Treating Hot Flashes in Breast Cancer Survivors: A Review of Alternative Treatments to Hormone Replacement Therapy

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Breast cancer is the most common cancer diagnosis among U.S. women (Jemal et al., 2003), and an estimated 2.5 million survivors of breast cancer currently are living in the United States (Hormone Foundation, 2003). The average woman has a 12.6% lifetime risk of developing breast cancer and a 3.6% risk of dying from the disease (Burstein & Winer, 2000). These statistics suggest that most women diagnosed with breast cancer do not die from the disease, resulting in a significant number of survivors who experience psychological and physical side effects related to diagnosis and treatment.

With a growing number of breast cancer survivors, factors associated with this population’s quality of life recently have received attention (Ganz et al., 2000). Hot flashes, the most prevalent menopausal-related symptom, significantly decrease quality of life in women. Although manageable with hormone replacement therapy (HRT), hot flashes often are especially problematic in breast cancer survivors, a population that typically is not treated with HRT because of controversial evidence of a relationship among estrogen and/or progesterone and breast cancer recurrence and mortality. Furthermore, hot flashes commonly are more severe in premenopausal women who experience acute menopause as a result of chemotherapy treatment. In recent years, several treatment alternatives to HRT have been investigated. Given the significant number of women affected by breast cancer and the negative impact that hot flashes can have on their quality of life, this article reviews alternatives to HRT for reducing hot flash symptoms in breast cancer survivors.

Key Words: breast neoplasms, hot flashes, alternative therapies

As the number of breast cancer survivors continues to grow, factors associated with quality of life are receiving increased clinical and research attention. This attention is imperative given the aftermath of psychological and physiologic side effects that commonly result from a cancer diagnosis and cancer-related treatments, including menopausal symptoms. Hot flashes, the most prevalent of these symptoms, have been shown to significantly decrease quality of life in women. Although manageable with hormone replacement therapy (HRT), hot flashes often are especially problematic in breast cancer survivors, a population that typically is not treated with HRT because of controversial evidence of a relationship among estrogen and/or progesterone and breast cancer recurrence and mortality. Furthermore, hot flashes commonly are more severe in premenopausal women who experience acute menopause as a result of chemotherapy treatment. In recent years, several treatment alternatives to HRT have been investigated. Given the significant number of women affected by breast cancer and the negative impact that hot flashes can have on their quality of life, this article reviews alternatives to HRT for reducing hot flash symptoms in breast cancer survivors.

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Menopause

Menopause is defined clinically as the permanent cessation of menses for at least 12 months (Derry, Gallant, & Woods, 1997). During the years prior to menopause, estrogen and progesterone steadily decrease, which can result in a number of adverse menopause-related symptoms, including hot flashes (Klock, 2000). HRT, which refers to non-contraceptive hormone treatment with estrogen or estrogen in combination with progestin, is currently the most prevalent and effective treatment for women experiencing hot flashes and other menopausal symptoms (Klock, 2000; Pritchard, 2001). However, for women at high risk for developing breast cancer or women who are breast cancer survivors, HRT typically is not available as a treatment option because of controversial evidence about the relationship among estrogen and/or progesterone and breast cancer onset, recurrence, and mortality (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; O’Meara et al., 2001; Ursin et al., 2002; Vikas & Sood, 2001).

Furthermore, recent findings, such as those
from the Women’s Health Initiative trial, contradicted the belief that HRT prevents cardiovascular disease (Writing Group for the Women’s Health Initiative Investigators, 2002). Controversial and inconclusive information about the risks and benefits of HRT complicates women’s decision to undergo this type of therapy.

**Hot Flashes**

Hot flashes, the most commonly reported menopausal symptom, are experienced by an estimated 80% of menopausal women (Klock, 2000). This symptom is described as episodic flushing, sweating, and a sensation of heat, which often are accompanied by heart palpitations and feelings of anxiety (Kronenberg, 1994). The physiology of hot flashes is associated with reduced hormone levels that affect the thermoregulatory system in the body and result in bodily sensations of heat (Stearns & Hayes, 2002).

For the majority of women experiencing hot flashes (and other menopause-related symptoms), symptoms gradually decrease after four to five years; however, research has suggested that hot flashes may be more severe and of longer duration in breast cancer survivors for several reasons (Rowland, 1998). First, premenopausal women undergoing chemotherapy treatment often experience the onset of acute menopause as a result of toxicity to the ovary through commonly used chemotherapy drugs such as doxorubicin, cyclophosphamide, methotrexate, or fluorouracil (Bines, Oleske, & Cobleigh, 1996; Burstein & Winer, 2000; Goodwin et al., 1999). Second, women taking tamoxifen, an antiestrogen that acts to inhibit the binding of estrogen to estrogen receptors, are at increased risk for experiencing adverse menopausal symptoms, with 50% of these women reporting symptoms of severe hot flashes (Osborne, 1998). Third, because women with breast cancer often are unable to take HRT, hot flashes are typically more severe and greater in frequency than those experienced by women taking HRT (Ursin et al., 2002).

**Alternatives to Hormone Replacement Therapy**

Although HRT is a controversial option for breast cancer survivors, several treatment alternatives, both prescription and over the counter, are available.

**Megestrol Acetate**

Megestrol acetate is a prescription synthetic substance that is similar to progesterone. Some researchers support its effectiveness because breast cancer survivors who were prescribed 40 mg of megestrol acetate daily for a period of four weeks were shown to have an 85% reduction in hot flashes compared to a 21% reduction in a placebo control group (Loprinzi et al., 1994). Although megestrol acetate is effective in reducing hot flashes, breast cancer survivors should be cautious because of the potential risks associated with low doses of a progestosterone-like substance (Pritchard, 2001). Whether megestrol acetate has a negative, positive, or neutral effect on breast cancer growth or recurrence currently is unknown (Quella, Loprinzi, Sloan, et al., 2000). In addition, the commonly reported side effects, including vaginal bleeding, increased appetite, and weight gain, may deter women from selecting megestrol acetate treatment (Quella, Loprinzi, Sloan, et al.).

**Soy**

Studies investigating soy phytoestrogens, a weak estrogen-like substance found in soy products such as tofu, soy milk, and soy supplements, have offered mixed results. Some studies have found soy to significantly reduce hot flash symptoms in healthy women (Albertazzi et al., 1998), whereas other studies do not support the use of soy as an effective treatment for hot flashes in breast cancer survivors (Quella, Loprinzi, Barton, et al., 2000; Van Patten et al., 2002). The women in these studies most frequently reported gastrointestinal side effects, including abdominal bloating and gas. Despite the easy availability of soy, at present, scientific evidence is insufficient to warrant its use as an effective alternative to HRT in reducing hot flashes for breast cancer survivors.

**Black Cohosh**

Black cohosh (Cimicifuga racemosa) is a plant extract that is available over the counter in capsule form. Research has documented a reduction in hot flashes in women using black cohosh, but these studies were conducted with few participants and unvalidated measures. Clinical trials research offers no empirical evidence to suggest that black cohosh reduces hot flashes in women with a history of breast cancer (Jacobson et al., 2001). In addition to the lack of evidence supporting the use of black cohosh in treating hot flashes, no research has examined the potential harmful effects that could result in breast cancer survivors who take the herb, as many over-the-counter forms contain low levels of estrogen. Because over-the-counter herbal remedies are not currently regulated, each brand may contain variations of the herb, as well as different amounts of estrogen.

**Vitamin E**

Women taking 800 IU daily of vitamin E, an antioxidant largely composed of fat-soluble compounds (e.g., tocopherols), showed a reduction in hot flash symptoms that was equivalent to approximately one hot flash less per day than a placebo group (Sloan et al., 2001). This decrease suggests a marginal clinical difference; in other words, vitamin E does not significantly reduce hot flash symptoms. Although vitamin E may not be prescribed fervently as a treatment for hot flashes because of its minimal reduction of symptoms, vitamin E is appealing for its low cost, over-the-counter availability, and lack of drug-related side effects such as those often reported with megestrol acetate, antidepressants, and clonidine (Barton et al., 1998).

However, as with many unregulated over-the-counter dietary supplements, the type and amount of vitamin E may be inconsistent across brands, schedule, or treatment duration (Barton et al.).

**Antihypertensives**

Transdermal clonidine, a prescription drug typically used as an antihypertensive, has been shown to moderately reduce hot flashes. Specifically, when compared to a placebo, a daily dose of 0.1 mg of transdermal clonidine for four weeks caused a 20% reduction in hot flash frequency and a 10% reduction in severity in breast cancer survivors experiencing tamoxifen-induced hot flashes (Goldberg et al., 1994). This investigation also revealed that clonidine was associated with increased side effects of constipation, dry mouth, and drowsiness. These results suggest that the toxicities related to clonidine may detract from the moderate clinical effects in reducing hot flashes.

**Antidepressants**

Antidepressants, available by prescription, are one of the newest nonhormonal treatment alternatives for hot flashes. The Mayo Clinic and North Central Cancer Treatment Group were the first to investigate the use of venlafaxine. Initial results showed a 55% reduction in hot flashes by the fourth week of treatment in patients taking venlafaxine compared to an 85% reduction of hot flashes with megestrol acetate, a 39% reduction with vitamin E, and a 33% reduction with clonidine (Loprinzi et al., 1998). The researchers...
reported that venlafaxine appeared to result in more immediate declines in hot flashes as 80% of the eventual decrease occurred in the first week of treatment compared to a 12% decrease of symptoms in the first week of megestrol acetate.

Loprinzi et al. (2000) found similar results in a placebo-controlled, randomized trial: a 61% reduction with 75 mg daily of venlafaxine compared to a 27% reduction in hot flashes with placebo. These results suggest that 75 mg daily of venlafaxine is the optimal dose as it was significantly more effective than 37.5 mg daily, was equally effective as 150 mg daily, and produced fewer venlafaxine side effects of dry mouth and constipation than 150 mg daily.

Recent studies have discovered that the selective serotonin reuptake inhibitors (SSRIs), paroxetine and fluoxetine, are more effective than a placebo in reducing hot flash severity and frequency (Loprinzi et al., 2002; Sloan et al., 2001). Paroxetine reduced hot flash frequency by 67% and the severity of hot flash symptoms by 75% when prescribed 10 mg daily for one week, followed by 20 mg daily for a four-week period (Stearns et al., 2000). Stearns et al. suggested that those women who did not respond to 20 mg of paroxetine may respond to a higher dose; however, the optimal dosage for this group of women has yet to be established. In another clinical trial, 20 mg daily of fluoxetine decreased hot flashes by 50% compared to a 36% reduction with the placebo (Loprinzi et al., 2002).

A significant number of women reported experiencing side effects common to SSRIs (e.g., dry mouth, nausea, constipation, fatigue); despite these side effects, 83% (25 of 30) of the participants chose to continue taking paroxetine at the end of one study (Stearns et al., 2000) and 64% (19 of 28) wished to continue taking venlafaxine in another study (Loprinzi et al., 1998). These percentages suggest that, although the antidepressants may produce unwanted side effects, many women find these side effects far more tolerable than hot flashes.

**Conclusion**

In reviewing these alternative treatments to HRT for reducing hot flash symptoms in breast cancer survivors, the most promising appear to be the antidepressants venlafaxine, fluoxetine, and paroxetine. These drugs frequently result in side effects, but their effectiveness in reducing the severity and frequency of hot flashes in breast cancer survivors seems to outweigh the inconvenience of their side effects. No research has revealed the potential risks for breast cancer recurrence by taking the estrogen-like substances found in megestrol acetate, soy, and black cohosh, which suggests antidepressants are currently not only the most effective alternative to HRT but the safest.

Future research is needed to provide additional empirically based information on the effectiveness and short- and long-term side effects of nonpharmacologic (e.g., soy, black cohosh) and pharmacologic (e.g., antidepressants, clonidine) treatments for hot flashes. Similarly, because current evidence is inconclusive, research must evaluate the risk of breast cancer recurrence that can result from taking “natural” or “herbal” products that contain estrogenic substances (e.g., black cohosh). Moreover, the consequences of potential interactions between “natural” remedies and prescription treatments remain uninvestigated. These consequences could range from offering potential additive benefits to posing life-threatening risks.

Researchers and healthcare providers must be aware of the role of placebo effects. Participants who took inactive substances in the placebo conditions in the clinical trials reviewed in this article reported notable reductions in hot flashes (i.e., 27%–36%). Nonspecific factors such as expectation of positive outcome and hopefulness, for example, may have influenced symptom levels. The influence of the placebo effect on clinical findings further highlights the importance of future research that uses the randomized placebo-controlled design, as well as the exploration of the nonpharmacologic explanations for hot flash symptom reduction.

A significant number of women are affected by breast cancer and the negative impact that hot flashes can have on quality of life; therefore, they should discuss the safest and most effective treatment for managing hot flashes with their healthcare providers. Given the lack of information about alternative treatments, women, especially breast cancer survivors, must inform their healthcare providers of all vitamins, herbal remedies, and prescription medications that they are taking, as well as any previous or current medical conditions.

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Rapid Recap

Treating Hot Flashes in Breast Cancer Survivors: A Review of Alternative Treatments to Hormone Replacement Therapy

- Menopausal-related symptoms, including hot flashes, develop when a steady decrease or an abrupt cessation of estrogen and progesterone release occurs.
- Hormone replacement therapy (HRT) refers to noncontraceptive hormone treatment with estrogen or estrogen in combination with progesterin.
- HRT is not typically a treatment option for breast cancer survivors because of growing evidence of a relationship among estrogen and/or progesterone and breast cancer occurrence, recurrence, and mortality.
- Alternative treatments to HRT for breast cancer survivors include megestrol acetate, soy, black cohosh, vitamin E, antihypertensives, and antidepressants.
- Placebo-controlled clinical trials of alternative treatments for managing hot flashes among breast cancer survivors are needed to identify methods for optimally managing this often distressing symptom.