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REVIEW



## Managing menopausal symptoms after cancer

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### ABSTRACT

The joint burden of cancer and menopause impacts millions of women globally. This review provides an approach to management of menopausal symptoms after cancer in all settings. This includes an overview of current evidence for both hormonal and non-hormonal treatments for vasomotor symptoms and vaginal dryness after cancer. Systemic menopausal hormone therapy provides symptom control and may be used after most cancers but should be avoided after estrogen receptor-positive breast cancer and after some other estrogen-dependent cancers. Non-hormonal therapies have been minimally studied in women after a cancer diagnosis and, where they have been studied, it is usually in women with breast cancer. Non-hormonal methods to manage vasomotor symptoms include cognitive behavioral therapy, hypnosis, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, clonidine, and gabapentin. Vaginal estrogen may be useful to address vaginal dryness. However, safety data in breast cancer patients are still lacking and there is currently no consensus. Lubricants may also help with pain with sexual activity. Management of menopausal symptoms after cancer may be challenging and should include information about induced menopause and possible symptoms as well as available treatments. Management then requires a holistic and multidisciplinary approach with individualized care.

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### Introduction

Menopause, the final menstrual period, is usually a normal life event, and most women do not seek medical intervention<sup>1</sup>. Natural menopause occurs around age 51 years in women of western origin<sup>2</sup>. Menopause may be induced early or symptoms exacerbated due to cancer treatment. Perimenopausal and postmenopausal women diagnosed with breast cancer using menopausal hormone therapy (MHT) will be advised to discontinue it, which may lead to resurgent menopausal symptoms<sup>3</sup>.

Menopausal symptoms include vasomotor symptoms (hot flushes and night sweats), vulvovaginal symptoms (dryness, itching, and discomfort), and pain with sexual activity<sup>1</sup>. Sleep, mood, and quality of life may also worsen across the menopause transition and this may exacerbate the consequences of cancer and its treatment<sup>4</sup>. Management of menopausal symptoms after cancer may be challenging and should include information about induced menopause and possible symptoms as well as available treatments. Management then requires a holistic and multidisciplinary approach with individualized care.

'Cancer' is a single word for a heterogeneous group of diseases. Thus, different cancers impact girls and women differently, and each woman experiences her illness and menopause uniquely. The joint burden of cancer and menopause impacts millions of women globally. Many treatment options

for menopausal symptoms are not equitably available worldwide, particularly in low and middle-income countries. Care for long-term medical and psychosocial needs is less available in low and middle-income countries, where resources are limited<sup>5,6</sup>. There is also variation in the availability of treatments for menopausal symptoms between high-income countries.

This review provides an approach to management of menopausal symptoms after cancer in all settings. This includes an overview of current supporting evidence for both hormonal and non-hormonal treatments for vasomotor symptoms and vaginal dryness after cancer. Where sufficient evidence is available, clinical recommendations are provided<sup>1</sup>.

### Current global cancer burden and trends

Cancer is an important cause of morbidity and mortality worldwide<sup>7</sup>, with 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018<sup>7</sup>. Breast cancer is the most common female cancer worldwide, followed by colorectal cancer in high-income countries and cervical cancer in low and middle-income countries<sup>7</sup>.

Worldwide, there were about 2.1 million newly diagnosed female breast cancer cases in 2018, accounting for almost one in four cancer cases among women<sup>7</sup>. Approximately 20% of new breast cancer diagnoses occur in women under

age 45, with almost all requiring chemotherapy and adjuvant endocrine therapy. With earlier detection and improved treatments, particularly in high-income countries, women are living longer after a breast cancer diagnosis.

In a meta-analysis of 45 studies of cancer survivors diagnosed from childhood to 40 years, the median age at menopause was found to be 44 years<sup>8</sup>. This has significant implications for morbidity of treatments and impact on quality of life including menopausal symptoms. After breast cancer, menopausal symptoms are among the most persistent and bothersome effects of treatment and may be more severe and persistent compared to natural menopause<sup>9,10</sup>.

While the diagnosis of reproductive stages in women, including menopause, has been standardized<sup>11</sup>, diagnosing menopause after cancer can be difficult, as ovulation may resume several years after prolonged amenorrhea and raised follicle stimulating hormone<sup>12</sup>. This has potential implications for accessing advice or treatment for menopausal symptoms. Little is known about care-seeking and treatment uptake for menopausal symptoms in women who have had cancer. A third of women with cancer report dissatisfaction with the quality and length of physician–patient discussions about reproductive health, including menopause, before their cancer treatment<sup>13</sup>.

### Mechanism for menopausal symptoms after cancer

Menopausal symptoms after cancer may be due to chemotherapy-induced or radiation-induced ovarian failure, bilateral oophorectomy, or anti-estrogen treatments (see Table 1)<sup>3</sup>.

**Table 1.** Mechanisms leading to menopause or menopausal symptoms in cancer patients (modified from Marino *et al.*<sup>3</sup>).

Cancer treatment modality	Indications for treatment
Chemotherapy (especially cyclophosphamide, procarbazine, and other alkylating agents)	Adjuvant therapy for premenopausal/perimenopausal breast cancer Chemotherapy for hematological cancer Conditioning chemotherapy prior to stem cell transplant
Surgical – removal of all ovarian tissue, usually bilateral salpingo-oophorectomy (with or without hysterectomy)	Diagnosis and/or treatment for ovarian and endometrial cancer Endocrine therapy for estrogen-responsive breast cancers in premenopausal women Risk-reduction surgery for women at high risk of ovarian cancer (e.g. carriers of BRCA1 and BRCA2 genetic mutations)
Antiestrogen endocrine therapy	Adjuvant therapy for estrogen-responsive breast cancers Risk-reducing medication for premenopausal women at high inherited risk of breast cancer (e.g. carriers of BRCA1 and BRCA2 genetic mutations)
Radiation therapy	Pelvic: adjuvant and/or primary therapy for uterine, cervical vaginal, vulvar, bladder, anal, and colorectal cancers; pelvic Ewing sarcoma and infra-diaphragmatic nodal involvement in Hodgkin's lymphoma Total body irradiation prior to stem cell transplant Craniospinal: central nervous system tumors

## Management of menopausal symptoms

### Menopausal hormone therapy

Systemic MHT is the most effective treatment for menopausal symptoms<sup>14</sup> but is contraindicated for some women and avoided by others<sup>1</sup>. Safety concerns about MHT after cancer include chances of disease progression or recurrence, and risk of venous thromboembolic disease, which is more prevalent in cancer patients irrespective of hormone receptor status. Some women can safely use MHT after cancer treatment but not those with hormone receptor-positive breast cancer, estrogen-dependent gynecological cancers, or a history of venous thromboembolic disease. Benefits of MHT after cancer include effective symptom management and improved bone health<sup>14</sup>. Estrogen-containing hormonal contraceptives are an effective alternative to MHT for younger postmenopausal women, but the same contraindications apply. MHT is recommended until the age of expected natural menopause (50 years) after early or premature menopause unless there are contraindications<sup>15</sup>.

For women with an intact uterus, combined hormone therapy (progesterone plus estrogen) should be used to prevent endometrial hyperplasia or endometrial cancer<sup>16</sup>. Tibolone is a selective estrogen receptor modulator with anti-estrogenic activity in the endometrium. Tibolone may be used to treat vasomotor symptoms, but appears to be less effective than estrogen-based MHT<sup>17</sup> and has been shown to increase the risk of breast cancer recurrence<sup>18</sup>. Safety after other cancers is unknown.

The evidence varies by cancer type (see Table 2), and considerations include whether the cancer is estrogen sensitive and whether there is human clinical evidence that estrogen therapy stimulates tumor growth or recurrence after definitive treatment.

For women at high inherited risk of cancer (e.g. BRCA1/2 mutation carriers) who do not have a personal cancer history, current evidence suggests that MHT is safe<sup>24</sup>. However, menopausal symptoms and sexual dysfunction may persist after risk-reducing bilateral salpingo-oophorectomy in premenopausal women and are not necessarily resolved by MHT<sup>25,26</sup>.

### Compounded bioidentical hormone therapy

The safety and efficacy of compounded MHT are not established and the composition of treatments is not standardized<sup>27</sup>. These drugs are generally not regulated by the therapeutic goods, drug, or equivalent administrations so manufacturing quality and dosage cannot be ensured. Use cannot be recommended.

### Vaginal estrogens

Low-level evidence suggests that local (vaginal) estrogens are effective in dealing with symptoms of vaginal dryness in postmenopausal women<sup>28</sup>. Studies have shown no increase in recurrence for women with breast cancer using low-dose vaginal estrogen preparations<sup>29–33</sup> but there are no prospective studies of safety or efficacy. Vaginal estrogens are

**Table 2.** Cancer type, hormone status, and menopausal hormone therapy recommendation.

Cancer type	Hormone receptor status	Use of MHT
Breast cancer	ER <sup>+</sup> /PR <sup>+</sup>	Avoid MHT <sup>14,19</sup> Avoid tibolone <sup>18</sup> No consensus on use of vaginal estrogen MHT can be used <sup>20,21</sup> No consensus
Colorectal cancer	Negative	
Lung cancer	ER <sup>+</sup>	
Gynecological cancers		
Vulvar, vaginal, and squamous cell cervical cancers	Negative	MHT can be used <sup>22</sup>
Cervical adenocarcinomas	ER <sup>+</sup> /PR <sup>+</sup>	Avoid MHT <sup>23</sup>
Endometrial cancer	ER <sup>+</sup> /PR <sup>+</sup>	Avoid MHT with advanced disease; limited evidence for safety after early disease <sup>23</sup>
Uterine sarcomas	ER <sup>+</sup>	Avoid MHT <sup>23</sup>
Epithelial ovarian cancer	ER <sup>+</sup> /PR <sup>+</sup>	Avoid MHT <sup>23</sup>
Other ovarian cancers (germ cell and sex cord stromal tumors)	Unclear	Avoid MHT <sup>23</sup>
Hematological cancers (e.g. lymphomas, leukemias)	Negative	MHT can be used <sup>20</sup>
Malignant melanoma	Considered ER <sup>+</sup>	No consensus

ER, estrogen receptor; MHT, menopausal hormone therapy; PR, progesterone receptor.

systemically absorbed at low levels and this has raised concerns about their safety in breast cancer patients taking aromatase inhibitors<sup>34</sup>. Systemic absorption may reduce with continued use of vaginal estrogens<sup>34</sup>. The use of vaginal estrogens in patients with breast cancer remains unclear. An individualized, case-dependent approach should be maintained. In all cases, it is recommended to liaise with the patient's treating oncology team and use the lowest dose possible.

### Non-hormonal therapies

There is currently minimal evidence for the use of most non-hormonal therapies – non-pharmacological and, to a lesser extent, pharmacological – to manage menopausal symptoms after cancer. Where there are data, they most commonly apply to women with breast cancer. Therefore, in the following section, much of the evidence relates to studies done in women without a cancer diagnosis. Whilst this review focuses on management of menopausal symptoms after cancer, in clinical practice many of the therapies proven to be safe and effective in well women are used unless there is a clear contraindication otherwise. More studies are needed in women who have had a cancer diagnosis.

#### Non-pharmacological therapies for vasomotor symptoms

**Cognitive behavioral therapy.** In group or self-help settings, cognitive behavioral therapy reduces the impact, but not the frequency, of vasomotor symptoms after breast cancer<sup>35</sup>. However, regarding nocturnal vasomotor symptoms, cognitive behavioral therapy has been shown to reduce the subjective frequency of night sweats and to reduce objectively measured vasomotor symptoms in well women but not in breast cancer patients<sup>36</sup>.

**Clinical hypnosis.** Clinical hypnosis reduces self-reported and physiologically measured vasomotor symptoms and hot flush scores and improves mood and sleep. This is based on randomized, controlled trials in women with and without a history of breast cancer<sup>37,38</sup>. Studies have shown a

statistically significant reduction in the frequency of subjective and objective vasomotor symptoms after five, weekly, hour-long treatment sessions plus practice at home<sup>38</sup>.

**Acupuncture.** Acupuncture, a component of Chinese medicine where thin needles are inserted into the skin, has been extensively tested for treating vasomotor symptoms. A systematic review published in 2013 concluded that acupuncture was more effective than no treatment but that improvements in vasomotor symptoms with acupuncture may be a placebo effect<sup>39</sup>.

**Exercise and yoga.** Whilst both exercise and yoga improve sleep quality<sup>40</sup> for women with menopausal symptoms and exercise can improve mood<sup>41</sup>, current evidence does not support the use of yoga<sup>42</sup> or exercise<sup>42</sup> to manage vasomotor symptoms.

**Mindfulness and relaxation.** Current evidence does not support the efficacy of mindfulness-based stress reduction or relaxation techniques for management of vasomotor symptoms<sup>43</sup>.

**Diet and supplements.** Small studies suggest that supplementary phytoestrogens and isoflavones may reduce vasomotor symptoms and vaginal dryness<sup>44</sup>. It should be noted that isoflavones may bind to the estrogen receptor so should be avoided after estrogen receptor-positive breast cancer<sup>45</sup>. Black cohosh has not been shown to be safe or effective and should not be used<sup>44</sup>.

**Lifestyle changes and weight loss.** Some women can identify specific triggers for their vasomotor symptoms. Avoiding these and facilitating cooling down (such as by dressing in layers) may help some women, but there is no high-quality evidence supporting this<sup>46</sup>. Longitudinal studies show that higher body mass index is a risk factor for vasomotor symptoms (odds ratio 1.03)<sup>47</sup>.

**Stellate ganglion block.** Stellate ganglion block – an injection of a local anesthetic into sympathetic nerve fibers to disrupt temperature regulation – is invasive and costly, and there is insufficient evidence for efficacy in treating vasomotor symptoms<sup>46</sup>. More evidence is needed from ongoing trials before stellate ganglion block can be recommended for vasomotor symptoms<sup>46</sup>.

**Table 3.** Comparative efficacy of pharmacological non-hormonal treatments for vasomotor symptoms in cancer (modified from Hickey *et al.*<sup>1</sup>).

Pharmacological therapy	Reduction in VMS frequency (unless stated otherwise)	Additional benefits	Adverse effects
<b>Selective serotonin reuptake inhibitors</b>			
Citalopram (10–20 mg/day) <sup>48</sup>	43–50% vs. placebo 23%	Decreased anxiety, no impact on libido No impact on sexual function, improved quality of life and sleep, reduced impact on VMS	Drowsiness, dry mouth palpitations Increased VMS after ceasing the medication
Escitalopram (1–20 mg/day) <sup>49</sup>	50–60% vs. placebo 30%		
Paroxetine (7.5–20 mg/day) <sup>50,51</sup>	41–60% vs. placebo 14–38%	Less effect on sexual function, improved sleep	Dry mouth, GI tract upset <sup>52</sup>
Fluoxetine (20 mg/day) <sup>48</sup>	50% vs. placebo 36%	No effect on libido, quality of life and mood improved	Dry mouth, GI tract upset <sup>52</sup>
<b>Serotonin noradrenaline reuptake inhibitors</b>			
Venlafaxine (extended release, 37.5–150 mg/day) <sup>52</sup>	37–61% vs. placebo 27%	Improved sleep, quality of life, and mood	Dry mouth, GI tract upset, headache, decreased sexual function
Desvenlafaxine (100 mg/day) <sup>53</sup>	64% vs. placebo 51%	Reduced night-time awakenings, no impact on sexual function	GI tract upset, dizziness, insomnia, higher in first week of treatment. Possibly hypertension
<b>Anticonvulsants and centrally acting medications</b>			
Gabapentin (divided doses, 300–2700 mg/day; or single nocte dose for dominant nocturnal VMS) <sup>54,55</sup>	35–38% more than placebo	Improved quality of life and sleep, reduced pain	Dizziness, drowsiness, increased appetite, weight gain
Pregabalin (divided doses, 150–300 mg/day) <sup>56</sup>	66–71% vs. 50% placebo		Dizziness, drowsiness with higher doses, cognitive problems, weight gain
Clonidine (0.1–0.15 mg/day) <sup>54</sup>	26–49%	Improved quality of life	Dry mouth, tiredness, restless sleep, can interact with antihypertensives

GI, gastrointestinal; VMS, vasomotor symptoms.

### Pharmacological therapies for vasomotor symptoms

Troublesome vasomotor symptoms may be treated effectively with selective serotonin reuptake inhibitors (citalopram, escitalopram, sertraline, fluoxetine, paroxetine), serotonin noradrenaline reuptake inhibitors (venlafaxine, desvenlafaxine), clonidine, and gabapentin (see Table 3)<sup>1,46</sup>.

**Clonidine.** Clonidine is a centrally active  $\alpha_2$ -adrenergic agonist that has long been used as an antihypertensive and for vasomotor symptoms. It is the only licensed non-hormonal medicine for the treatment of vasomotor symptoms in the UK<sup>1</sup>. Clonidine is superior to placebo alone but women may not tolerate side-effects that include dizziness, hypotension, headache, constipation, and dry mouth<sup>57</sup>.

**Selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors.** Citalopram (10–20 mg daily) reduces the frequency of vasomotor symptoms for up to 7 weeks in breast cancer patients<sup>48</sup>. Sertraline has not been as well studied in patients with breast cancer and therefore should not be recommended<sup>57</sup>. Fluoxetine and paroxetine should be avoided in patients using tamoxifen, as they may impair conversion of tamoxifen to its active metabolite<sup>58</sup>. Venlafaxine (75 mg extended-release daily) reduces the frequency of hot flushes in patients with breast cancer by 10–40%, requires fewer weeks to improve symptoms than clonidine, and patients prefer it to gabapentin<sup>54</sup>.

**Gabapentin and pregabalin.** Gabapentin is an anticonvulsant also used for neuropathic pain. Gabapentin (300 mg three times per day) and pregabalin (75 mg twice a day) reduce the severity and frequency of vasomotor symptoms in women who have had breast cancer<sup>54</sup>. Up to 900 mg/day (in divided dosage) of gabapentin is generally well tolerated, but side effects are dose related and may include somnolence, dizziness, and fatigue<sup>55,58</sup>. Gabapentin at night may reduce night-time vasomotor symptoms and help with

sleep<sup>54</sup>. Gabapentin and pregabalin are not licensed for the treatment of vasomotor symptoms in the UK<sup>1</sup>.

### Non-hormonal therapies for vaginal dryness

**Lubricants and moisturizers.** Despite being widely recommended for vaginal dryness, there is little evidence to support the effectiveness of vaginal moisturizers and lubricants<sup>59</sup>. The intended benefit of vaginal lubricants is to reduce friction during sexual activity, and so reduce discomfort and pain. Common lubricant bases include water, mineral oils, plant oils, and polymerized siloxanes (i.e. silicone-based lubricants). In practice, oil-based lubricants cannot be used with latex condoms, and both oil-based and silicone-based products dry more slowly than water-based products, and thus persist longer during sexual activity<sup>60</sup>. Glycols (e.g. glycerin and propylene glycol) may be added to water-based lubricants to slow drying, but this may actually worsen symptoms as they increase osmolality and the risk of epithelial disruption<sup>59</sup>, which may cause microtears and pain.

A randomized controlled trial of water-based and silicone-based lubricants found that the silicone-based lubricant was more effective at reducing pain during sexual activity in patients with breast cancer<sup>61</sup>. A pilot study of olive oil (as a lubricant), vaginal moisturizer, and pelvic floor muscle relaxation significantly improved dyspareunia, sexual function, and quality of life after breast cancer<sup>62</sup>.

**Vaginal lidocaine.** Topical vulvar lidocaine (4%) applied for 3 min prior to penetration reduces pain during intercourse after breast cancer<sup>63</sup>.

**Other.** There is currently insufficient evidence on safety and efficacy to recommend vaginal laser treatment. Several studies are ongoing in breast cancer patients to evaluate this treatment<sup>64</sup>.

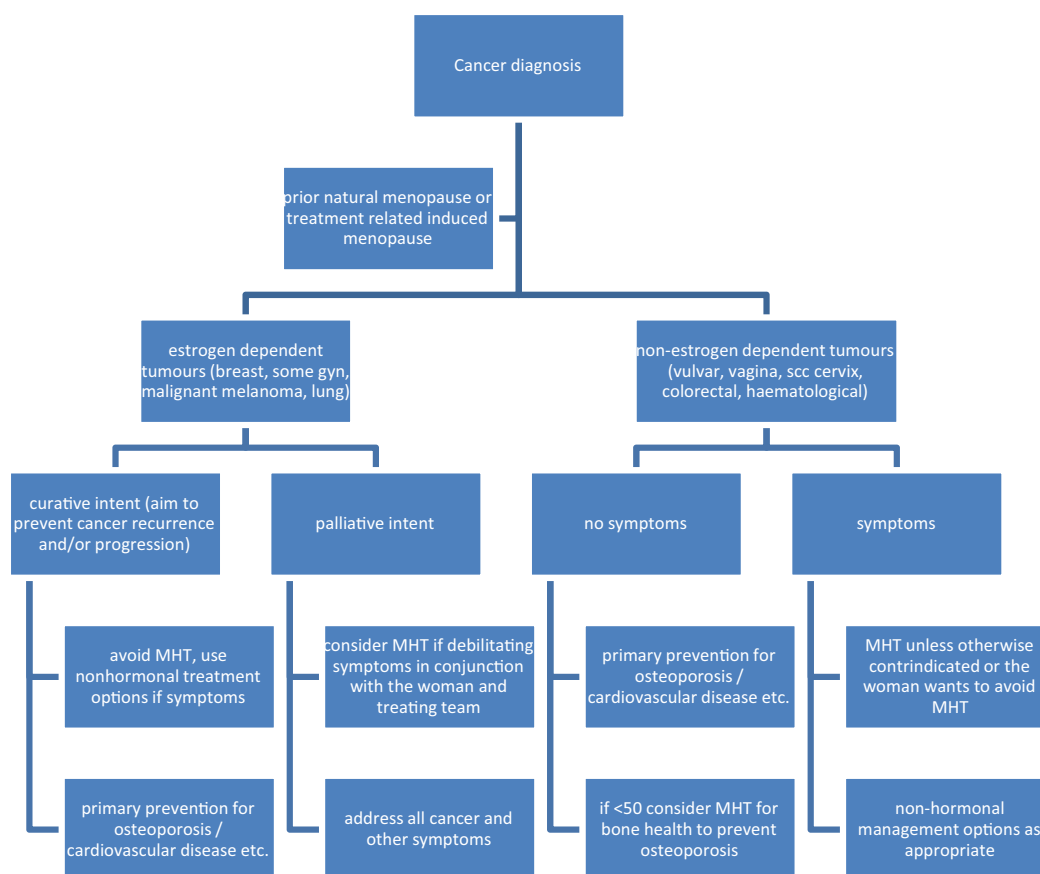


Figure 1. Management of troublesome menopausal symptoms after cancer. MHT, menopausal hormone therapy. scc = squamous cell carcinoma.

### Managing menopausal symptoms after cancer using a multidisciplinary model of care

A new model for managing menopausal symptoms in women after a cancer diagnosis has been developed and implemented across Australia, offering multidisciplinary care (Figure 1). This model brings together gynecologists, endocrinologists, and general practitioners to manage menopausal symptoms, sexual dysfunction, mood, and sleep disturbance after cancer<sup>65–67</sup>. Collaborative care with oncologists and breast surgeons ensures that consistent information is provided about treatment safety and efficacy.

### Conclusion

The global burden of cancer is such that millions of women are impacted. It must be acknowledged that not all treatments will be available to women worldwide. For many women who live with or who have had cancer, menopausal symptoms are persistent and often compounded by the troubling effects of cancer treatment.

Women should be offered evidence-based educational information about menopause and effective treatments for managing menopausal symptoms after cancer. These include both hormonal and non-hormonal options. Treatment should focus on symptoms that most affect quality of life; this may require different approaches to manage both vasomotor and

vaginal symptoms. Evidence for non-hormonal therapies, in particular non-pharmacological therapies, comes largely from studies in women without a cancer diagnosis. More research is needed.

A holistic and multidisciplinary approach with individualized care should be available for all women to comprehensively manage menopausal symptoms after a cancer diagnosis.

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