.
13. Pimentel-Parra, GA, García-Vivar C, Escalada-Hernández P, San Martín-Rodríguez L, Soto-Ruiz N. Systematic Review of Clinical Practice Guidelines for long-term breast cancer survivorship: Assessment of quality and evidence-based recommendations. British J Cancer.2025;133(2):178-93.
14. McEwen BS, Akil H.Revisiting the stress concept: Implications for affective disorders. J Neurosci. 2020;40(1):12-21.
15. Cheng WH, Teo RH, Cheng LJ, Lau Y, Lau ST.Global prevalence of sleep disturbances among breast cancer survivors: A systematic review with meta-analysis. Sleep Health. 2023;9(5):704-16.
16. Narusawa E, Sadeghi S, Tane K, Alkhaifi M, Kikawa Y. Updates on the prevention and management of post-mastectomy pain syndrome beyond medical treatment: A comprehensive narrative review. AnnPalliat Med. 2024;13(5):1258-64.
17. Bell BK, Cha J, Cavanaugh KA, O'Riordan DL, Rabow MW, Yang AK, et al. Integrative management of cancer pain: A scoping review of the literature. Cancer Med. 2025;14(9):70833.
18. Volcheck MM, Graham SM, Fleming KC, Mohabbat AB, Luedtke CA. Central sensitization, chronic pain, and other symptoms:

Better understanding, better management. Cleveland Clin J Med. 2023;90(4):245-54.

19. Herbetko K, Kaczor J, Sołtyk A, Kisielewska M, Opęchowski M, Sztuder A, et al. The impact of chronic stress on treatment outcomes of cancer patients with divergent survival rates: A systematic review. Int J Mol Sci. 2026;27(2):686.

20. Ren Y, Gao R, Zhang S, Geng X, YangQ, Ouyang L, et al. Associations between breast radiation dermatitis and post-mastectomy pain syndrome in patients with breast cancer: A multicenter retrospective study. AsiaPac J OncolNurs. 2024;11(12):100602.

21. Krawczyk M, Solbrække KN, Thoresen L. Extending the concept of total pain to cancer survivorship. Fron Sociol. 2025;9:1387096.

22. Jaffal SM.Neuroplasticity in chronic pain: Insights into diagnosis and treatment.Korean J Pain. 2025;38(2):89-102.

23. Paice JA, Lacchetti C, Bruera E.Management of chronic pain in survivors of adult cancers: Asco clinical practice guideline summary. J OncolPract. 2016;12(8):757-762.

24. Kelkar RA, KayeAD, PerillouxDM, HawkinsAM, Wester GC, Ragland AR, et al. Evolving role of immunology in chronic pain medicine: Tissue necrosis factor and interleukin modulatory treatments. Exploration of Immunology. 2024;4:523-32.

25. Grace PM, TawfikVL, Svensson CI, Burton MD, Loggia ML, HutchinsonMR. The neuroimmunology of chronic pain: From rodents to humans. J Neurosci.2020;41(5):855-65.

26. Zhang M, Li N, Zhao S, Feng X. Hyperalgesic priming in the transition from acute to chronic pain: Focus on different models and the molecular mechanisms involved. J Pain Res. 2025;18:1491-1501.

27. Inoue K, Tsuda M.Microglia in neuropathic pain: Cellular and molecular mechanisms and therapeutic potential. Nat Rev Neurosci. 2018;19(3):138-152.

28. Butry L, Thomä J, Elsenbruc S, Icenhour A, Rehmann R, Enax-KrumovaE, et al. Brain network properties in chronic paina systematic review and meta-analysis of graph-based connectivity metrics. Front Neurosci. 2025;19:1672542.

29. Daibes M, Almarie B, Andrade MF, Vidigal Gde, Aranis N, Gianlorenco A, et al. Do pain and autonomic regulation share a common central compensatory pathway? A meta-analysis of HRV metrics in pain trials. NeuroSci. 2025;6(3):62.

30. Alexandre C, Miracca G, Holanda VD, Sharma A, Kourbanova K, Ferreira A, et al. Nociceptor spontaneous activity is responsible for fragmenting non–rapid eye movement sleep in mouse models of neuropathic pain. Sci Transl Med. 2024;16(743):3036.

31. Al-dardery NM, Khaity AM, Albakri KA, Abdelsattar AT, Benmelouka AY, Lee T, et al. Preservation versus dissection of the intercostobrachial nerve for breast cancer surgeries: A systematic review and meta-analysis. Annals of Medicine & Surgery, 2023;86(2):1003-11.

32. Kim JY, Ha JH, Jin US. Effect of intercostal nerve coaptation on postoperative pain in implant-based breast reconstruction: A double-blind, randomized controlled pilot study. J Breast Cancer. 2025;28(2):108.

33. Chen Y, Wu X, Li J, Ren Y, Miao H, Zhai X, et al. The mechanisms of specialized pro-resolving mediators in pain relief: Neuro-immune and neuroglial regulations. Fron Immunol. 2025;16:1634724.

34. Shirvalkar P, Prosky J, Chin G, Ahmadipour P, Sani OG, Desai M, et al. First-in-human prediction of chronic pain state using intracranial neural biomarkers. NatNeurosci. 2023;26(6):1090-99.

35. Del Mauro G, Li Y, Yu J, Kochunov P, Sevel LS, Boissoneault J, et al. Chronic pain is associated with greater brain entropy in the prefrontal cortex. J Pain. 2025;32:105421.

36. Shkodra M, Mulvey M, FallonM, Brunelli C, Zecca E, Bracchi P, et al. Application and accuracy of the EAPC/IASP diagnostic algorithm for neuropathic cancer pain and quantitative sensory testing profile in patients with pain due to cancer. Pain Reports. 2024;9(2):e1140.

37. Tan Z, He Q, Zhang X, Feng J, He Y, LiX.The interaction between pain and mental disorders: An interdisciplinary analysis through Bibliometrics. Ibrain. 2025;11(4):476-91.

38. Pu T, Sun J, Ren G, Li H.Neuro-immune crosstalk in cancer: Mechanisms and therapeutic implications. Signal Transduct Target Ther. 2025;10(1):176.

39. Varrassi G, Leoni ML, Farì G, Al-Alwany AA, Al-Sharie S,Fornasari D. Neuromodulatory signaling in Chronic pain patients: A narrative review. Cells. 2025;14(17):1320.

40. MaM, Jiang W, Zhou R. Damps and damp-sensing receptors in inflammation and diseases. Immunity. 2024;57(4):752-771.

41. Kawai T, IkegawaM, Ori D, Akira S. Decoding toll-like receptors: Recent insights and perspectives in innate immunity. Immunity. 2024;57(4):649-73.

42. Maisat W, Yuki K.The role of damage-associated molecular patterns in perioperative neurocognitive disorders: A narrative review. Anesthes Analgesia. 2025;142(2):312-25.

43. Zipp F, BittnerS, Schafer DP. Cytokines as emerging regulators of central nervous system synapses. Immunity. 2023;56(5):914-925.

44. Dib-Hajj SD, Yang Y, Black JA, WaxmanSG.The nav1.7 sodium channel: From Molecule to man. Nature Reviews Neuroscience. 2012;14(1):49-62.

45. Waxman SG, ZamponiGW. Regulating excitability of peripheral afferents: Emerging ion channel targets. Nature Neuroscience. 2024;17(2):153-63.

46. Gomez Kimberly, Stratton HJ, Duran P, Loya S, TangC, Calderon-Rivera A, et al. Identification and Targeting of a Unique Nav1.7 Domain Driving Chronic Pain.Proc Natl Acad Sci U S A. 2023;120(32):e2217800120.

47. Damani-Yokota P, Khanna KM. Innate immune memory: The evolving role of macrophages in therapy. eLife. 2025;14.

48. Dourson ML. Probabilistic methods for non-cancer health effects. Regul Toxicol Pharmacol. 2023;142:105411.

49. Qiu JM, FuMR, Finlayson CS, TilleyCP, Martín Payo R, Korth S, et al. Lymphatic pain in breast cancer survivors: An overview of the current evidence and recommendations. WomenChildNur. 2024;2(2)33-38.

50. Jørgensen MG, Toyserkani NM, Hansen FG, Bygum A, Sørensen JA.The impact of lymphedema on health-related quality of life up to 10 years after breast cancer treatment. Npj Breast Cancer.2021;7(1).

51. Zhang Q, Niu Y, Li Y, Xia C, Chen Z, Chen Y, et al. Meningeal lymphatic drainage: Novel insights into central nervous system disease. Signal Transduct Target Ther. 2025;10(1):142.

52. Lu HJ, Gao YJ.Astrocytes in chronic pain: Cellular and molecular mechanisms. Neuroscience Bull. 2022;39(3):425-39.

53. Di Spiezio, Gómez-Gonzalo M, Chiavegato A, Zonta, M.Recent insights on supraspinal astrocytes in chronic pain. NeurochemRes. 2025;50(5):276.

54. Zhang S, NingY, YangY, Mu G, YangY, Ren C, et al. Decoding pain chronification: Mechanisms of the acute-to-chronic transition. Front Mol Neurosi. 2025;18:1596367.

55. Hu Z, Yu X, Chen P, Jin K, Zhou J, Wang G, et al. BDNF-TrkB signaling pathway-mediated microglial activation induces neuronal KCC2 downregulation contributing to dynamic allodynia following spared nerve injury. Mol Pain. 2023;19:17448069231185439.

56. Voshart DC, Oshima T, Jiang Y, van der Linden GP, Ainslie AP, Nazario LR, et al. Radiotherapy Induces Persistent Innate Immune Reprogramming of Microglia into a Primed State.Cell Rep. 2024;43(2):113764.

57. McCaffrey D, Lawther AJ, Weickert CS, Walker AK.Cancer

activates microglia to the same extent as chronic stress throughout stress neurocircuitry in a mouse model of breast cancer. Psychoneuroendocrinology. 2022;146:105938.

58. Chen J, Huang J, Han T, Kojima N.Chronic stress modulates microglial activation dynamics, shaping priming responses to subsequent stress. Brain Sci. 2025;15(5):534.

59. Nishigami T, Manfuku M, LahousseA. Central sensitization in cancer survivors and its clinical implications: State of the art. J Clin Med. 2023;12(14):4606.

60. Hurth A, Nijzink-Ter Steege J, Scheepbouwer P, Roose E, Lahousse A, Leysen L, et al. Assessment of central sensitization in breast cancer survivors: Convergent validity and use of the Central Sensitization Inventory (CSI) and its short-form as a clustering tool. Clin Pract. 2021;11(3):607-18.

61. LinJ, Epel E. Stress and telomere shortening: Insights from cellular mechanisms. Ageing ResRev. 2022;73:101507.

62. Kanter NG, Cohen-Woods S, BalfourD, Burt MG, Waterman AL, Koczwara, B.Hypothalamic–pituitary–adrenal axis dysfunction in people with cancer: A systematic review. Cancer Med. 2024;13(22):70366.

63. Gomez A, Wu Y, Zhang C, Boyd L, Wee TL, Gewolb J, et al. A Brain-Body Feedback Loop Driving Hpa-Axis Dysfunction in Breast Cancer. Biorix. 2024.

64. Wang F, Giskeødegård GF, Skarra S, Engstrøm MJ, HagenL, Geisler J, et al. Association of serum cortisol and cortisone levels and risk of recurrence after endocrine treatment in breast cancer. Clin Exp Med. 2023;23(7):3883-93.

65. Benarroch E. What is the role of dorsal horn astrocytes in chronic pain and itch? Neurology, 2022;99(20):891-97.

66. TraceyKJ. The inflammatory reflex. Nature. 2022;420(6917):853-59.

67. Zhang Q, Li W, Yu S, Xu J, Tang L, Yao S, et al. Heart rate variability and cytokines are involved in anxiety in breast cancer patients: A cross-sectional study. Clin Breast Cancer. 2025;25(3):233-41.

68. Irwin MR, Opp MR.Sleep health: Reciprocal regulation of sleep and innate immunity. Neuropsychopharmacology. 2017;42(1):12-155.

69. Diester C, Joo W. At the intersection of pain and sleep: A roadmap for preclinical pain research. Frontiers in Pain Research. 2025;6:1609524.

70. Shin J, Kober KM, Harris C, Oppegaard K, Calvo-SchimmelA, Paul SM, et al. Perturbations in neuroinflammatory pathways are associated with a worst pain profile in oncology patients receiving chemotherapy. JPain. 2023;24(1):84-97.

71. Kuner R, FlorH. Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci. 2016;18(1):20-30.

72. Feenstra RA, den Dunnen WFA, Laman JD. The neuroimmune axis and chronic pain disorders. iScience. 2026;29(1):114250.

73. Francis N, Bobringer JC.Cancer as a homeostatic challenge: The role of the hypothalamus. Trends Neurosci. 2024;44(11:903-14.

74. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2011;152(3):2-15.

75. Cayrol T, van den Broeke EN. Central sensitisation: Causes, therapies, and terminology. The Lancet Rheumatol.2021;3(8):548.

76. Saracoglu I, Isintas M, Turk A, Leysen L, Nijs J.Phenotyping of chronic pain in breast cancer survivors: An original study using the cancer pain phenotyping (canpphe) network multidisciplinary international guidelines. Support CareCance. 2024;32(6):383.

77. Yang JX, Wang HF, Chen JZ, Li HY, Hu JC, Yu A, et alPotential neuroimmune interaction in chronic pain: A review on immune cells in peripheral and central sensitization. Front Pain Res. 2022;3:946846.

78. Ma H, Pan Z, Lai B, Li M, WangJ.Contribution of immune cells to cancer-related neuropathic pain: An updated review. Molecular Pain. 2023;19:17448069231182235.

79. Strijbos BT, Janssen L, Voogd AC, Zwaans WA, Roumen RM, Maaskant-Braat AJ.Persistent pain after breast cancer treatment, an underreported burden for breast cancer survivors. Ann SurgOncol. 2024;31(10):6753-763.

80. YukselSS, ChappellAG, Jackson BT, Wescott AB, Ellis MF.Post mastectomy pain syndrome: A systematic review of prevention modalities." JPRAS Open. 2022;31:32-49.

81. Fuller AM, Bharde S, SikandarS. The mechanisms and management of persistent postsurgical pain. Frontiers in Pain Research. 2023:4:1154597.

82. VinanteL, Polesel J, Sacilotto A, Giroldi A, Caroli A, Revelant A, et al. Baseline systemic inflammatory indices predict late radiation-induced fibrosis and toxicity in patients with early breast cancer. The Breast. 2023;85:104685.

83. Scheff NN, Saloman, JL.Neuroimmunology of cancer and associated symptomology. Immunol Cell Biol. 2021;99(9):949-61.

84. Pergolizzi JV, LeQuang JA, Magnusson P, Varrassi G.Identifying risk factors for chronic postsurgical pain and preventive measures: A comprehensive update. Expert Rev Neurother. 2023;23(12):1297-1310.

85. Bjerkeset E, Röhrl K,Schou-Bredal I.Symptom cluster of pain, fatigue, and psychological distress in breast cancer survivors: Prevalence and characteristics. Breast Cancer Research and Treatment. 2020;180(1):63-71.

86. Lu X, Geng W, Liu F, Yin Y, Yin J, Zhang Y, et al. Symptom clusters and Sentinel symptoms in breast cancer survivors based on self-reported outcomes:A cross-sectional survey. J Clin Nurs. 2024;34(3):1072-80.

87. McGarragle KM, Zheng S, Gagliese L, Howell D, Edwards E, Pritlove C, et al. Pain self-management behaviors in breast cancer survivors six months post-primary treatment: A mixed-methods, descriptive study. Cancers. 2025;17(7):1087.

88. Liou KT, Ashare R, Worster B, Jones KF, Yeager KA, Acevedo AM, et al. Sio-ASCO guideline on Integrative Medicine for Cancer Pain Management: Implications for racial and ethnic pain disparities. JNCI Cancer Spectrum. 2023;7(4):042.

89. Balordi M, Tiberio P, Castaldo M, Viganò A, Jacobs F, Zambelli A, et al. Empowering beyond pain: Pain neuroscience education interventions in breast cancer survivorship care. Cancers. 2024;16(16):2806.

90. Verspyck E, Attal N. Diagnosing nociplastic pain in cancer survivors: A major step forward. Br Jof Anaesthes. 2023;130(5):515-18.

91. Haenen V, Dams L, Meeus M,De Groef A.Altered somatosensory functioning and mechanism-based classification in breast cancer patients with persistent pain. AnatRec.2022;307(2):273-84.

92. Amber G, Lore D, Elien VG, Jan S, Michel M, An G, et al. From breast cancer diagnosis to survivorship: Analyzing perioperative biopsychosocial phenotypes and their relationship to pain on long term. J Pain. 2025;26:104709.

93. Herrero BabiloniA, Fonseca Alonso B, Martel MO, BoggeroIA, Lavigne GJ, Goode AP, et al. The Association of Sleep-related issues with chronic pain and high-impact chronic pain incidence in U.S. adults: A 1-year representative cohort study. J Pain. 2025;36:105541.

94. Velasco E, Flores-Cortés M, Guerra-Armas J, Flix-Díez L, Gurdiel-Álvarez F, Donado-Bermejo A, et al. Is chronic pain caused by central sensitization? A review and critical point of View. Neuroscience & Biobehavioral Reviews. 2024;167:105886.

95. Fernández-Gualda MÁ, Ariza-Vega P, Galiano-Castillo N, Tovar-Martín I, Ortiz-Comino L, Lozano-Lozano M. Pained app. assessing central sensitization in survivors of breast cancer: A reliability study. Digit

Health. 2024:10:20552076241260150.

96. LuoJ, Zhu HQ, Gou B, Wang XQ.Neuroimaging assessment of pain. Neurotherapeutics. 2022;19(5):1467-88.

97. Devarajan J, Mena S, Cheng J.Mechanisms of complex regional pain syndrome. Frontiers in Pain Research. 2024;5:1385889.

98. Sahbaie P, Li WW, Guo TZ, Shi X, KingeryWS, Clark JD.Autonomic regulation of nociceptive and immunologic changes in a mouse model of complex regional pain syndrome. J Pain, 2022;23(3:472-86.

99. Geraldes V, Caldeira E, AfonsoA, Machado F, Amaro-Leal Â, Laranjo S, et al. Cardiovascular dysautonomia in patients with breast cancer. Open Cardiovascular MedJ. 2022;16(1).

100. Fooladi S, Hasoon J, Kaye AD, Abd-Elsayed A. Diagnostic criteria and technical evaluation of Complex Regional pain syndrome: A narrative review. Diagnostics. 2025;15(17):2281.

101. Fitzgerald Jones K, Fu MR, McTerna ML, Ko E, Yazicioglu S, Axelrod D. Lymphatic pain in breast cancer survivors. Lymphatic Research and Biology. 2022;20(5):525-32.

102. Rosenberger DC, Pogatzki-ZahnEM. Chronic post-surgical pain update on incidence, risk factors and preventive treatment options. BJA Edu. 2022;22(5):190-196.

103. So WK, Law BM, Ng MS, HeX, ChanDN, Chan CW, et al. Symptom clusters experienced by breast cancer patients at various treatment stages: A systematic review. Cancer Medicine. 2021;10(8):2531-65.

104. Sur D, Zeng Y, Kobayashi H, Zhi X, Goetz MR, Müller CM, et al. Entangled cellular and molecular relationships at the sensory neuron-cancer interface. Neuron. 2025;113(17):2760-90.

105. Erin N. Role of sensory neurons, neuroimmune pathways, and transient receptor potential vanilloid 1 (TRPV1) channels in a murine model of breast cancer metastasis. Cancer ImmunolImmunother. 2020;69(2):307-14.

106. He Z, Liu F, Lin L, Huang, Z, Wang Y.Interplay between Schwann cells and peripheral cancers: Mechanisms and therapeutic targets in cancer progression. Glia. 2025;73(8):1553-64.

107. Haack M, Simpson N, Sethna N, Kaur S, Mullington, J. Sleep deficiency and chronic pain: Potential underlying mechanisms and clinical implications. Neuropsychopharmacology.2019;45(1):205-16.

108. Rosner J, de Andrade DC, Davis KD, Gustin SM, Kramer JLK, Seal RP, et al. Central neuropathic pain. Nature reviews. Nat Rev Dis Primers. 2023;9(1):73.

109. Raffaeli W, Tenti M, CorraroA, Malafoglia V, Ilari S, Balzani E, et al. Chronic pain: What does it mean? A review on the use of the term chronic pain in clinical practice. J Pain Res.2021;14:827-35.

110. Radwan RM, Schuster AL, Hertz DL, Lustberg MB, Vachhan HR, Hickey Zacholski E, et al. Toleranr chemotherapy-induced peripheral neuropathy among women with metastatic breast cancer: A discrete-CHOICE experiment. Breast Cancer Res Treat. 2025;212(1):149-59.

111. Abd-Elsayed A, Johnson TN, Ruprecht KK, Argall TR, Henjum LJ, Fiala KJ. Outcomes of cooled radiofrequency ablation of lumbar nerves as treatment for chronic low back pain. PainTherapy. 2025;14(3):949-56.

112. Wang Y, Zhu Y, Xue Q, JiM, Tong J, Yang JJ,et al. Predicting chronic pain in postoperative breast cancer patients with multiple machine learning and Deep Learning Models. J Clin Anesth. 2021;74:110423.

113. Kreuder L, Bissey PA, Yip KW, Liu FF. Exploring radiation-induced fibrosis: Biological Mechanisms and new frontiers in research and Therapeutics. Int J Radiat Biol. 2025;1-16.

114. Ring M.An Integrative Approach to HPA Axis Dysfunction: From Recognition to Recovery. 2025;38(10):1451-61.

115. Nunez SG, Rabelo SP, Subotic N, Caruso JW, Knezevic NN. Chronic stress and autoimmunity: The role of Hpa Axis and cortisol dysregulation. Int J MolSci. 2025;26(20):9994.

116. Mao JJ, Greenlee H, BaoT, Ismaila N, BrueraE. Integrative medicine for pain management in oncology: Society for integrative oncology-ASCO. 2022;40(34):3998-4024.

117. Wooden S. Multimodal approach to chronic pain management. NursClin North Am. 2025;60(4),619-29.

118. Zaglauer K, Kunsorg A, Jakob V, Görg L, Oehlschlägel A, Riedel R, et al. Effect of a multimodal pain therapy concept including intensive physiotherapy on the perception of pain and the quality of life of patients with chronic back pain: A prospective observational multicenter study named "Rütmus." Pain Res Management. 2025;(1):6693678.

119. Alhazmi LSS, BawadoodMAA, Aljohani AMS, Alzahrani AAR, Moshref L, Trabulsi N, et al Pain management in breast cancer patients: A multidisciplinary approach. Cureus. 2021;13(16):15994.

120. Donati CM, Zamagni A, Zamfir AA, Aristei C, CammelliS, Zamagni C, et al. Exploring pain management in breast cancer: Key findings from the arise study. Front Oncol. 2025;15:1536709.

121. Sakai Y, Kobayashi A, Akata M, Tojo K, Mihara T, Yamada A, et al.Effects of anesthetic management on persistent pain after breast cancer surgery. PLOS One. 2025;20(10).

122. Lee, M O. A comprehensive review of opioid-induced hyperalgesia. Pain Physician, 2011;3;14(2): 145–161.

123. Klimke R, Ott A, Romero CS, Berendes A, Urman RD, Luedi MM, et al. Transitional pain service: An update. Current Pain and Headache Reports>2024;28(6):457–64.

124. Thota RS, Ramkiran S, Jayant A, Kumar KS, Wajekar A, Iyer S, et al. Bridging the pain gap after cancer surgery – evaluating the feasibility of transitional pain service to prevent persistent postsurgical pain – a systematic review and meta-analysis. Indian Journal of Anaesthesia.2024a;68(10):861–74.

125. Carlson LE, Tripathy D, Zick SM, Balneaves LG, Lee RT, Greenlee H. The Society for Integrative Oncology-American Society of Clinical Oncology Joint Guidelines on Integrative Therapies for Symptom Management-overview and key recommendations. JIntegrative Complementary Med.2024;30(7):596–601.

126. Witt CM, Balneaves LG, Cardoso MJ, Cohen L, Greenlee H, Johnstone P, et al. A comprehensive definition for integrative oncology. JNCI Monographs.2017;2017(52).

127. Sanft T. NCCN Guidelines® insights: Survivorship, version 1.2023. Journal of the National Comprehensive Cancer Network : JNCCN. 2023.

128. Greenlee H, DuPont-Reyes MJ, Balneaves LG, Carlson LE, Cohen MR, Deng G, et al. Clinical practice guidelines on the evidence-based use of Integrative Therapies during and after breast cancer treatment. CA: A Cancer Journal for Clinicians.2017;767(3):194–232.

129. Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How many cancer patients use complementary and alternative medicine. IntegrCancer Ther.2011;11(3):187–203.

130. Danon N, Al-Gobari M, Burnand B, Rodondi P. Are mind–body therapies effective for relieving cancer-related pain in adults? A systematic review and meta-analysis. Psycho-Oncology.2021;31(3): 345–371.

131. Do M, Tyler WJ. Transcutaneous Vagus Nerve Stimulation in Breast Cancer: A Neuroimmune Model to Improve Quality of Life. 2026.

132. Mayer DK, Nekhlyudov L, Snyder CF, Merrill JK, Wollins DS, Shulman LN. American Society of Clinical Oncology Clinical Expert Statement on Cancer Survivorship Care Planning. J OncolPract.2014;10(6):345–351.

133. Turvill A, Maratos F, Sheffield D. Assessing the impact of interdisciplinary

multimodal pain treatment on health-related quality of life in Chronic pain: A systematic review and Meta-analyses. EurJ Pain.2025;30(1).

134. Chen F, Deng Y, Li S, Zhang Q, Xiao Z, Tish Knobf M, et al. Fear of cancer recurrence and perceived pain in patients with breast cancer: A network analysis approach. Asia-Pacific J Oncol Nurs.2025;12:100763.

135. Martínez-Miranda P, Jiménez-Rejano JJ, Muñoz-Fernández MJ, García-Muñoz C, Casuso-Holgado MJ. Effectiveness of an interactive online group intervention based on pain neuroscience education and graded exposure to movement in breast cancer survivors with chronic pain: A randomised controlled trial. Supportive Care Cancer.2024;32(10).

136. Harel K, Czamanski-Cohen J, Cohen M, Lane RD, Allen JJ, Caspi O, et al. Cardiac vagal control and emotional awareness associated with pain among breast cancer survivors. Psychophysiology.2025;62(6).

137. Mejdahl, M. K., Andersen, K. G., Gartner, R., Kroman, N., & Kehlet, H. Persistent pain and sensory disturbances after treatment for breast cancer: Six Year nationwide follow-up study. BMJ.2013;346(apr11 1).

138. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The Revised International Association for the Study of Pain Definition of pain: Concepts, challenges, and compromises. Pain.2022;161(9):1976–82.

139. De Schoenmacker I, Mollo A, Scheuren PS, Sirucek L, Brunner F, Schweinhardt P, et al. Central sensitization in CRPS patients with widespread pain: A cross-sectional study. Pain Med.2023;24(8):974–984.

140. Dams L, Van der Gucht E, Meeus M, Devoogdt N, Smeets A, Penen F, et al. Quantitative sensory testing in women after surgery for breast cancer. ClinJPain.2021;37(7):538–64.

141. Marell PS, Vierkant RA, Larson NL, Ehlers SL, Donovan KA, Stan DL, et al. Factors associated with sleep disturbance in breast cancer survivors over time. The Oncologist.2025;30(10).

142. Bolanos J, Hneiny L, Gonzalez J, O'Malley M, Wong ML. Prognostic and Diagnostic Utility of Heart Rate Variability to Predict and Understand Change in Cancer and Chemotherapy Related Fatigue, Pain, and Neuropathic Symptoms: A Systematic Review. 2025.

143. Lawson McLean A, Kahr J, Régis J, Kamp MA, Senft C. Epidemiology of resistant cancer pain: Prevalence, clinical burden, and treatment gaps. StereotactFunctNeurosurg.2025;103(6):489–501.

144. Sommer C, Klose P, Welsch P, Petzke F, Häuser W. Opioids for chronic non-cancer neuropathic pain. An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. Eur J Pain.2019;24(1):3–18.

145. Hange N, Poudel S, Ozair S, Paul T, Nambakkam M, Shrestha R, et al. Managing chronic neuropathic pain: Recent advances and new challenges. Neurol Res Int.2022;2022:1–14.

146. Vargas-Schaffer G, Paquet S, Neron A, Cogan J. Opioid induced hyperalgesia, a research phenomenon or a clinical reality? results of a Canadian survey. J Pers Med.2020b;10(2), 27.

147. Todorovic SM. Opioid-induced hyperalgesia: Are thalamic T-type calcium channels treatment targets? JClinInvest.2022;132(24).

148. Schroyen G, Blommaert J, van Weehaeghe D, Sleurs C, Vandenbulcke M, Dedoncker N, et al. Neuroinflammation and its association with cognition, neuronal markers and peripheral inflammation after chemotherapy for breast cancer. Cancers.2021;13(16):4198.

149. Tanaka M, Battaglia S. From biomarkers to behavior: Mapping the neuroimmune web of pain, mood, and memory. Biomedicines.2025a;13(9), 2226.

150. Matsuoka H, Morita T, Ishiki H, Satomi E. A literature review of management for opioid-refractory neuropathic cancer pain: An update and future perspectives. AME Med J.2025;10:26–26.

151. Galloway KS, Smith RJ, Patel LM, Hernandez AR. Patient perspectives on long-term opioid therapy: Tolerance, side effects, and functional trade-offs in chronic pain management. JPain Res.2020;13:2145–57.

152. Haque R, Chen LH, Shi J, Gu Z, Brady-Rogers M, Chlebowski RT, et al. Opioid use and adverse health effects in breast cancer survivors. The Oncologist.2024;30(3).

153. Tripolt S. Opioids and cancer progression: The role of immune modulation. Cancers.2021;13(4):789.

154. Lucia A. Opioid use and cancer recurrence: A review of mechanistic and clinical evidence. J ClinMed.2021;10(12):2594.

155. Thomas JM, Opioid exposure and oncologic outcomes: A systematic review and meta-analysis. Pain Med.2023;24(2):123–138.

156. Kennedy SKF, Sadeghi S, Raeisi Dehkordi S, Lee SF, Kirk D, Cheung YT, et al. Efficacy of multimodal psychological interventions on pain after surgery in breast cancer survivors: A systematic review. JCO Oncol Pract. 2025.

157. Soliman N, Mois X, Ferraro M. Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: A systematic review and meta-analysis - sciencedirect. Sciencedirect.2025.

158. Lemoine A, et al. Procedure-specific postoperative pain management: A systematic review of multimodal strategies. Br J Anaesth.2020;124(3):272–89.

159. Ilala A. Pain management in cancer survivorship: A multidisciplinary, long-term safety framework. Supportive Care Cancer.2023;31(2):889–902.

160. Talwar A, Rege S, AparasuRR. Pain management practices for outpatients with breast cancer. Exploratory Research in Clinical and Social Pharmacy.2022;6:100155.

161. Snijders R, Brom L, Theunissen M, van den Beuken-van Everdingen M. Update on prevalence of pain in patients with cancer 2022: A systematic literature review and meta-analysis. Cancers.2023;15(3): 591.

162. Hofbauer H, Kieselbach K, Wirz S, Bundscherer A, Stamer UM, Rapp F. Cancer-related pain in long-term survivors of oncological diseases: Results of a survey on the current care situation. Supportive Care Cancer.2024;33(1).

163. Boivin MJ, Sikorskii A, Haan P, Smith SS, Symonds LL, Khattree R, et al. Health-related quality of life: Longitudinal analysis from the time of breast biopsy into the post-treatment period. Frontiers in Global Women's Health.2021;2.

164. Gao Y. Longitudinal patterns of symptom burden among breast cancer survivors: A multi-year cohort analysis. Breast Cancer Res Treat.2023;197(2):421–35.

165. Liu, X, Yang M, Ma Y. Living beyond survival: Experiences of self-management among long-term breast cancer survivors – a qualitative study. IntJNursStudAdv.2026;10:100462.

166. Khajoei R, AzadehP, ZohariAnboohi S, Ilkhani M, Nabavi FH. Breast cancer survivorship needs: A qualitative study. BMC Cancer.2024;24(1).

167. Wang S. Perceptions of symptoms and quality of life in breast cancer patients: A qualitative comparative study of young and older adults. Holistic Integrative Oncology. 2025.

168. Balitsky AK, Rayner D, Britto J, Lionel AC, Ginsberg L, Cho W, et al. Patient-reported outcome measures in cancer care. JAMA Network Open 2024;7(8).

169. Gonçalves J, Silva A, Almeida V. Chronic pain and functional outcomes in cancer survivors: A systematic review. Support Care Cancer.2021;29(12):7891–7903.

170. Thong MSY, van der Heide A, van de Poll-Franse L. Symptom clusters and functional impairment in long-term cancer survivors: A population-based study. Psycho-Oncology.2025;34(1):112–24.

171. Vaz-Luis I, Partridge AH, Burstein HJ. Optimizing survivorship care: Expert consensus recommendations for long-term follow-up and management of chronic symptoms in breast cancer survivors.J Clin Oncol.2022;40(12):1345–56.

172. Franzoi MA, Degousee L, Martin E, Aupomerol M, Soldato D, Di Meglio A, et al. Proact: Implementing a proactive care pathway to empower and support breast cancer (BC) survivors. JClinOncol. 2022;40(28_suppl):221–221.

173. Glare P, Aubrey K, Gulati A, Lee YC, Moryl N, Overton, S. Pharmacologic management of persistent pain in cancer survivors. Drugs.2022;82(3):275–91.

174. Lawn T, Sendel M, Baron R, Vollert J. Beyond biopsychosocial: The Keystone Mechanism Theory of Pain. BrainBehaviImmun.2023;114:187–92.

175. De Groef A, Meeus M, Heathcote LC, Wiles L, Catley M, Vogelzang A, et al. Treating persistent pain after breast cancer: Practice gaps and future directions. JCancer Surviv.2022;17(6), 1698–1707.

176. Samuels N, Ben-Arye E. Integrative medicine for cancer-related pain: A narrative review. Healthcare.2024;12(3):403.

177. Bower JE, Kuhlman KR. Psychoneuroimmunology: An introduction to immune-to-brain communication and its implications for clinical psychology. AnnuRevClinPsychol.2023;19(1):331–59.

178. Sun Y, Koyama Y, Shimada S. Inflammation from peripheral organs to the brain: How does systemic inflammation cause neuroinflammation? FrontAging Neurosci.2022;14.

179. Leschak CJ, Dutcher JM, Byrne Haltom KE, Breen EC, Bower JE, Eisenberger NI. Associations between psychosocial factors and circulating cytokines in breast cancer survivors. Psychology & Health.2021;38(8):1074–1088.

180. Whisenant MS, Williams LA, Mendoza TR, Shah N, Cleeland CS. Symptom burden, symptom clusters, and functional outcomes in cancer survivors. Cancer.2021;127(9):1440–51.

181. Louw A, Puentedura EJ, Zimney K. Pain neuroscience education: A clinical guide to reconceptualizing pain and improving patient outcomes. Orthopaedic Section of the American Physical Therapy Association.2024.

182. Mackey S, Aghaeepour N, Gaudilliere B, Kao M-C, Kaptan M, Lannon E, Pfyfferet al. Innovations in acute and chronic pain biomarkers: Enhancing diagnosis and personalized therapy. Regional Anesthesia & Pain Medicine.2025;50:110–20.

183. Shirvalkar P, Prosky J, ChinG, Ahmadipour P, Sani OG, Desai M, et al. First-in-human prediction of chronic pain state using intracranial neural biomarkers. NatNeurosci.2023b;26(6):1090–9.

184. Neta G. Implementation science to enhance the value of cancer research in Latinos: A perspective from the National Cancer Institute. Advancing the Science of Cancer in Latinos.2022;143–148.

185. Adsul P, Pergolotti M, & Schmitz KH. Implementation science as the secret sauce for integrating exercise screening and triage pathways in oncology. AmSocClinOncolEducBook.2020;45(3).

186. Borges VF. Implementation strategies to integrate supportive care interventions into oncology practice: A pragmatic framework for real-world survivorship care. J Clin Oncol.2025;43(4):512–20.

187. Cascella M, Miranda B, Gagliardi C, Santaniello L, Mottola M, Mancusi A, et al. Dissecting the link between PD-1/PD-L1-based immunotherapy and cancer pain: Mechanisms, research implications, and Artificial Intelligence Perspectives. Exploration of Immunology.2024;802–21.

188. Mahalati KM. A whole-person integrative approach to a chronic non-healing post-mastectomy wound in a breast cancer survivor. Ann Clin Case Rep.2025;10:2467.

189. Mahalati K, Collins J, Forman D. Phytotherapy for post-mastectomy neuropathic pain in breast cancer survivors: Mechanistic insights and integrative clinical perspectives. Ann ClinCase Rep. 2025.

190. Giza DE, Gonzalez A, Karuturi MS, Ghosh S, Holmes HM, Naik A. Patient priorities care for older breast cancer survivors: A patient-centered approach to improve quality of breast cancer survivorship. J ClinOncol.2025;43(16_suppl).

191. Jenkins V, Matthews L, Solis-Trapala I, Gage H, May S, Williams P, et al. Patients' experiences of a supported self-management pathway in breast cancer (pragmatic): Quality of life and service use results. Supportive Care Cancer.2023;31(10):570.