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ACUPUNCTURE FOR VASOMOTOR SYMPTOMS IN HORMONE-SENSITIVE CANCER PATIENTS: A NARRATIVE REVIEW

Scarsella Secondo

Italian Academy of Chinese Medicine
L'Aquila Italy, Visiting Professor
Nanjing University of Chinese
Medicine, Nanjing China

Dal Pozzo Lisa

Tianjin University of Traditional
Chinese Medicine, School of Integrative
Medicine, Jinghai, China

Abad Arranz Maria

Acupuncturist, Medical Oncology
Giuseppe Mazzini Hospital, Teramo-Italy

Irelli Azzurra

Medical Oncology Giuseppe
Mazzini Hospital, Teramo-Italy

Patruno Leonardo

Medical Oncology Giuseppe
Mazzini Hospital, Teramo-Italy

D'Ugo Carlo

Director, Oncologic Department Giuseppe
Mazzini Hospital, Teramo-Italy

Cannita Katia

Director, Medical Oncology Giuseppe
Mazzini Hospital, Teramo-Italy



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Abstract: Vasomotor symptoms (VMS), including hot flashes and night sweats, significantly impact the quality of life in patients with hormone-sensitive cancers such as breast and prostate cancer. Conventional hormone-suppressive therapies frequently exacerbate these symptoms, posing a clinical challenge, especially for patients contraindicated for hormone replacement. Acupuncture, a key component of Traditional Chinese Medicine, has emerged as a potential integrative treatment option for managing VMS with a favorable safety profile. This narrative literature review synthesizes current evidence on the efficacy, safety, and proposed mechanisms of acupuncture in alleviating VMS among cancer patients. The review highlights the predominance of research in female populations and identifies a critical gap concerning male patients, despite the high prevalence of VMS in men undergoing androgen deprivation therapy. Mechanistic insights include modulation of neurotransmitters such as serotonin and β -endorphins, as well as regulation of the hypothalamic-pituitary-adrenal axis. Limitations of existing studies, including heterogeneity in acupuncture protocols and outcome measures, are discussed. Further high-quality, standardized clinical trials, particularly focusing on male patients, are warranted to establish acupuncture as a validated supportive therapy for VMS in oncology.

Keywords: Acupuncture, Vasomotor Symptoms, Hot Flashes, Hormone-Sensitive Cancer, Integrative Oncology.

Abbreviations: EA, electroacupuncture; GCS, Greene Climacteric Scale; HFS, hot flash score; HPA, hypothalamic-pituitary-adrenal (axis); RA, rheumatoid arthritis; RCT, randomized controlled trial; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TA, traditional acupuncture; TCM, Traditional Chinese Medicine; VMS, vasomotor symptoms.

INTRODUCTION

Hot flashes are involuntary and sudden-onset sensations of warmth, mainly located on the neck, face, chest, and upper back [1]. They are common and transient symptoms associated with menopause, with data suggesting that 85% of menopausal women suffer from them [2]. Although the exact mechanism is still under investigation, the primary event is strong peripheral vasodilation due to uncontrolled hypothalamic stimuli. As a compensatory response, chills may occur, causing notable discomfort and embarrassment. Among the neurotransmitters involved, serotonin participates in thermoregulation via receptors 1α and 2α . Upon the onset of menopause, a reduction in serotonin may lead to an imbalance between these two receptors—responsible for hypothermia and hyperthermia, respectively—which may cause hot flashes [3]. The kisspeptin, neurokinin B, and dynorphin system is also involved, with evidence indicating that central injection of kisspeptin in animals causes tail skin hyperthermia [4].

Night sweats are defined as recurrent, drenching, and unusually excessive sweats that occur during nighttime. They are classified as mild, moderate, or severe based on the amount of fluid loss. This phenomenon has been associated with autoimmune diseases, cardiovascular problems, diabetes, hyperthyroidism, gastrointestinal disorders, infectious diseases, chronic inflammatory conditions, circadian variations, and mental disorders such as anxiety and depression [5]. Similarly to hot flashes, serotonin and hormonal alterations can disrupt normal thermoregulation, inducing excessive sweating [6]. Overall, night sweats and hot flashes are classified as vasomotor symptoms (VMS).

VMS are frequently present in hormone-sensitive cancers, such as prostate and breast cancers. Patients with advanced prostate carcinoma who undergo castration and hormo-

nal therapy often experience menopause-like symptoms. With the decrease in testosterone levels resulting from total androgen ablation therapy and androgen deprivation therapy, VMS arise in both older and younger men. A meta-analysis by Spetz et al. highlighted the relevance of these symptoms, which are often regarded as marginal in the clinical setting [7]. A survey conducted by Cole and colleagues involving 373 women with breast cancer indicated that almost half of the participants experienced hot flashes and sweating [8], while a review by Zhu and others supported the high incidence in both women and men undergoing oncological therapy [9]. VMS represent a significant burden and greatly affect the quality of life. Sudden hot flashes may cause embarrassment and discomfort in public or workplace settings, while night sweats may aggravate marital and intimate relationships, causing emotional distress in patients.

Hormone therapy is the primary therapeutic approach to VMS; however, for specific categories of patients, such as women with breast cancer, substitutive hormones may increase the risk of recurrence, often leading to poor compliance and unresolved symptoms [10]. Polypharmacy is also a potential risk to consider in hormone-related tumors, especially among older patients, which may interfere with the success of chemotherapy or predispose them to other conditions [11].

MATERIALS AND METHODS

A literature search was conducted using electronic databases including PubMed, Wanfang Data, VIP, and CNKI, from inception to May 2025. Search terms combined keywords related to “acupuncture,” “vasomotor symptoms,” “hot flashes,” “night sweats,” “breast cancer,” “prostate cancer,” and “hormone-sensitive cancers,” along with their Chinese equivalents. Only articles published in English and Chinese were considered. Eligible

studies primarily included open-access randomized controlled trials, observational studies, clinical reports, and relevant reviews or overviews investigating acupuncture for vasomotor symptoms in cancer populations. Data were extracted and qualitatively synthesized to provide an overview of therapeutic efficacy, safety, mechanisms of action, and current research gaps. Due to heterogeneity in study design, populations, and outcomes, a formal meta-analysis was not conducted.

HOT FLASHES IN CANCER PATIENTS

Hot flashes and night sweats are frequently found in predisposed individuals, and factors such as age, race, smoking habits, cardiovascular pathology, body mass index, and genetic predisposition may influence their relevance and incidence [12]. In cancer patients, the most common cause of VMS onset is rapid hormonal withdrawal—either estrogen or testosterone [13]. More complex causes include endocrine therapies, chemotherapy-induced ovarian disruption, ovarian damage or removal, anti-androgen therapy, and orchidectomy. Other types of cancer-related flashes and sweating include those associated with thyroid cancer, carcinoid tumors, and pancreatic cancer, where the presence of VMS is believed to be linked to tumor secretion of specific mediators; however, data are insufficient [14].

Among pharmaceutical compounds, cisplatin combined with decapeptyl has been linked to an increased incidence of hot flashes in patients [15]. Carboplatin is also associated with local abnormal reactions (carboplatin hypersensitivity), which ranges from facial flushing to dyspnea and anaphylaxis [16]. Regarding docetaxel, a study involving 150 men with prostate cancer reported that the incidence of hot flashes was similar between those receiving both docetaxel and androgen deprivation therapy and those receiving androgen

deprivation therapy alone [17]. A 10% incidence of vasomotor symptoms has also been theorized with paclitaxel therapy [18].

Thermoregulatory disruption naturally occurs during menopause and, to a lesser extent, with the onset of andropause in non-castrated men [19]. In cancer-free patients, estrogen replacement therapy mitigates the intensity and burden of VMS, although progesterone appears more promising due to a lower incidence of withdrawal rebound increases [20]. Recently, elinzanetant has also been proposed given its efficacy in postmenopausal subjects, and ongoing trials are assessing its benefits in the male population [21].

Although definitive data are unavailable, VMS in oncologic conditions may be more severe compared to those experienced during normal aging, due to the complex biochemical alterations induced by cancer and its treatments. The difficulty of treatment and the lack of guidelines for oncologic patients remain major issues, often resulting in ineffective therapeutic choices [22].

CURRENT TREATMENT OPTIONS FOR CANCER-RELATED VASOMOTOR SYMPTOMS

Numerous and diverse molecules are employed to treat VMS in cancer patients. The main classes include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, antidepressants, and hormones. SSRIs, by regulating serotonin bioavailability, mediate heat loss and lower body temperature. Similarly, compounds that reduce hypothalamic norepinephrine, such as clonidine, raise the sweating threshold and improve symptoms [23]. Clonidine, an SSRI, was reported to reduce hot flashes by 20% compared to placebo in menopausal subjects [24].

Gabapentin acts on GABAergic transmission and modulates neuronal calcium cur-

rents. It has been proposed that it may also mitigate tachykinin activity at the hypothalamic level, thereby treating hot flashes. In a randomized controlled trial (RCT) on menopausal women, gabapentin showed significant anti-hot flash activity, reducing both frequency and severity [25]. In a double-blind RCT involving 420 women with breast cancer, similar beneficial effects were reported in the intervention group treated with 900 mg/day of gabapentin [26].

Venlafaxine was also assessed in cancer survivors and postmenopausal women with VMS. A single RCT including 191 patients with a history of breast cancer reported a reduction in hot flashes following intervention; however, side effects such as reduced appetite, nausea, constipation, and dry mouth were noted, especially at dosages of 75 and 150 mg/day [27]. In menopausal women, venlafaxine confirmed its efficacy along with similar side effects. The 75 mg/day dosage was identified as effective in managing VMS [28]. Cetirizine has also been proposed as an unconventional therapy for hot flashes, though supporting data are lacking.

Hormones are often excluded in breast cancer patients, particularly estrogen, but megestrol acetate, a synthetic progestin, has shown promise in both female and male oncology patients. In a randomized trial involving 97 women with breast cancer and 66 men with prostate cancer undergoing androgen deprivation therapy and experiencing VMS, megestrol acetate reduced the frequency of hot flashes by 85% ($p < 0.001$) [29]. Men also respond positively to estrogens such as estradiol. Russell and colleagues reported a statistically significant reduction in the burden of hot flashes using estrogen protocols [30].

Nutraceuticals have also been proposed. Vitamins C and B have emerged anecdotally, but no definitive studies have yet been conducted. A systematic review proposed vitamin

E as an adjuvant to drug therapy, although estrogen showed superior efficacy in reducing VMS [31]. Soy, which contains phytoestrogens, is commonly used to treat menopause-related conditions; however, evidence in oncological settings remains unclear. A single RCT reported no beneficial effect from soy beverage intake in women with breast cancer [32], and similar findings were reported in prostate cancer patients [33].

Black cohosh extract has also been proposed to manage hot flashes. A randomized trial involving 85 women with breast cancer reported no significant reduction in VMS frequency [34]; however, a pilot study involving the same type of patients seemed to suggest the opposite [35].

One major drawback of oral therapies—whether drug-based, herbal, or mineral preparations—is the risk of polypharmacy or possible herb-drug interactions, particularly in combination with chemotherapy and immune checkpoint inhibitors. Therefore, a safer and alternative approach for oncologic patients is urgently needed.

ACUPUNCTURE: A RATIONALE

Acupuncture is one of the therapeutic strategies in Chinese medicine, involving the insertion of needles into specific points on the body surface. Based on Traditional Chinese Medicine (TCM) theories, the connection between the internal and external parts of the body, operated through meridians and collaterals, allows acupuncture to produce both local and distal effects. In many Western countries, acupuncture is primarily used to treat joint and muscle pain or localized musculoskeletal disorders. However, in Asia—and particularly in China—acupuncture is also employed to regulate blood pressure [36], assist in metabolic disorders such as diabetes [37] and hyperlipidemia [38], and promote general health.

Acupuncture is also applied in the treat-

ment of vasomotor symptoms (VMS). As reported in the Synopsis of the Golden Chamber, night sweating is associated with Yin deficiency, often Kidney Yin deficiency [39]. Other possible causes include blood deficiency or combined Qi and blood deficiency. In *Other Considerations on Yin and Yang in The Book of Plain Questions*, it is stated that Yin decreases are followed by Yang rising, reinforcing the concept that VMS result from a loss of Yin-Yang harmony, regardless of the underlying cause.

Data indicate that acupuncture can alleviate both postmenopausal and perimenopausal symptoms such as hot flashes and night sweats. A Chinese trial involving 60 women showed that oral Wushi Yougui formula combined with acupuncture at Baihui (GV20), Guanyuan (CV4), Qihai (CV6), Zigong (EX-CA1), Zusanli (ST36), Sanyinjiao (SP6), Fengchi (GB20), Taixi (KI3), Kunlun (BL60), and Taichong (LV3), among others, resulted in greater improvement in the Kupperman index compared to estradiol tablets ($p < 0.05$) [40].

A small preliminary study on perimenopausal and menopausal women administered Juejing Fuchun Decoction—including Curculigo Rhizome (Black Cohosh Rhizome), Morinda Root, Astragalus Root (Milkvetch Root), Aemarrhena Rhizome, Chinese Angelica Root (Dong Quai), Ligustrum Fruit (Glossy Privet Fruit), Bupleurum Root, Albizia Bark (Silk Tree Bark), White Peony Root, Cuscuta Seed (Dodder Seed), and Poria cocos—alongside acupuncture at Guanyuan (CV4), Sanyinjiao (SP6), and Shenshu (BL23). A statistically significant improvement in the Kupperman index ($p < 0.05$), and reduction in follicle-stimulating hormone ($p < 0.05$), were reported [41].

According to a retrospective analysis of 30 years of clinical practice by Professor Tian Liying in the field of menopausal-related symptoms, combining herbal prescriptions with acupuncture can effectively treat internal and external imbalances associated with perimeno-

pausal syndrome. Acupoints such as Zhongji (CV3), Qihai (CV6), Guanyuan (CV4), Yinjiao (CV7), Sanyinjiao (SP6), Zusanli (ST36), Xuehai (SP10), Baichongwo (EX-LE2), Baihui (GV20), and Sishencong (EX-HN1)—with different tonifying and reducing needle manipulations based on the case—may aid in the reduction of VMS [42].

A small preliminary study on menopausal hyperhidrosis involved 51 women and reported resolution or symptom improvement (40–80%) within one year ($p < 0.05$) using ear acupuncture and acupuncture combined with cupping [43].

The beneficial effects of acupuncture on thermoregulation may be attributed to several mechanisms. It is known that acupuncture can increase central β -endorphin levels [44]. A reduction in β -endorphin has been associated with hot flashes and thermoregulatory anomalies [45]. Moreover, decreased β -endorphin levels fail to counteract the stress response, whereas increased endogenous levels have been shown to reduce prostate and breast cancer burden in animals [46].

As mentioned, a disrupted serotonin pathway and serotonin deficiency may underlie hot flashes. Acupuncture has been shown to increase serotonin release in the nucleus accumbens in animals [47]. Norepinephrine levels were also found to increase in the skin at acupuncture points, suggesting a role of norepinephrine deficiency in the onset of hot flashes [48].

The hypothalamic–pituitary–adrenal (HPA) axis may also be involved. Evidence indicates that HPA axis alterations can aggravate the severity of VMS. Patients with hot flashes often show a blunted HPA response, suggesting a dysregulated stress response [49]. Acupuncture and electroacupuncture have been reported to regulate the HPA axis, modulating serotonin and its receptors [50, 51].

Beyond its therapeutic effects, acupuncture offers important advantages in terms of safety,

particularly in the oncologic setting. A 2022 systematic review and meta-analysis evaluated the efficacy of acupuncture compared to sham acupuncture in cancer patients. Results indicated a favorable safety profile for both manual and electroacupuncture [52]. A more recent systematic review focused on pediatric oncology patients reported several beneficial effects of acupuncture with only limited, transient, and minor side effects. Although the study acknowledged limitations, the data support acupuncture's safety among pediatric cancer patients [53]. Another study involving 684 patients corroborated these findings, adding further evidence to the safety and validity of acupuncture in oncology care [54]. Nevertheless, precautions must be taken in cases of elevated bleeding risk, debilitated individuals, vasovagal risk, and lymphedema [55]. Figure 1 summarizes the proposed central and local mechanisms by which acupuncture may alleviate VAS.

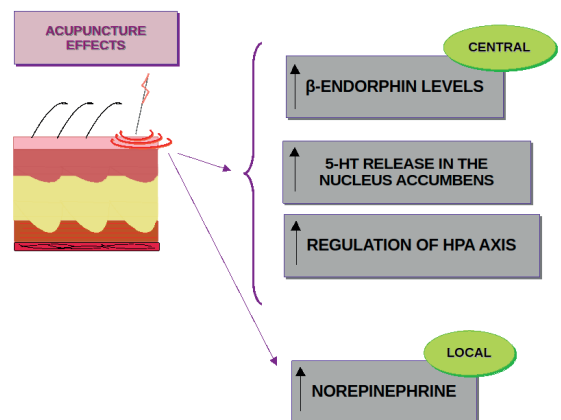


Figure 1. Visual summary of the central (increased β -endorphin, serotonin release, hypothalamic–pituitary–adrenal (HPA) axis modulation) and local (norepinephrine increase) mechanisms through which acupuncture may alleviate VAS.

EVIDENCE OVERVIEW

In recent years, and with the increasing burden of cancer, researchers have shown

growing interest in evaluating the benefits of acupuncture for vasomotor symptoms (VMS) among cancer patients. In a two-arm randomized controlled trial (RCT) involving 190 women with breast cancer and spontaneous or induced amenorrhea, the intervention group received acupuncture based on TCM syndrome differentiation. The most common TCM diagnosis was *Kidney and Liver Yin and Yang deficiency, and Liver Yang fire* (36.40%). Based on these findings, the following acupoints were selected: LV3, LI4, GB20, KI6, PC7, LU7, LV2, and ST37.

The primary outcome was the daily mean hot flash score (HFS), assessed at the end of the 12-week study period. Secondary outcomes included climacteric symptoms and quality of life, measured through the Greene Climacteric Scale (GCS) and the Menopause Quality of Life scale. Compared to the enhanced self-care control group, HFS was significantly lower in the acupuncture group ($p < 0.001$), as was the GCS score ($p < 0.001$) [56].

Improvement was also reported in an American RCT conducted by Lu and his team on a similar population. A 50% reduction in HFS (including both frequency and severity of hot flashes) was reported [57].

In men with prostate cancer, an open-label, single-arm phase II study reported a 50% reduction in HFS by week 8 of treatment in 9 out of 22 participants (41%, 95% CI: 21–64%; p -value not reported). Additionally, meaningful improvements in sleep quality were observed according to the Pittsburgh Sleep Quality Index [58].

A single medical case report described symptom amelioration using cooled needles inserted at the following acupoints: KI3, KI6, LV3, LV8, SP4, SP6, CV2, CV5, GV20, HT6, HT7, and LU7. The study proposed an interesting method: regularly cooling the needles with an ice-cold sponge to facilitate the dispersal or release of energy [59]. However, it

lacked key methodological information such as evaluation indices, or statistical analysis, and differs from other studies due to its less conventional technique.

A prospective multicenter study compared two acupuncture modalities for treating hot flashes in men with prostate cancer: traditional acupuncture (TA) and electroacupuncture (EA). The trial involved 31 patients randomly assigned to either group. Both received treatment at the same acupoints: BL15, BL23, BL32, GV20, HT7, PC6, LV3, SP6, and SP9. In the EA group, 2 Hz electrostimulation was applied to the lower back points. The primary outcome was the change in the number of hot flashes per 24 hours. After 12 weeks, a significant reduction was observed in both groups: TA group median flashes decreased from 6.4 to 3.4 ($p = 0.001$); EA group decreased from 7.4 to 4.1 ($p = 0.002$). The difference between the two groups was not statistically significant [60].

Although many studies highlight the efficacy of acupuncture in managing VMS, they often present methodological limitations. A recent systematic review and meta-analysis involving 963 cancer patients with hot flashes, reported a high risk of bias due to unclear or inappropriate randomization, inadequate allocation concealment, and improper participant blinding. Studies from both Western and Chinese research groups frequently lacked crucial information. Missing data and dropout rates were often unclear or unreported, increasing the risk of bias. Additionally, many studies did not report adverse event assessments. Despite these issues, the authors concluded that acupuncture showed benefits in reducing hot flash scores among women with breast cancer [61]. However, the identified limitations may weaken the reliability of these findings.

In the case of prostate cancer, research remains in its early stages, and a comprehensive meta-analysis is currently lacking.

The main findings of clinical studies in-

investigating acupuncture for vasomotor symptoms in hormone-sensitive cancer patients are summarized in Table 1.

DISCUSSION

The incidence of hormone-sensitive cancers has increased in recent years. While chemotherapy, radiotherapy, and surgery remain effective strategies, additional interventions such as male castration and hormone suppression therapies are commonly used to prevent recurrence and improve both quality and expectancy of life. Despite the success of early diagnosis and therapeutic advances, several problems remain—primarily as a consequence of endogenous hormone suppression. Vasomotor symptoms (VMS) significantly impact patients' lives, often causing embarrassment and impairing social relationships. Due to the biochemical nature of cancer, various drugs and herbal remedies may interfere with alkylating agents or hormone therapies. In this scenario, acupuncture may represent a valid complementary approach to VMS management.

Acupuncture has proven helpful in mitigating a range of cancer-related symptoms. An overview of systematic reviews including 592 RCTs and over 35,000 individuals reported beneficial effects for arthralgia, fatigue, lymphedema, insomnia, neuropathic pain, anxiety, quality of life, bone marrow suppression, xerostomia, nausea, vomiting, and VMS [62]. However, some limitations were noted. Several meta-analyses showed a high risk of bias due to unclear or inappropriate eligibility criteria, poor definition of search terms, data extraction errors, unclear data collection methods, and small sample sizes. Pain was among the most frequently investigated outcomes, with relief assessed using visual analog scales (VAS), numerical rating scales, or other validated tools. Some studies failed to show

acupuncture's superiority over drug therapy or sham acupuncture, but these studies often had high risk of bias due to unclear randomization procedures and inadequate blinding.

Meta-analyses focusing on VMS generally presented a lower overall risk of bias. Most studies involved breast cancer patients and reported significant reductions in hot flash frequency and severity compared to control groups. However, the number of RCTs included in each meta-analysis was limited, and a high overlap rate among reviews (51.75%) was noted, suggesting that the same RCTs may have been included in multiple analyses, potentially inflating perceived effectiveness [62].

Despite these initially favorable findings, the limited number of high-quality RCTs on VMS, and the lack of sufficient data on male patients, raise several concerns. Some studies did not specify the acupoint protocol, needle manipulation techniques, or the TCM diagnostic rationale, which limits interpretability and reproducibility. Reporting the study design (e.g., single-arm or two-arm) increases the validity of the findings, yet some studies omitted such detail. The use of unconventional techniques, such as cooled-needle acupuncture, without clearly stating prior supporting evidence or scientific rationale, also weakens methodological credibility.

Finally, the use of standardized outcome measures is crucial for comparing results across studies and for developing clinical protocols. Several studies did not report or clearly define the outcome assessment tools used, relying solely on changes in VMS frequency or intensity. Clear clinical guidelines for VMS management in oncology would facilitate the design of better clinical trials, thereby improving the quality and reliability of future research.

LIMITATIONS

This review is narrative in nature. The available literature on vasomotor symptoms in

First Author (Year)	Study Type	Population (n)	Cancer Type	Primary Acupuncture Points	Main Outcome Index	Main Result	Reference
Lesi (2016)	Two-arm RCT	190	Breast	LV3, LI4, GB20, KI6, PC7, LU7, LV2, ST37	Hot Flash Score (HFS); Greene Climacteric Scale (GCS); Menopause Quality of Life (MenQoL) scale	Improvement in all scores	[56]
Lu (2024)	Parallel RCTs	158	Breast	SP-6, LI-11, EX-HN3, GV-20, TF4	Functional Assessment of Cancer Therapy – Endocrine Symptoms (FACT-ES); HFS; FACT-Breast score	Improvement in all scores	[57]
Beer (2010)	Single-arm Phase II Study	22	Prostate	Not reported	HFS; Pittsburgh Sleep Quality Index (PSQI)	50% reduction in 9 of 22 participants; improved sleep quality	[58]
Hirsch (2015)	Small study report	7	Prostate	KI3, KI6, LV3, LV8, SP4, SP6, CV2, CV5, GV20, HT6, HT7, LU7	Daily number of hot flashes (unclear method)	Reported 50% reduction in daily hot flashes	[59]
Frisk (2009)	Prospective multi-center study	31	Prostate	BL15, BL23, BL32, GV20, HT7, PC6, LV3, SP6, SP9	Number of hot flashes per 24 hours	Significant reduction after 12 weeks of treatment	[60]

Table 1. Summary of clinical studies on acupuncture for vasomotor symptoms in hormone-sensitive cancer patients. Key outcomes include hot flash score (HFS), Greene Climacteric Scale (GCS), Menopause Quality of Life scale (MenQoL), and Pittsburgh Sleep Quality Index (PSQI). Acupuncture points are listed using WHO-standard nomenclature where available.

male cancer patients is sparse, limiting the generalizability of conclusions for this population. Additionally, the included studies exhibit considerable heterogeneity in acupuncture protocols, overall risk of bias, diagnostic criteria, and outcome measures, complicating direct comparisons. Due to these factors, a quantitative synthesis is currently not feasible. Future systematic reviews using standardized methodologies are needed to strengthen the evidence base.

CONCLUSION

This work gathered preliminary evidence supporting the application of acupuncture in managing night sweats and hot flashes in men and women with hormone-sensitive can-

nuscripts.

Irelli Azzurra, Patruno Lorenzo, D'Ugo Carlo and Cannita Katia: revised the manuscripts for critical intellectual content.

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cers. As an integrative approach, acupuncture may contribute to symptom relief while minimizing adverse effects or interactions with hormone-suppressant therapies. Although vasomotor symptoms affect both male and female patients, most studies have focused on women, leaving the male population largely underrepresented. Given the high incidence and global rise of prostate cancer, further investigation into integrative oncology approaches—particularly for managing hot flashes and night sweats in men—is urgently needed.

AUTHOR CONTRIBUTIONS

Scarsella Secondo, Dal Pozzo Lisa and Abad Arranz Maria: contributed to the study conception, writing and revision of the ma-

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