Survival rates for people treated for breast or prostate cancer have increased steadily since 2000, which has been attributed to advances in early detection and improvements in treatments. However, breast and prostate cancer therapies that target estrogen and testosterone production are associated with hormone-deprivation symptoms—most commonly hot flashes—that may have a significant negative impact on quality of life. Compared to the healthy population, hot flashes occur most often in these two groups, so the authors conducted a literature search specifically for evidence-based interventions to manage hot flashes experienced by women treated for breast cancer and men treated for prostate cancer. The interventions reviewed were divided into two broad categories—pharmacologic and nonpharmacologic interventions—and categorized according to Oncology Nursing Society weights of evidence. Most of the interventions were rated effectiveness not established or lower; however, two drugs, venlafaxine and gabapentin, were rated likely to be effective. In addition, the placebo effect was noted to produce a high percentage of positive results in mitigating hot flashes.

Putting Evidence Into Practice: Evidence-Based Interventions for Hot Flashes Resulting From Cancer Therapies

Prostate and breast cancers remain the most frequently diagnosed cancers in men and women in the United States. In 2010, prostate cancer was estimated to account for 28% of all new cases of cancer in men and breast cancer was estimated to account for 28% of all new cases of cancer in women (Jemal, Siegel, Xu, & Ward, 2010). From 1999–2006, breast and prostate cancer overall survival rates have shown a steady increase, at 89% and 99%, respectively (National Cancer Institute, 2010b, 2010c). Early detection and improvements in treatment have contributed to improved survival rates. However, breast and prostate cancer therapies that target estrogen and testosterone production are associated with hormone-deprivation symptoms, most commonly hot flashes. Because hot flashes occur most often in these two groups...

At a Glance
- Hot flashes can be a distressing side effect of treatment for women treated for breast cancer and men treated for prostate cancer.
- An evidence-based review of pharmacologic and nonpharmacologic interventions for managing hot flashes in these two groups revealed that only two pharmacologic measures, gabapentin and venlafaxine, are likely to be effective.
- This systematic review demonstrates that more randomized, controlled studies are needed to identify safe and effective measures to decrease the frequency, intensity, and duration of hot flashes in cancer survivors.
compared to the healthy population, the current study’s authors confined the literature search to evidence-based interventions for managing hot flashes experienced by women treated for breast cancer and men treated for prostate cancer.

A hot flash is “a subjective sensation of heat that is associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature” (Boekhout, Beijnen, & Schellens, 2006, p. 642). The frequency, duration, and intensity of hot flashes can vary widely, occurring anywhere from several times a month to every hour, and lasting anywhere from a few seconds to several minutes, with an intensity ranging from mild, moderate, and severe to very severe (Finck, Barton, Loprinzi, Quella, & Sloan, 1998).

Hot flashes are reported to be significantly more frequent and severe in women diagnosed with breast cancer and breast cancer survivors (Carpenter, 2005). Women with chemotherapy-induced menopause experience rapid changes in hormone concentrations and more severe symptoms than healthy women whose estrogen levels decline gradually during normal aging (Baber, Hickey, & Kwik, 2005). Hormonal agents used in breast cancer adjuvant or primary treatment settings to suppress ovarian function and cause estrogen withdrawal, such as tamoxifen and aromatase inhibitors, are associated with increased frequency and severity of hot flashes (Howell et al., 2005). In addition, about 80% of premenopausal women who receive chemotherapy and endocrine therapy will experience premature menopause in the first year following their diagnosis (Baber et al., 2005).

Men with prostate cancer who are treated with hormonal ablation therapies, such as androgen-deprivation therapy (ADT) or surgical castration, commonly experience vasomotor symptoms manifested by hot flashes and sweating (Lee, Kim, Shin, Choi, & Ernst, 2009). Hot flashes occur in 35%–80% of men who have been treated with ADT for advanced prostate cancer and may persist for at least eight years following treatment (Frisk, 2010). The persistence of hot flashes in men treated with ADT can have a negative effect on quality of life and has been associated with their decision to discontinue ADT (Engstrom, 2008).

Women who experience hot flashes as a result of antiestrogen therapies may discontinue treatment prematurely because of this side effect and lose the potential survival benefit conferred by these therapies. Five years of tamoxifen use is associated with a 50% reduction in risk of breast cancer recurrence (Batur, Blixen, Moore, Thacker, & Xu, 2006), yet early discontinuation rates for tamoxifen therapy range from 15%–35%, particularly in women reporting bothersome side effects (Buijs et al., 2009). To improve treatment adherence and, ultimately, quality of life, researchers must identify strategies to reduce the frequency and severity of hot flashes in women treated for breast cancer and men treated for prostate cancer.

Methods and Search Strategy

The first step in the process of developing this Putting Evidence Into Practice resource was defining what constitutes a hot flash and the population at risk for hot flashes. The working group decided to limit the at-risk populations to women treated for breast cancer and men treated for prostate cancer. Various pharmacologic and nonpharmacologic interventions used in the treatment of hot flashes, including supplements and complementary or alternative medicine (CAM), also were defined (see Figure 1).

In consultation with a librarian, the researchers conducted computerized searches of a variety of databases in August 2009 to identify meta-analyses, systematic reviews, research studies, and practice guidelines for interventions related to the prevention and treatment of hot flashes. The search was limited to English-language publications in the PubMed (Ovid), CINAHL®, EMBASE, Cochrane Collaboration, and Google™ Scholar databases. Search terms included hot flashes, breast cancer, prostate cancer, lifestyle, complementary therapy, supplements, naturopathy, and pharmacologic interventions.

A total of 242 articles initially were identified. After discussion and group consensus, several types of articles were eliminated from evaluation, including review articles, articles that addressed only healthy populations, and articles that reported pilot data if a subsequent full study was later reported; as a result, only 70 evidence-based articles were included. The references from the articles were reviewed for possible inclusion, but no additional references were added. In February 2010, the databases again were searched and 14 possible additional articles were identified. After discussion, six of those articles were included for a total of 76 articles.

Three dyads of advanced practice nurses and staff nurses extracted data in a systematic fashion from the 76 publications in evidence-based management of hot flashes. Two of the dyads reviewed all of the pharmacologic interventions and the third dyad reviewed the interventions that used supplements and CAM strategies.

Studies were grouped by intervention and were rated and assigned an Oncology Nursing Society (ONS) level of evidence based on their type and quality. The strength of evidence supporting each intervention was weighted based on seven categories of evidence identified by ONS, ranging from recommended for practice to not recommended for practice.

Each article was summarized on the evidence synthesis table by a team member and then presented to the entire team for discussion and ranking of evidence. The synthesis table noted the characteristics of the intervention: sample, setting, design, outcome measures, findings, conclusion, limitations, and ONS levels of evidence. The synthesis table was reviewed by the entire team and also by three content experts for completeness. To view the Hot Flash Evidence Table, visit www.ons.org/Research/PEP.

Clinical Measurement Tools for Hot Flashes

Hot flashes, a subjective experience, have been measured predominately in clinical trials through the use of patient self-reported diaries. No standard hot flash diary exists, but most diary logs include the recording of hot flash frequency and severity. To objectively measure hot flashes, electronic monitoring devices that assess skin temperatures have been used (Carpenter, 2005). The use of objective and subjective hot flash measurement approaches remains controversial (see Table 1).
Acupuncture
A technique in which very thin needles of varying lengths are inserted through the skin to treat a variety of conditions. A number of different acupuncture techniques exist, including some that use sound waves and tiny electrical charges.

Androgen-Deprivation Therapy
A treatment to suppress or block the production or action of male hormones by having the testicles removed, taking female sex hormones, or taking drugs called antiandrogens; also called androgen ablation and androgen suppression.

Black Cohosh
A North American perennial herb. It is being studied in the treatment of hot flashes and other symptoms of menopause.

Cimifuga Racemosa
This is the scientific name of black cohosh. Also called black snakeroot, bugbane, bugwort, and rattlesnake root.

Dong Quai
An herb native to China. A substance taken from the roots has been used in traditional Chinese medicine to treat menstrual and menopausal issues. Dong quai may increase the effect of the drug warfarin (a blood thinner). The scientific name is Angelica sinensis.

Hot Flash Diary
A paper-and-pencil subjective diary in which patients record hot flash occurrence and intensity. The use of self-report diaries for data collection has been long established as a valid approach to obtaining data on subjective phenomena such as patient-reported symptoms and perceptions. Prospective diaries can obtain information on the subjective experience of each hot flash as well as the simple recording of hot flash frequency.

Figure 1. Definition of Terms
Note. Based on information from Boekhout et al., 2006; Jacobs et al., 2005; National Cancer Institute, 2010a; National Center for Complementary and Alternative Medicine, 2011; Sloan et al., 2001.

The Placebo Effect on Hot Flashes
In numerous hot flash intervention studies, participants receiving a placebo reported significant reductions in hot flash activity. About 25% of those who received a placebo reported a reduction in hot flashes of at least 50%; 15% had greater than 75% reduction (Boekhout et al., 2006). The perceived beneficial effects of a placebo were demonstrated in a review of data from 375 participants in seven randomized clinical trials that had a placebo arm. Investigators found that those receiving the placebo intervention reported an average decrease of 25% in hot flash frequency and hot flash scores at four weeks (Sloan et al., 2001). On the basis of those results, the placebo effect should be taken into account when considering anecdotal reports of new hot flash interventions.

Pharmacologic Interventions
The literature review for hot flash interventions using pharmacologic agents revealed that weights of evidence fell into two categories: likely to be effective and effectiveness not established.

Likely to Be Effective

**Gabapentin:** Two randomized, controlled trials in women with breast cancer showed a significant difference in hot flashes with gabapentin 900 mg per day versus placebo (Loprinzi et al., 2009; Pandya et al., 2005). In another randomized, controlled trial, gabapentin 900 mg per day showed a significant difference in hot flashes in women with breast cancer compared with vitamin E 800 IU per day (Biglia et al., 2009).

**Venlafaxine:** One double-blind, placebo-controlled randomized trial showed that venlafaxine can effectively reduce hot flashes at a dose of 75 mg per day. The trial included breast cancer survivors taking tamoxifen (69%) and healthy women (Loprinzi et al., 2000). Two randomized crossover studies compared venlafaxine to clonidine and found both to be effective in relieving hot flashes (Buijs et al., 2009; Loibl et al., 2007). One randomized, double-blind, placebo-controlled crossover trial compared low-dose (37.5 mg) and high-dose (75 mg) venlafaxine and found that it resulted in modest hot flash reduction at both doses (Carpenter et al., 2007). One small open-label study reported that venlafaxine was effective in relieving hot flashes at a low dose (37.5 mg) (Biglia et al., 2005).

Effectiveness Not Established

**Clonidine:** A randomized, double-blind, placebo-controlled trial evaluated oral clonidine 0.1 mg per day versus placebo for eight weeks in postmenopausal women receiving tamoxifen for breast cancer. The mean decrease in hot flash frequency was...
A stellate ganglion block is an intervention in which a needle is inserted into the neck to deliver local anesthetic to the sympathetic nervous system. This can cause sweating in a clinical setting.

Note. Based on information from Carpenter, 2005; Loprinzi & Barton, 2009.

A small randomized trial compared intra-muscular depot medroxyprogesterone to oral megestrol for six weeks in women with breast cancer. Seventy-five percent of those receiving medroxyprogesterone and 67% of those receiving megestrol experienced a reduction in hot flash frequency (see Evidence Table). The difference in responses between the two groups was not significant. The trial did not include a placebo group (Bertelli et al., 2002).

Paroxetine: Results of a small randomized, controlled trial of paroxetine versus placebo for treatment of hot flashes in women with breast cancer showed a significant reduction in hot flashes with paroxetine 10 mg per day and paroxetine 20 mg per day versus placebo (Stearns et al., 2005). However, a recent retrospective study investigating women with breast cancer using concomitant tamoxifen therapy and a single selective serotonin reuptake inhibitor (SSRI) antidepressant agent showed a significant increased risk of death from breast cancer with overlapping use of tamoxifen and paroxetine (Kelly et al., 2010). Therefore, concomitant tamoxifen and paroxetine should be used with caution.

Sertraline: In a double-blind, placebo-controlled crossover study, women with early-stage breast cancer taking tamoxifen were given sertraline 50 mg per day for six weeks followed by six weeks of placebo and then six weeks of sertraline 50 mg per day. Results indicated no statistically significant difference in the effect of sertraline versus placebo (Kimmick, Lovato, McQuellon, Robinson, & Muss, 2006).

Stellate ganglion block: A stellate ganglion block is an injection of local anesthetic in the sympathetic nerve tissue. Lipov et al. (2008) investigated its effectiveness in the treatment of hot flashes in a small number of women with breast cancer (N = 13). After 12 weeks, hot flashes had decreased to a mean of 8 episodes per week from a mean of 79 episodes per week prior to intervention.

Testosterone replacement therapy: A retrospective review was conducted of 10 patients treated for prostate cancer who subsequently received testosterone replacement therapy for symptoms of hypogonadism, including hot flashes. Median duration of therapy was 19 months, during which participants reported a reduction in hot flashes and no recurrence of disease. Future research involving a large placebo-controlled, multi-center prospective trial to evaluate the safety and feasibility of testosterone replacement therapy in patients with hypogonadism after radical prostatectomy for prostate cancer is needed (Agarwal & Oefelein, 2005).
**Tibolone:** One randomized, double-blind placebo-controlled trial compared tibolone versus placebo in postmenopausal women with breast cancer receiving adjuvant tamoxifen. Daily diary reports showed no change in daily number of hot flashes with tibolone or placebo after three months. Effects of tibolone on recurrence of breast cancer are unknown (Kroiss et al., 2005).

**Nonpharmacologic Interventions**

The review of the literature for hot flash interventions using dietary supplements revealed that weights of evidence fell into two categories: effectiveness not established and effectiveness unlikely.

**Effectiveness Not Established**

**Black cohosh:** In two double-blind, randomized controlled trials of black cohosh versus placebo, no evidence was found that black cohosh reduced hot flashes more than the placebo (Jacobson et al., 2001; Pockaj et al., 2006). One of the studies, which stratified for tamoxifen use, demonstrated no significant differences in hot flash activity between the treatment and placebo groups (Jacobson et al., 2001). One randomized open-label study of premenopausal breast cancer survivors experiencing tamoxifen-related hot flash activity showed that the combination of tamoxifen plus a black cohosh preparation was associated with a significant reduction in vasomotor episodes induced by tamoxifen over a 12-month period (Hernández Muñoz & Pluchino, 2003).

**Vitamin E:** One randomized, double-blind crossover trial of vitamin E versus placebo, in which participants were stratified by age and tamoxifen use, showed that vitamin E was associated with one less hot flash per day than was seen with a placebo (p ≤ 0.05). At the study end, however, participants did not prefer vitamin E over the placebo and no toxicity was demonstrated (Barton et al., 1998).

One randomized, nonplacebo-controlled nonblinded study, designed to assess the efficacy and tolerability of gabapentin 900 mg per day for the control of vasomotor symptoms in women with breast cancer, included vitamin E as a placebo-equivalent comparator. Results demonstrated that vitamin E only had a marginal effect on vasomotor symptoms, reducing hot flash frequency and severity by 10.02% and 7.28%, respectively (p ≥ 0.05). Gabapentin 900 mg per day was reported effective for relieving hot flashes in patients previously treated for breast cancer (Biglia et al., 2009).

**Effectiveness Unlikely**

**Homeopathy:** The homeopathy approach to treating hot flashes generally incorporates consultation with a homeopathic practitioner and the prescription of an individualized homeopathic remedy designed to address each individual's reported symptoms. In general, ingredients and doses of the homeopathic remedies were unclear or lacking. One randomized, controlled trial, stratified for age, breast cancer stage, and tamoxifen use, showed no significant difference in hot flash activity over one year (Jacobs, Herman, Heron, Olsen, & Vaughters, 2005). Two observational studies conducted at an outpatient homeopathic clinic reported improvement in hot flashes with homeopathic treatment, but methodologic flaws were too numerous for the studies to be useful (Clover & Ratsey, 2002; Thompson & Reilly, 2003).

**Soy supplements:** Depending on the study, soy supplements were provided to participants in the form of capsules, tablets, powder, or beverage. Four double-blind, randomized controlled trials of soy supplements versus placebo for treatment of hot flashes in women with breast cancer, stratified for tamoxifen use, did not demonstrate significant differences in hot flash symptoms between the placebo and soy supplement arms of the studies (MacGregor, Canney, Patterson, McDonald, & Paul, 2005; Nikander, Metsä-Heikkilä, Ylikorkala, & Tiitinen, 2004; Quella et al., 2000; Van Patten et al., 2002). In men undergoing ADT for prostate cancer, one randomized, controlled trial did not show any significant improvement in hot flashes between men receiving soy isoflavones compared to those on the placebo (Sharma et al., 2009).

**Nonpharmacologic Interventions: Complementary and Alternative Medicine**

The literature review identified a number of CAM approaches—acupuncture, hypnosis, peer counseling, relaxation therapy, and yoga—that have been evaluated for the management of hot flashes in oncology and other populations. All of the interventions were ranked as effectiveness not established.

**Effectiveness Not Established**

**Acupuncture:** Acupuncture is the procedure of inserting and manipulating needles into various points on the body for pain relief or other therapeutic purposes. It typically is administered by a trained acupuncturist, but with personalized training and practice, some self-administer. Six randomized trials of acupuncture in various groups were identified that demonstrated a decrease in hot flashes. Sample size was less than 72 total participants in all studies. Follow-up was limited and did not exceed six months (Deng et al., 2007; Filshie, Bolton, Browne, & Ashley, 2005; Frisk et al., 2008; Hervik & Mjåland, 2009; Nedstrand, Wijma, Wyon, & Hammar, 2005; Walker et al., 2010). One pilot study of seven men who received acupuncture showed a decrease in hot flashes (follow-up was 10 weeks) (Hammar et al., 1999). A convenience sample of 60 consecutive women receiving acupuncture for 10 weeks showed a decrease in hot flashes (Harding, Harris, & Chadwick, 2008). A second convenience sample of 12 women with breast cancer receiving tamoxifen showed that acupuncture demonstrated some decrease in hot flashes (Towlerton, Filshie, O’Brien, & Duncan, 1999).

**Hypnosis:** Hypnosis, a popular CAM in oncology, is a form of relaxation therapy in which the person reaches a state of restful alertness with deeply focused concentration and may be more open to suggestion. One randomized trial of 60 women with breast cancer showed a decrease in hot flashes following hypnosis. Follow-up was five weeks (Elkins et al., 2008). Three pilot studies with a sample size of 16 or fewer also showed a decrease in hot flashes (Elkins et al., 2008; Elkins, Marcus,
Peer counseling: Peer counseling can be provided by individuals who have experienced a certain situation or diagnosis and have received training on how to facilitate a group. One randomized study of 60 African American women with breast cancer demonstrated a decrease in menopausal symptoms, including hot flashes, after participating in a peer counseling group (Schoder et al., 2006).

Relaxation therapy: Relaxation therapy is another popular CAM used in oncology practice and consists of techniques to calm the body and mind. One trial of 150 women with breast cancer demonstrated a decrease in hot flashes (Fenlon, Corner, & Haviland, 2008). Attrition was significant (final sample size was 104) and follow-up was three months.

Yoga: Yoga is a form of nonaerobic exercise that involves a program of precise posture, breathing exercises, and meditation. One randomized trial of 37 women who either received instruction in yoga techniques or were in a control group showed a decrease in hot flashes in the intervention group (Carson, Carson, Porter, Keefe, & Seewaldt, 2009). Follow-up was three months.

Survivorship and Late Effects

An estimated 2.5 million women are alive with breast cancer and 2.2 million men are alive with a diagnosis of prostate cancer in the United States (ACS, 2010; Altekruse et al., 2010). As the number of survivors has increased, quality-of-life issues, including management of hot flashes, have become more important to address. Hot flashes are more common in women who have survived breast cancer because of the hormonal manipulation used in treatment (Carpenter, 2005), in part because young women treated with chemotherapy for breast cancer often experience premature menopause and many women of all ages receive hormonal therapy following chemotherapy or as their primary breast cancer treatment. Hot flashes are reported as the most prevalent side effect of hormonal agents such as the selective estrogen receptor modulator tamoxifen and aromatase inhibitors. Healthy women may resort to estrogen replacement therapy to ameliorate the hot flashes of menopause, but estrogen replacement therapy is contraindicated in women with a history of breast cancer because of concerns about potentiating disease recurrence (Holmberg et al., 2008; Loprinzi et al., 2000).

Reviews of evidence-based studies suggest that an agent likely to be effective in alleviating hot flashes belongs to the drug class of SSRIs. However, SSRIs are known to inhibit the enzyme system P450 2D6 (CYP 2D6), which is important in metabolizing tamoxifen to its active form. Recent pharmacogenomic studies have identified a reduction in the effectiveness of tamoxifen when taken with drugs such as SSRIs that inhibit tamoxifen bioactivation by the CYP 2D6 system (Henry, Stearns, Flockhart, Hayes, & Riba, 2008). Studies have shown that the SSRIs fluoxetine and paroxetine are strong CYP 2D6 inhibitors and should be avoided by women taking tamoxifen (Henry et al., 2008). Retrospective data indicate a potential for increased rates of breast cancer recurrence and decreased relapse-free survival for women taking tamoxifen concurrently with these strong CYP 2D6 inhibitors (Henry et al., 2008; Kelly et al., 2010).

Implications for Clinical Practice and Future Research

Hot flashes can have a negative impact on quality of life in patients treated for breast and prostate cancer. More research is needed to identify effective means to decrease or manage hot flashes and, ultimately, ways to prevent hot flashes in at-risk populations (see Figure 2). In the case of CAM and other nonpharmacologic approaches, randomized trials of significant power and duration should be conducted to identify effective strategies, particularly for those who are unwilling or cannot tolerate pharmacologic therapies.

Few tools exist that have been validated to accurately assess and document the presence and intensity of hot flashes; more research in this area is needed. A more effective assessment tool would enable researchers to better determine the usefulness of an intervention and provide clinicians with a simple tool when evaluating an intervention’s efficacy in patients. In addition, few of the studies reviewed for this article contained follow-up data beyond three months. Data are needed to evaluate durability of reported positive responses, as well as to assess for potential long-term negative effects of the interventions. Additional randomized clinical trials with long-term follow-up are needed in men and women experiencing hot flashes as a result of cancer treatments.

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