According to the National Cancer Institute, more than 230,000 new cases of prostate cancer will occur in the United States in 2005. Prostate cancer is the second leading cause of cancer death in men, with an estimated 29,900 deaths in 2004 (American Cancer Institute, 2004). The standard palliative treatment for men with advanced disease is androgen deprivation, which can be accomplished through bilateral orchiectomy or the administration of estrogens or luteinizing hormone-releasing hormone (LHRH) analogues (Sartor et al., 2003). Common adverse effects associated with the use of androgen ablation in men with prostate cancer include sexual dysfunction; gynecomastia; changes in body composition, metabolism, and the cardiovascular system; osteoporosis; anemia; psychiatric and cognitive disorders; fatigue and overall diminished quality of life; and hot flashes (Chen & Petrylak, 2004).

The incidence of hot flashes in men undergoing androgen deprivation therapy has been estimated at 55% to 80%; however, the true incidence of hot flashes secondary to hormone ablation therapy has not been well documented nor accurately measured (Higano, 2003). Among patients who underwent orchiectomy, 58% to 76% experienced hot flashes (Frödin, Alund, & Varenhorst, 1985; Charig & Rundle, 1989, as cited in Karling, Hammar, & Varenhorst, 1994). Vasomotor hot flashes are characterized by a subjective sensation of increased temperature that typically occurs in the upper body and face. Peripheral vasodilation causes a visible reddening of the skin and is followed by profuse sweating. Often, hot flashes occur spontaneously; however, they may be triggered by external factors such as changes in the ambient temperature, ingesting hot fluids, or changes in body position (McCallum & Reading, 1989, as cited in Smith, 1994). Mild hot flashes may be tolerable. However, moderate hot flashes may produce a level of discomfort that is sufficient to interfere with daily activities, and severe hot flashes may be incapacitating (Walsh & Worthington, 1995, as cited in Higano, 2003). Treatment of hot flashes in men undergoing androgen deprivation therapy includes diethylstilbestrol and other estrogens, megestrol acetate, medroxyprogesterone acetate, and venlafaxine (Higano, 2003).

In pre and post-menopausal women, hot flashes are a natural consequence of decreasing estrogen levels. However, hot flashes are not observed in healthy men, despite the decrease in serum testosterone levels that is associated with aging-related Leydig cell dysfunction (Smith, 1994). The most widely accepted theory on the pathogenesis of hot flashes involves the dynamic reduction (momentum) of sex hormones rather than their absolute levels (Kouriefs, Georgiou, & Ravi, 2002). The negative feedback of plasma sex hormones is thought to regulate the generation of hot flashes. Peripheral sex hormones activate the production of hypothalamic-endorphin and catecholestrogen, which inhibits the synthesis of hypo-

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Note: CE Objectives and Evaluation Form appear on page 21.
Hot Flashes Are Not Self-Limiting

Some researchers believe that hot flashes associated with the treatment of prostate cancer are self-limiting; therefore, this condition has received little attention in the published literature. However, hot flashes are reported to persist long after chemical or surgical castration (Karling et al., 1994; Schow, Renfer, Rozanski, & Thompson, 1998; Spetz et al., 2001). One study reported that hot flashes persisted for up to 8 years in more than 40% of patients with prostate cancer who underwent surgical (orchiectomy) or medical castration (Karling et al., 1994). Another study of 43 patients who received neoadjuvant hormonal therapy prior to radical prostatectomy reported that 11% of patients continued to experience hot flashes secondary to leuprolide or goserelin therapy and assessed treatment response (severity, frequency, and duration of hot flashes) via patient interview (Bressler et al., 2002b; Bressler, Murphy, Shevrin, & Warren, 1993; Gerber, Zagaja, Ray, & Rukstalis, 2000; Loprinzi et al., 1994; Spetz et al., 2001). A study of 12 men with advanced prostate cancer who experienced moderate to severe hot flashes while receiving leuprolide used a combination of methods including daily logs, a questionnaire, and a visual analog scale to rate hot flashes during treatment with estrogen (Gerber et al., 2000). The daily log was designed to evaluate the frequency, severity, and duration of hot flashes and was completed at the end of weeks 1, 5, 9, and 13. Because the results from the daily logs were similar for each week, the investigators used results from the questionnaires to report changes in the duration of hot flashes and the visual analog scale to interpret changes in severity (Gerber et al., 2000). Another small study of four men evaluated the efficacy of combined estrogen for hot flashes secondary to leuprolide or goserelin therapy and assessed treatment response (severity, frequency, and duration of hot flashes) via patient interview (Bressler et al., 1993).

The Assessment of Hot Flashes During Quality-of-Life Studies

Hot flashes may affect psy-
Studies in men with prostate cancer have included questions to assess the incidence and/or severity of hot flashes (Albertsen, Aaronson, Muller, Keller, & Ware, 1997; Clark et al., 1997; Fossa, 1996; Krupski, Petroni, Bissonette, & Teodorescu, 2000; Ward-Smith, Wittkopp, & Sheldon, 2004). However, there are no known QOL instruments to specifically evaluate the impact of hot flashes in men with prostate cancer. Studies in men with prostate cancer have used a general questionnaire and a prostate-specific module to evaluate QOL in this population (Albertsen et al., 1997; Clark et al., 1997; Krupski et al., 2000; Wei, Dunn, Litwin, Sandler, & Sanda, 2000).

One study assessed QOL in men with prostate cancer by means of a 12-item questionnaire, which evaluated symptom severity including hot flashes, and the Functional Assessment of Cancer Therapy (FACT-G), an instrument that reports general QOL issues relating to personal, social/family, emotional, and functional well-being in relation to cancer (Cella et al., 1993; Krupski et al., 2000). Interestingly, this study reported a high correlation between the findings of the FACT-G and symptom severity. These data suggested that hot flashes may impact QOL (Krupski et al., 2000).

A similar method was used in an earlier study to assess QOL in men with advanced prostate cancer in remission (Albertsen et al., 1997). The investigators used a prostate-specific module that was developed for use during the study, which evaluated urinary symptoms and sexual functioning as well as single-item measures such as weight loss, weight gain, and hot flashes. Other questionnaires included the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the Medical Outcomes Study Short Form Health Survey (SF-36) (Aaronson et al., 1993; Ware & Sherbourne, 1992, as cited in Albertsen et al., 1997).

The Expanded Prostate Index Composite (EPIC) was designed to address the limitations of existing prostate-specific QOL instruments; these limitations include a lack of validated multi-item summary scores to specifically measure the effects and related bothers of hormonal therapy (Wei et al., 2000). EPIC measures androgen-deprivation symptoms and related bother in urinary, bowel, sexual, and hormonal domains; the hormonal domain evaluates hot flashes, depression, weight gain, and fatigue. A study that used EPIC to compare QOL among patients who underwent brachytherapy, external-beam radiation, or radical prostatectomy reported a significant difference in hormonal QOL between patients with progression-free disease and those with increasing prostate-specific antigen levels (Wei et al., 2002).

The use of symptom-specific tools is important for evaluating QOL as nonspecific instruments have been associated, in part, with the failure to distinguish between patients with no or mild hot flashes and those with severe hot flashes, despite trends noted between these groups in physical and emotional functioning. Standard QOL measures were designed to serve as global measures of functioning and not as disease or symptom-specific tools (Carpenter, 2001). Furthermore, historical studies have measured QOL using pain scores and performance status; however, other factors such as social interactions and mental health can have a considerable impact on QOL (Albertsen et al., 1997). In patients with prostate cancer, body image, masculine image, and self-image have been reported to correlate with symptoms such as hot flashes (Clark et al., 1997). Therefore, a symptom-specific instrument is needed that measures the daily impact of hot flashes on psychosocial and functional status. Such an instrument would allow the health care community to gain insight as to how men perceive the effects of hot flashes in relation to their well-being during treatment of prostate cancer.

QOL is an important factor that should not be ignored, because it may have a substantial effect on treatment decisions and comparisons (Kattan, 2003). Patients and physicians may use QOL data to help weigh the advantages and disadvantages of various treatment regimens. For example, when QOL issues are considered, less-effective treatments for the underlying disease may be preferred to those that are associated with more favorable outcomes (McNeil, Weichselbaum, & Pauker, 1978, 1981; McQuellon et al., 1995; Silvestri, Pritchard, & Welch, 1998). Effects on QOL should, therefore, be considered in conjunction with the survival advantages of different treatments. Utility assessment takes both of these factors into account in computing quality-adjusted survival (Kattan, 2003). However, the effect of hot flashes on overall QOL, as measured by utility, is unknown. Studies are needed to address this issue.

Additional Methods Are Needed for Men with Prostate Cancer

Few scientific investigations have studied objective measures of hot flashes in men with prostate cancer. One such measure was evaluated approximately 20 years ago with a sample of 13 men who had undergone orchietomy for prostate cancer. A laser Doppler flowmeter and evaporometer were used to assess skin blood flow and water evaporation. Results demonstrat-
ed that the rate of water evaporation increased by 10 to >60 g/m²/h in approximately 65% of patients experiencing hot flashes. Moreover, increased evaporation was synchronous with increased cutaneous blood flow (Frödin et al., 1985). Although objective measures may be useful in this patient population, some investigators believe that the patient’s subjective experience and opinion are more important determinants of symptom severity and that the patient’s opinion should take precedence over an objective skin temperature reading (Sloan et al., 2001). Furthermore, the correlation between skin conductance measures and self-reported hot flashes is lower in the ambulatory setting than in the laboratory because of underreporting of self-reported hot flashes, and there are physical limitations associated with the use of sternal skin conductance monitors that prohibit their long-term use in the ambulatory setting (Miller & Li, 2004).

There is a clear need for additional methods of evaluating hot flashes in men receiving androgen ablation therapy. Because hot flashes described in men on androgen ablation therapy are similar to those described in menopausal women and breast cancer survivors, it may be useful to explore the methods of evaluating hot flashes in these patients to determine their utility in men.

**Measures of Hot Flashes In Menopausal Women And Breast Cancer Survivors**

In pre-menopausal women with breast cancer, chemotheraphy can precipitate menopause and lead to the rapid onset of hot flashes. Furthermore, more than 50% of patients treated with tamoxifen (an anti-estrogen agent) develop hot flashes (Hoda, Perez, & Loprinzi, 2003). The severity of hot flashes in breast cancer survivors varies and has been described as mild or uncomfortable in some and as boiling eruptions in others (Finck, Barton, Loprinzi, Quella, & Sloan, 1998). In post-menopausal women with breast cancer, hot flashes have been correlated with poorer sleep quality, more fatigue, and worse physical health (Stein, Jacobsen, Hann, Greenberg, & Lyman, 2000). In a study that compared post-menopausal women with and without hot flashes, those with hot flashes experienced 66% more fatigue, 63% poorer sleep quality, and 20% poorer health (Stein et al., 2000).

Trials that evaluated treatment of hot flashes in breast cancer survivors used patient diaries, daily logs, and questionnaires (Barton et al., 1998; Barton et al., 2002a; Loprinzi et al., 2002a; Loprinzi et al., 2002b). Many of these tools are similar to those that have been used in studies of hormone ablation therapy. However, in women, a QOL instrument has been developed exclusively to assess the impact of hot flashes on daily activities and overall QOL; the Hot Flash Related Daily Interference Scale (HFRDIS) is a psychometrically sound instrument that has been evaluated in breast cancer survivors (see Table 1) (Carpenter, 2001). The HFRDIS was used to analyze the impact of hot flashes on overall QOL and daily activities, including work, social activities, leisure activities, sleep, mood, concentration, relationships with others, sexuality, and enjoyment of life by rating the impact of hot flashes on a scale from 0 (do not interfere) to 10 (completely interferes). When this instrument scale was tested in breast cancer survivors and age-matched healthy controls, it exhibited high internal consistency and validity. Frequency, severity, and bother (for example, distress) were more important determinants of the impact of hot flashes on daily activities than the duration of hot flashes. Hot flashes interfered most with sleep, mood, and concentration (Carpenter, 2001). Interestingly, every item on the HFRDIS was affected by hot flashes. Although the HFRDIS was used to evaluate hot flashes in women, it is not a gender-specific tool. Thus, this tool may be considered for use in the clinical setting when assessment of hot flashes in females or males is desired.

A number of studies suggest that hot flashes in menopausal women can be objectively evaluated using various objective measures such as sternal skin con-
ductance or skin conductance changes in combination with circulation changes (deBakker & Everaerd, 1996; Freedman, 1989; Freedman, Norton, Woodward, & Cornelissen, 1995; Freedman, Woodward, & Norton, 1992; Swartzman, Edelberg, & Kemmann, 1990; Tataryn et al., 1981). However, changes in skin temperature are not always correlated with subjective assessments of hot flashes (Tataryn et al., 1981). Furthermore, sternal skin conductance pattern changes do not explain variations among subjectively experienced hot flashes, and the perception of bodily sensations is less accurate under experimental versus real-world conditions (deBakker & Everaerd, 1996; Pennebaker & Roberts, 1992, as cited in deBakker & Everaerd, 1996). Since objective techniques have been evaluated only in small studies, their relative validity for hot flash measurements is questionable.

### Conclusion

Hot flashes are one of the most common side effects of androgen ablation treatment in men with prostate cancer. Their incidence in these patients is not self-limiting, and they can be incapacitating if severe. Thus, reliable subjective and objective evaluation tools are needed to determine the impact of hot flashes on daily functioning in patients who receive androgen suppression therapy. Information collected from patient diaries, charts, and questionnaires can be used to make subjective assessments of symptoms, but the reliability of these sources is often questionable. The currently available objective methods for evaluating symptoms do not accurately reflect the subjective experiences of patients with hot flashes. The feasibility of using a symptom-specific QOL tool such as the HFRDIS to evaluate hot flashes in men should be investigated. Moreover, additional instruments should be developed and validated to gain a better insight into the QOL effects of hot flashes in men with prostate cancer who are receiving androgen ablation therapy.

### References


