Key role of the autonomic nervous system in breast cancer (Review)

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Abstract. Evidence from tumor neuroscience and clinical observations have implicated the autonomic nervous system (ANS) in breast cancer pathobiology. Sympathetic activation (norepinephrine/β-adrenergic signaling) aligns with pro-angiogenic, pro-invasive programs and distant spread, whereas increased vagal activity is associated with an anti-inflammatory state and restraint of progression. The present review summarizes mechanistic, translational and clinical data supporting a bidirectional regulatory model and evaluates a variety of ANS-targeted strategies, including β-adrenergic modulation, non-invasive vagus nerve stimulation and related neuromodulatory approaches. Whilst biologic plausibility is strong, clinical evidence remains heterogeneous and limited by study design. To the best of our knowledge, no adequately powered randomized trials have demonstrated sufficient survival benefits. The present review outlines principles for standardized autonomic phenotyping (such as heart rate variability), candidate patient selection and trial endpoints to test whether ANS modulation can improve recurrence, metastasis, toxicity and quality-of-life outcomes. Through integrating convergent evidence and articulating testable hypotheses, the present review provides an ANS-informed framework to guide future breast cancer research and care.

Contents

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1. Introduction

Breast cancer is a notable global public health issue, ranking as the second most common cancer worldwide after lung cancer and the most commonly diagnosed malignancy among women (1). Recent epidemiological data has reported ~2.31 million new cases annually, accounting for 11.6% of all cancer diagnoses, resulting in 670,000 mortalities each year. These figures underscore the profound impact of breast cancer on global mortality rates and healthcare burden (1,2). Despite advances in treatment and early detection, the pathogenesis and progression of breast cancer remain incompletely understood, necessitating further exploration of the underlying mechanisms to inform prevention and therapeutic strategies.

One emerging area of interest is the role of the autonomic nervous system (ANS), which primarily consists of the sympathetic and vagus nerves in the regulation of nearly all tissues and organs, excluding cartilage and lens (3). Traditionally considered peripheral to cancer progression, the ANS has previously been identified as exhibiting a key role in the pathophysiology of breast cancer. Dysregulation of the ANS, characterized by sympathetic overactivation and reduced vagal tone, has been previously implicated in both the onset and progression of breast cancer, linking neuro-tumor crosstalk with unfavorable prognosis and increased recurrence rates (4-7). High nerve fiber density within tumors has also been associated with poorer clinical outcomes, suggesting that the ANS serves a key regulatory role in breast cancer development (8,9).

Mechanistically, overactivation of sympathetic nerves facilitates tumor growth and metastasis through the release of various neurotransmitters, such as norepinephrine, promoting angiogenesis through upregulation of vascular endothelial growth factor (VEGF) (7,10-12). By contrast, increased vagal tone has been shown to exert protective effects, potentially mitigating tumor progression (6,7,10,13).

This bidirectional influence highlights the balance between sympathetic and parasympathetic systems in breast cancer pathogenesis. Furthermore, the ANS can modulate the tumor microenvironment through secretion of neurotrophic factors (such as nerve growth factor) and through regulation of immune cell activity and angiogenesis, further contributing to tumor progression (12,14). Therefore, investigating the interactions between the ANS and breast cancer should deepen understanding of the pathophysiological mechanisms underlying this disease and offer novel anti-cancer strategies for enhancing treatment (Fig. 1).

The present review summarizes and critically evaluates current literature regarding the interactions between the ANS and breast cancer. By highlighting the ANS as a key regulator in breast cancer pathophysiology, the present review aims to provide insight into the novel mechanistic pathways and therapeutic targets. The present review is intended for researchers and clinicians in the field of breast cancer and tumor-nervous system interactions, including translational and clinical investigators.

2. Survey methodology

To ensure a comprehensive and unbiased coverage of the literature, a systematic search was conducted across multiple databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/) and China National Knowledge Infrastructure (CNKI; https://www.cnki.net/). The primary search period spanned from 2010-2024, with additional inclusion of earlier seminal articles that remain relevant to the field. To identify pertinent studies, a combination of the following keywords and their Boolean operators were used: 'Autonomic nervous system', 'nerves', 'sympathetic nervous system', 'vagus nerve', 'parasympathetic nervous system', 'breast cancer', 'cancer neuroscience' and 'cancer neurotherapy'. Key word equivalents and variations in Chinese were also included for searches conducted in CNKI. Inclusion criteria focused on articles addressing the interaction between the ANS and breast cancer, with particular attention to mechanistic studies, clinical observations and translational research. Articles were screened for quality, relevance and originality. Low-quality studies, articles with limited relevance to the topic and duplicate entries were excluded following appraisal. Low-quality studies were defined as those exhibiting substantial methodological limitations, such as unclear study design, insufficient sample size, incomplete data reporting or inability to assess study validity, and were excluded along with articles of limited relevance and duplicate records.

After this screening process, a total of 75 high-quality articles were selected to form the basis of the present review. This curated selection ensured a balanced representation of the literature, integrating foundational studies and recent advancements to provide a holistic perspective on the topic.

3. Impact of the nervous system on breast cancer

Autonomic innervation of breast tissue and its role in tumor development. Breast tissue primarily receives innervation from sympathetic and sensory nerves originating from the chest wall, whilst parasympathetic nerves indirectly influence breast physiology through their effect on other organs, such as the intestines and lungs (15). For example, vagal signaling can regulate intestinal barrier integrity and mucosal immune responses, thereby shaping gut microbial metabolism; the gut microbiota ('estrobolome') may in turn influence enterohepatic estrogen recycling and systemic immune tone, which are both implicated in breast cancer biology (16). In addition, vagal activity can modulate pulmonary inflammation through the cholinergic anti-inflammatory pathway, and lung/systemic inflammatory states have been shown to facilitate breast cancer lung metastatic colonization and even awaken dormant disseminated tumor cells in the lung (17). Under normal conditions, these autonomic components maintain a dynamic equilibrium, supporting both breast function and local physiological processes. However, pathological conditions may disrupt this balance, contributing to the development of breast cancer. Pathological conditions such as chronic psychosocial stress (sustained sympathetic activation/β-adrenergic signaling) and obesity-associated chronic low-grade inflammation can disrupt autonomic balance and thereby foster a tumor-promoting systemic milieu (4-6). A previous study has indicated that in patients with invasive ductal carcinoma, >33% display neural fiber infiltration in the breast tissue. Importantly, the density of these fibers is positively associated with tumor aggressiveness (18). Sympathetic nerve activity has been shown to promote metastasis of breast cancer to bone, but β-blockers have been shown to inhibit such metastatic processes (19,20).

Furthermore, sensory nerves serve a key role in tumorigenesis and metastasis. The depletion of local sensory neuromediators (such as substance P, calcitonin gene-related peptide, vasoactive intestinal peptide and neurokinin A) changes the phenotype of cancer cells within the primary tumor, encouraging the proliferation of metastatic subsets. Activation of sensory nerves using the transient receptor potential vanilloid 1 agonist olvanil has been shown to markedly reduce lung and liver metastases (21-23).

Therefore, the ANS is implicated in the pathophysiology of breast cancer. This can be mediated by regulating tumor behavior directly through neurotransmitters (such as norepinephrine/epinephrine acting on β-adrenergic receptors or acetylcholine acting on muscarinic/nicotinic receptors) (24). By contrast, indirectly this can be achieved by skewing the immune-inflammatory tumor microenvironment toward a pro-tumor state, such as that exhibited by β-adrenergic signaling, which increases IL-6/IL-8 and VEGF levels to promote M2-like tumor-associated macrophage polarization and regulatory T-cell/myeloid-derived suppressor-cell expansion whilst diminishing natural killer cell cytotoxicity (25,26). All of the aforementioned processes contribute to facilitating angiogenesis, invasion and immune evasion.

Additionally, breast cancer and its treatment methods (including surgery, chemotherapy, radiotherapy and endocrine therapy) can perturb the ANS, sustaining sympathetic activation and attenuating vagal tone, thereby promoting a feed-forward loop that aggravates the disease (27,28). In accordance, patients with breast cancer frequently exhibit autonomic dysfunction, operationalized as reduced heart rate variability [HRV; for example, standard deviation of NN intervals (SDNN) and root mean square of successive differences

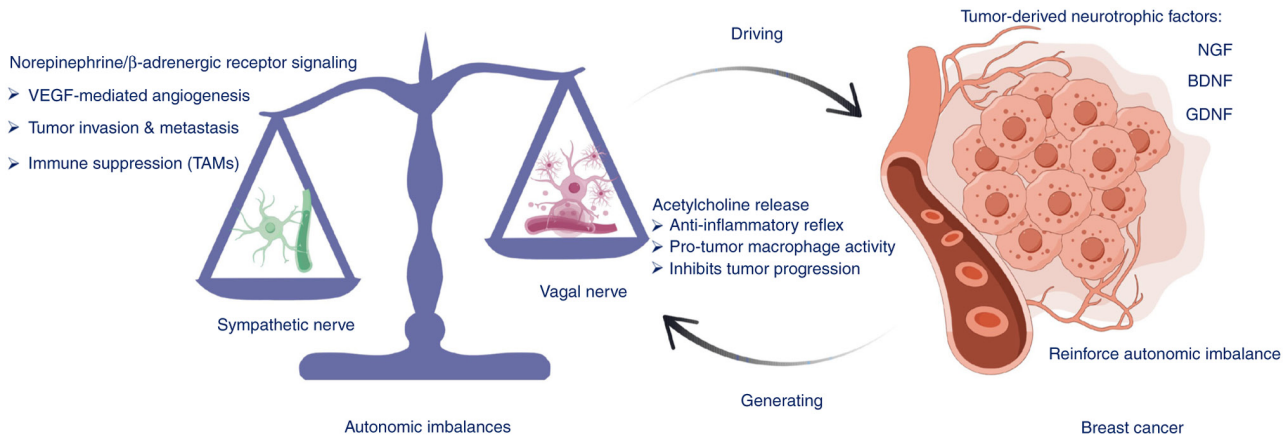

Figure 1. Autonomic imbalance in breast cancer. Sympathetic overactivation together with reduced vagal tone biases the tumor microenvironment toward angiogenesis, immune evasion, invasion and metastasis. Tumor-derived neurotrophic factors (such as NGF, BDNF and GDNF) can promote tumor-nerve crosstalk and reinforce this autonomic imbalance, establishing a feed-forward loop that supports disease progression. By contrast, vagal (cholinergic) signaling may exert tumor-inhibitory effects, in part via anti-inflammatory mechanisms and suppression of pro-tumor immune activation.

(RMSSD)], together with an increased low frequency/high frequency (HF) ratio (reflecting reduced HF power and a relative shift toward sympathetic predominance), higher resting heart rate and blunted baroreflex sensitivity (29). These abnormalities are positively associated with clinical severity, including greater tumor burden (for example, larger size/advanced stage) and higher symptom load (for example, fatigue, pain, sleep disturbance), and they are exacerbated during therapy and linked to a higher risk/severity of treatment-related toxicities (for example, cardiotoxicity).

Sympathetic nervous system and breast cancer. Immunohistochemical analysis of the sympathetic neuronal marker tyrosine hydroxylase (TH) has demonstrated that TH-positive sympathetic nerve fibers can innervate the breast cancer tumor microenvironment (20,30). Overactivation of the sympathetic nervous system has been demonstrated to promote breast cancer growth and metastasis, whereas a higher density of sympathetic nerves within cancerous tissues is associated with poorer clinical outcomes in patients with breast cancer (20,30). Sympathetic signaling primarily functions through the release of norepinephrine by peripheral sympathetic nerve endings or systemic release from the adrenal medulla, directly impacting the development and progression of breast cancer (31-33). Norepinephrine and adrenaline act by binding to adrenergic receptors (ARs), present in breast cancer cell lines and patient tumor samples (32). Liu *et al* (34) previously showed that β2-AR expression is elevated in several HER2-overexpressing breast cancer subtypes, and that higher β2-AR levels are associated with lymph node metastasis and poorer prognosis in patients with HER2-positive breast cancer.

Similarly, Kurozumi *et al* (35) found that high β2-AR levels are associated with poor prognosis in patients with estrogen receptor-positive breast cancer, accompanied by low tumor-infiltrating lymphocyte grades and lower expression levels of programmed death ligand 1. In addition, high expression of α2-AR has been shown to further breast cancer progression. Previous studies suggest that selective activation of α2-adrenergic receptors by dexmedetomidine can significantly enhance the proliferation, migration and invasion of the breast cancer cell line MCF-7 *in vitro*, potentially via activation of the α2-AR/STAT3/ERK signaling pathway (36-39). By contrast, administration of tramadol has been observed to markedly inhibit the α2-AR/ERK signaling pathway, thereby suppressing the proliferation, invasion and migration of breast cancer cells (40). Therefore, antagonizing the β2-AR or α2-AR pathways may represent potential targets for the prevention and treatment of breast cancer.

Distant metastasis represents the predominant pattern of breast-cancer recurrence and is the principal cause of disease-specific mortality (41). Clinical evidence shows that nerve fibers are detected in 15% of lymph node-negative tumors compared with 28% of lymph node-positive tumors, indicating a substantially higher prevalence of tumor-associated nerves in metastatic disease. This enrichment in lymph node-positive cases supports an association between increased nerve presence/density and lymph node involvement, rather than a random distribution of nerve fibers (18). Initial research suggested that activation of the sympathetic nervous system serves a key role in the metastasis of breast cancer to distant sites, such as the lymph nodes and lungs, primarily mediated by β-ARs. This activation promotes the infiltration of CD11b(+) and F4/80(+) macrophages into the primary tumor mass, leading to the upregulation of metastatic genes associated with M2 macrophage differentiation, such as ARG1, CD163, MRC1 (CD206), IL10, TGFB1 and VEGFA, thereby fostering a pro-metastatic tumor microenvironment (20). Furthermore, the β-blocker propranolol has been shown to inhibit sympathetic activation, restrict macrophage infiltration and thereby reduce the dissemination of breast cancer cells to distant tissues (20).

In clinical practice, β-adrenergic receptor blockers are commonly used to inhibit sympathetic nervous system activation. Numerous studies have shown that patients with breast cancer treated with β-blockers exhibit markedly lower mortality rates compared with those who do not use these medications (42-49). Another meta-analysis involving patients with breast cancer receiving cardiovascular drugs revealed that β-blockers can substantially reduce both recurrence and mortality rates associated with breast cancer (49). Additionally,

recent findings from a retrospective cohort study conducted in Sweden by Strell *et al* (50) suggested that β-blockers may provide a protective effect against invasive breast cancer, with cumulative exposure associated with a dose-dependent decrease in breast cancer risk (50).

Hiller *et al* (51) previously conducted a triple-blind, placebo-controlled clinical trial, which demonstrated that preoperative administration of β-blockers markedly reduced the expression of pro-tumorigenic intratumoral stromal genes, including IL6, CXCL8 (IL8), VEGFA, PTGS2 (COX-2) and MMP9, in early operable breast cancer, while concomitantly enhancing immune cell infiltration, such as macrophages and CD8□ T cells (51). By contrast, a cohort study involving nearly 200,000 patients with breast cancer across Europe conducted by Cardwell *et al* (52) revealed no association between the use of propranolol before and after breast cancer diagnosis and breast cancer-specific or all-cause mortality. Similar ineffectiveness was observed with non-selective β-blockers, indicating that neither propranolol nor non-selective β-blockers are able to improve survival rates (52). Additionally, other meta-analyses have shown no statistically significant association between β-blocker use and breast cancer mortality [19 studies; hazard ratio (HR), 0.90; 95% CI, 0.78-1.04] or recurrence (16 studies; HR, 0.87; 95% CI, 0.71-1.08) (53-56). These findings underscore the need for future research, particularly large-scale prospective randomized controlled trials, to provide robust clinical evidence regarding the efficacy of β-blockers in the prevention and treatment of breast cancer.

Overall, sympathetic activation, principally via β- and α2-adrenergic signaling can drive pro-metastatic, immunomodulatory programs in breast cancer and is associated with adverse outcomes. Although preclinical data and a number of observational studies are supportive, current clinical evidence remains heterogeneous, since β-blockers are not indicated for anticancer use outside of trials (53-56). Adequately powered randomized controlled trials with standardized autonomic phenotyping are needed.

Vagus nervous system and breast cancer. Although studies have previously documented promoting effects of the sympathetic nervous system on breast cancer, the role of the vagus nervous system remains ambiguous. Notable insights emerged in 2008 when a study demonstrated that severing the cervical vagus nerve in a breast cancer mouse model promoted the distant metastasis of tumor cells to the lungs, liver, heart and kidneys (57). Additionally, vagotomy was found to decrease adrenal metastasis and reverse tumor-induced adrenal functional changes in the same model (58). Immunohistochemical analysis using the vesicular acetylcholine transporter (VAChT), a marker for vagal neurons, revealed that VAChT-positive vagus nerve fibers tend to innervate the tumor microenvironment in breast cancer (59). However, vagal fibers appear to exert a tumor-suppressive (inhibitory) influence on breast-cancer progression compared with sympathetic fibers (57,59). Consistent with this concept, reduced intratumoral vagal fiber density and where measured, lower vagal tone/HRV, has been associated with poorer clinical outcomes, whereas higher vagal input has been associated with more favorable prognosis in observational cohorts (60-62). These associations warrant further investigation with the standardized quantification of neural elements and prospective clinical phenotyping.

It has been previously established that activation of the vagus nerve can trigger the classic cholinergic anti-inflammatory pathway, effectively suppressing inflammatory immune responses (63-65). This mechanism may underpin the vagus nerve's antitumor effects. Inflammation is intricately associated with cancer progression, since macrophages and various pro-inflammatory factors (such as TNF-α, IL-6, IL-1β, CXCL8 and CCL2) within the tumor microenvironment can stimulate tumor cell proliferation, angiogenesis, invasion and metastasis (66,67). Consequently, reducing macrophage activity and pro-inflammatory factor levels may diminish tumor growth and metastasis (68,69). Previous studies have increasingly associated higher vagal activity with improved long-term survival rates in patients with breast cancer, suggesting that vagal regulation of immune functions may also restrict tumor occurrence and progression (60-62).

Clinical evidence has indicated that increased vagal tone in patients with advanced breast cancer is positively associated with long-term survival (60,61). Furthermore, vagal activation may inhibit distant metastasis of breast cancer by elevating substance P levels, subsequently reducing inflammatory cytokine levels (70). Substance P is a neuropeptide found in the afferent fibers of the vagus nerve that notably influences immune-inflammatory regulation, thereby impeding tumor development. Previous studies have suggested that vagus nerve stimulation (VNS) can mitigate the development and distant metastasis of breast cancer by correcting the cardiac autonomic imbalance and lessening the cardiotoxicity induced by chemotherapy agents, such as doxorubicin (71-73). This dual therapeutic potential of VNS, which includes reducing chemotherapy-induced cardiotoxicity, indicates its potential for cancer treatment. VNS is already being utilized clinically for managing epilepsy, depression and strokes (74-76), with both preclinical and clinical studies preliminarily reporting that vagal regulation can be effectively applied in preventing and treating central nervous system disorders, autoimmune diseases and cardiovascular diseases (77-79). However, further investigations are required to explore the safety and efficacy of VNS in treating breast cancer, thereby providing novel insights and strategies for clinical application. Overall, the vagus nerve appears to be tumor suppressive and anti-inflammatory in breast cancer, since reduced vagal tone/fiber density is associated with worse outcomes. Given the controversial preclinical findings and observational human data, non-invasive VNS may be confined to clinical studies, with future trials integrating autonomic phenotyping, mechanistic readouts and cardio-oncology endpoints.

4. Application of autonomic nervous function monitoring in breast cancer

HRV, which measures minute fluctuations in heart rate (R-R intervals), is the most widely used indicator for monitoring the activity of sympathetic and vagus nerves in clinical settings at present (80). Time-domain and frequency-domain analyses of HRV can be used to reflect the dynamic balance of the ANS, encompassing both the sympathetic and vagus nerve systems (80,81). Arab *et al* (82) found that the overall standard

deviation of HRV (SDNN) and the RMSSD are inversely associated with patient staging in patients with breast cancer. Notably, a lower SDNN is associated with a poorer long-term prognosis in patients with advanced breast cancer (82).

In addition, previous studies have identified impairments in autonomic function, such as reduced HRV, diminished aerobic adaptability, altered metabolic indicators and increased fatigue, as markers of clinical phenotype in breast cancer survivors (60-62,83). Previous clinical studies have demonstrated that the overall autonomic function in breast cancer survivors is compromised and closely associated with tumor staging, compared with patients with early-stage breast cancer, since those with advanced disease demonstrate decreased vagal tone and heightened sympathetic activity (84-86). A meta-analysis that included 12 studies evaluated the impact of autonomic nervous function on staging, treatment efficacy and long-term prognosis in patients with breast cancer by analyzing their HRV. It was then revealed that higher HRV parameters were closely associated with improved long-term survival rates (62). HRV was also found to be associated with common effects caused by breast cancer, such as fatigue, depression and stress. In clinical practice, HRV assessment can assist in evaluating the side effects of chemotherapy in patients with breast cancer (28).

Therefore, HRV can serve as a supplementary, non-invasive tool for the early diagnosis of autonomic dysfunction in patients with breast cancer and assist in assessing their long-term survival rates. In addition, the levels of certain neurohormones in bodily fluids, such as adrenaline, noradrenaline and cortisol, can also indicate autonomic activity. A previous study has indicated that in patients with breast cancer, elevated plasma levels of adrenaline, adrenocorticotropic hormone, noradrenaline and cortisol are positively associated with symptoms of pain, depression and fatigue (87). These findings suggest that monitoring serum neurohormone levels may serve as a novel biomarker for assessing prognosis in patients with breast cancer.

5. ANS regulation strategies for preventing and treating breast cancer

Overview of ANS modulation strategies. ANS serves a key role in both preventing and treating breast cancer by directly or indirectly regulating the tumor microenvironment. Developing strategies to modulate the ANS for the prevention and treatment of breast cancer whilst translating these neuroregulatory concepts into clinical practice represent notable future directions for breast cancer management. This section will now outline the main methods of modulating the ANS.

Pharmacological approaches. A number of the most extensively investigated drugs are β-adrenergic receptor blockers. Numerous clinical studies have previously demonstrated that β-blockers can markedly reduce the recurrence and mortality rates of breast cancer (48,88-92). However, retrospective designs are vulnerable to confounding by indication and comorbidities, immortal-time bias (a 'guaranteed' event-free interval before exposure classification that can spuriously favor the exposed group) and time-window biases, exposure misclassification and variable adjustment for concomitant therapies. In addition, effect estimates differed by tumor subtype (estrogen receptor, progesterone receptor or HER2), stage, timing of exposure (perioperative, adjuvant or chronic) and by agent class (β1-selective vs. non-selective), with meta-analyses reaching inconsistent conclusions (48,54,58). Although several pilot perioperative trials (typically enrolling 20-100 participants) have reported modulation of stress-adrenergic and inflammatory pathways, these studies were not powered to detect differences in clinical endpoints such as disease-free or overall survival (91,92). Taken together, definitive survival benefit has not been established. Accordingly, β-blockers should be used for cardiovascular indications only and oncologic use should be limited to clinical trials that incorporate standardized autonomic phenotyping and prespecified survival endpoints.

Vagus nerve intervention. One of the most researched surgical procedures for this strategy is vagotomy. Previous studies have shown that cervical vagus nerve resection can inhibit the growth and distant metastasis of breast cancer to some extent (57,58). However, this approach causes irreversible nerve damage, resulting in loss of the inherent physiological regulatory and protective function of the nerves. It also lacks tumor tissue specificity and selective nerve fiber type resection, limiting its clinical translation. Xie *et al* (93) demonstrated that auricular VNS can regulate the local parasympathetic innervation of tumors, promoting a shift in the tumor immune microenvironment from inflammatory to cytotoxic, thereby enhancing antitumor immune responses. This approach is synergistic with the antitumor effects of doxorubicin, slowing tumor tissue growth, reducing local infiltration of breast cancer and inhibiting distant pulmonary metastasis and alveolar infiltration.

Genetic neuro-manipulation techniques based on adenoviral vectors. These techniques address the inherent limitations in pharmacological, surgical and electrical neural stimulation methods. By targeting specific nerve fibers for gene delivery, these methods facilitate precise and reversible manipulation of nerve fiber types, thereby enabling diverse forms of neural regulation, including stimulation, inhibition or denervation (94-96). Viral-vector approaches (most commonly AAV) have already been applied in breast-cancer mouse models to enable circuit-specific chemogenetic/optogenetic neuromodulation that reshapes intratumoral autonomic activity and tumor growth (97,98). The application of these neuroregulatory strategies across different tumor types may represent a novel approach for cancer treatment. However, the use of adenoviral vectors raises potential biosafety concerns. Consequently, additional research is imperative to verify the safety and efficacy of these techniques.

6. Conclusions

The accumulated evidence indicates that autonomic imbalance, characterized by sympathetic overactivation and reduced vagal tone, interfaces with breast-cancer biology in ways that are clinically observable and potentially targetable. For current practice, the present review recommends the following: i) Where feasible, incorporating simple autonomic phenotyping (resting heart rate and HRV indices such as

SDNN and RMSSD) into baseline assessment and survivorship follow-up to flag patients at higher risk of symptom burden or treatment toxicity; ii) optimizing perioperative and on-treatment stress, anxiety, sleep and pain management, alongside exercise and cardiometabolic risk control, to mitigate excessive sympathetic drive; iii) using β-blockers only for established cardiovascular indications and not for anticancer intent outside a trial, whilst considering clinical-trial enrollment when ANS-modulating strategies are contemplated; iv) coordinating early with cardio-oncology (especially for anthracycline-based regimens) to individualize cardioprotection in patients with autonomic imbalance; and v) reserving non-invasive VNS and other neuromodulatory interventions for ethically approved investigations rather than routine care. Investigational approaches, such as adenoviral vector-based local neuro-manipulation, remain preclinical and are not recommended for clinical use at this time. Priority research should include adequately powered randomized trials that incorporate standardized ANS phenotyping, perioperative and adjuvant β-adrenergic modulation strategies and non-invasive vagal neuromodulation, with metastasis, survival, toxicity and quality-of-life endpoints, alongside harmonized methods for quantifying neural elements in tumor tissue.

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Authors' contributions

MW and XC conceptualized the review framework and supervised revision of the final manuscript. MW was also responsible for drafting the manuscript. ZZ and LZ were primarily responsible for the literature search and data analysis pertaining to the role of the autonomic nervous system in breast cancer. SL, QC, CG and SZ contributed to drafting and revising the content critically for important intellectual content. XC also coordinated the team efforts and integrated feedback from all authors. All authors read and approved the final version of the manuscript for publication. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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