State of the Science: Hot Flashes and Cancer, Part 1: Definition, Scope, Impact, Physiology, and Measurement

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Purpose/Objectives: To critically evaluate and synthesize multidisciplinary research related to hot flashes in the context of cancer. Topics include the definition, scope, and impact of hot flashes; physiologic mechanisms; and measurement issues.

Data Sources: Published, peer-reviewed articles and textbooks; editorials; unpublished data; and computerized databases.

Data Synthesis: Hot flashes can affect a diverse group of men and women diagnosed with or at high risk for certain cancers with a resulting negative impact on quality of life. Although the exact physiologic mechanisms underlying hot flashes remain unclear, a complex interplay of thermoregulatory, gluconeuroendocrine, genetic, and behavioral factors appears to be involved. Measurement of hot flashes should be considered carefully because they can be operationalized objectively and subjectively.

Conclusions: The large and diverse evidence base and current national attention on measurement of hot flashes highlight the importance of the symptom to healthcare professionals, including oncology nurses.

Implications for Nursing: Careful attention to assessment and measurement of hot flashes in patients with cancer is needed.

Key Points . . .

- Several factors place women and men with cancer at risk for hot flashes, including agents used in the prevention of cancer, tumor characteristics, and cancer treatments.
- A complex interplay of factors appears to be involved in the physiologic mechanisms of hot flashes.
- Hot flashes tend to be underreported when subjective reports are compared to objective measurements.

Part one of this state-of-the-science review relates to hot flashes in the context of cancer and focuses on three broad topics. First, the definition, scope, and impact of hot flashes in the context of cancer are discussed. Second, physiologic mechanisms of hot flashes are presented. Third, measurement issues are identified. Although much of the information presented is specific to cancer, where information is missing or currently unknown, data from healthy populations of men and women are used.

Throughout the review, the phrase hot flash is used. However, hot flashes also are known as hot flushes, night sweats, and vasomotor symptoms. The phrase hot flash is used commonly in the United States, whereas hot flush is used more commonly in Great Britain. The term night sweats often is used to refer specifically to hot flashes that occur while sleeping, although night sweats can result from other conditions, such as fever. The phrase vasomotor symptoms was coined in reference to the flushing and vasodilation that occur with hot flashes. Each of the terms refers to a single phenomenon.

Definition, Scope, and Impact

In this section, hot flashes are defined and risk factors relevant to cancer prevention, diagnosis, and treatment are discussed. Differences and similarities in risk factors for women and men with cancer are identified. The prevalence and negative impact of hot flashes also are presented. The question of whether hot flashes are identical in all groups is raised.

Definition

A hot flash is defined as a sudden rush of heat and is considered to be a discrete physiologic event and a subjective phenomenon. When hot flashes were studied as discrete physiologic events, the following were noted to occur in healthy women. An inspiratory sigh precedes most menopausal hot flashes (Woodward, Greville, & Freedman, 1995). During a hot flash, sweat gland activity increases (Freedman, 1989), heart rate increases (Kronenberg, 1990; Kronenberg, Cote, Linkie, Dyrenfurth, & Downey, 1984), respiratory quotient (an indicator of metabolic rate) increases (Freedman, 1998), and blood pH falls slightly (e.g., acidosis) (Aktan, Kaleli, & Sungurtekin, 1998). Although one case study reported a profound drop in systolic blood pressure of 40 mmHg during a hot flash in a hypertensive African American woman (Nelesen, Krohn, & Dimsdale, 2004), another study of 20 nonhypertensive women

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showed no meaningful changes in blood pressure during hot flashes (James, Sievert, & Flanagan, 2004). In breast cancer survivors, similar increases in sweating and respiratory quotient have been noted (Carpenter, Andrykowski, Freedman, & Munn, 1999; Carpenter, Gilchrist, Chen, Gautam, & Freedman, 2004), whereas other parameters (e.g., sighing, blood pH, heart rate, blood pressure) have not been studied.

Subjectively, hot flashes are described as transient episodes of flushing, sweating, and heat and are noted to occur with palpitations, anxiety, or chills in healthy women and breast cancer survivors (Carpenter, Johnson, Wagner, & Andrykowski, 2002; Finck, Barton, Loprinzi, Quella, & Sloan, 1998; Knobf, 2001; Kronenberg, 1994). In one study directly comparing 69 breast cancer survivors and 63 healthy women with hot flashes, no differences in the number or type of hot flash descriptors were found (Carpenter, Johnson, et al.). The most commonly endorsed descriptors were heat (93%), sweating or perspiring (89%), flushing (77%), and clamminess (46%) (Carpenter, Johnson, et al.). Similarly, in a grounded theory study of 27 women with breast cancer, hot flashes were described as mild ("all of a sudden feel very warm and it would pass") to severe ("I have awful hot flashes. . . . I had a huge one today. . . . [It] was a doozy. . . . It was a construction worker in 95-degree weather.") (Knobf, p. 203).

Two definitions for categories of hot flash severity have been proposed for breast cancer survivors and healthy women. Research by Finck et al. (1998) suggested that breast cancer survivors rate hot flash severity as mild, moderate, and severe based on duration and three other factors: (a) somatic sensations such as location of warmth or heat, inability to breathe, or feeling weak or faint; (b) emotional perceptions such as whether a hot flash is unexpected and feeling anxious, irritated, or embarrassed; and (c) behavioral consequences such as the need to remove clothing, adjust thermostats, or change clothes and bed linens. In addition, definitions of mild, moderate, and severe hot flashes were offered in draft recommendations put forth by the U.S. Food and Drug Administration (FDA) in January 2003 (U.S. Department of Health and Human Services [DHHS], 2003). The FDA recommendations pertain to the clinical evaluation of estrogen and estrogen and progestin products to treat hot flashes (and other menopausal symptoms) but have been adopted more widely by investigators evaluating a variety of pharmacologic and nonpharmacologic hot flash treatments. The definitions are "mild: sensation of heat without sweating; moderate: sensation of heat with sweating, able to continue activity; and severe: sensation of heat with sweating, causing cessation of activity" (DHHS, p. 2). The appropriateness of the FDA definitions has been questioned (Miller & Li, 2004). The FDA definitions combine heat, sweating, and functioning but do not address other somatic sensations, emotional perceptions, or behavioral consequences. Whether either set of definitions has applicability across cancer populations is unclear.

Risk Factors

Although healthy women and men can experience hot flashes as part of the natural aging process (Kronenberg, 1990; Spetz, Hammar, & Varenhorst, 2003; Stanford, Hartge, Brinton, Hoover, & Brookmeyer, 1987), several additional factors in the context of cancer predispose women and men to hot flashes (see Table 1). Among women, the risk factors most commonly are related to estrogen withdrawal and include (a) discontinuation of hormone replacement therapy for chemoprevention or treatment of hormonally dependent cancers (Hammar, Ekblad, et al., 1999); (b) endocrine therapies for the prevention or treatment of hormonally dependent cancers, including selective estrogen receptor modulators, aromatase inhibitors, and gonadotropin-releasing hormone analogs (Biglia et al., 2003; Carpenter et al., 1998; Gajdos & Jordan, 2002; Johnston, 2001; Love, 1989; Love, Cameron, Connell, & Leventhal, 1991; Morales et al., 2004; Mouridsen et al., 2001; Pasacreta & McCorkle, 1998); (c) systemic chemotherapy (Biglia et al.; Carpenter et al., 1998; Lo Presti, Ruvolo, Gancitano, & Cittadini, 2004); (d) oophorectomy, either prophylactically or as a cancer treatment; and (e) radiation-induced ovarian damage (Lo Presti et al.). For men, the most common risk factors include (a) endocrine therapies used for neoadjuvant or adjuvant treatment of prostate cancer and (b) orchiectomy for the treatment of advanced or metastatic prostate cancer (Charig & Rundle, 1989; Holzbeierlein, Castle, & Thrasher, 2004; Holzbeierlein, McLaughlin, & Thrasher, 2004; Kouriefs, Georgiou, & Ravi, 2002; Schow, Renfer, Rozanski, & Thompson, 1998). In addition, women and men who are diagnosed with carcinoid tumors, medullary thyroid cancer, pancreatic cancer, or renal cell carcinoma may experience hot flashes, primarily caused by tumor secretion of various compounds (Mohyi, Tabassi, & Simon, 1997).

Table 1. Hot Flash Risk Factors in the Context of Cancer

Population	Cancer Prevention	Tumor Characteristics	Cancer Treatment
Women			
Discontinue hormone replacement therapy	X	–	X
Endocrine therapy	X	–	X
Systemic chemotherapy	–	–	X
Oophorectomy	X	–	X
Radiotherapy	–	–	X
Men			
Endocrine therapy	–	–	X
Orchiectomy	–	–	X
Women and men			
Carcinoid tumors	–	X	–
Medullary thyroid cancer	–	X	–
Pancreatic cancer	–	X	–
Renal cell carcinoma	–	X	–

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The effects of the risk factors vary. For example, women who discontinue hormone replacement therapy are most likely to experience hot flashes if they have experienced them in the past or if they are having them at the time of discontinuing the medication (Hammar, Ekblad, et al., 1999). In addition, the effects of chemotherapy on the ovaries vary depending on age, dose, and type of treatment (Lo Presti et al., 2004). Younger women are better able to tolerate higher doses of chemotherapy and are less likely to experience induced menopause (Lo Presti et al.). However, younger postmenopausal women report significantly more hot flashes during endocrine therapy than older postmenopausal women (Morales et al., 2004). Similarly, the effects of radiation therapy vary based on patient age and radiation field. Older patients and those with both ovaries in the radiation field suffer the most serious

ovarian damage and thus are at greatest risk for hot flashes (Lo Presti et al.). Hot flashes in individuals with carcinoid syndrome, medullary thyroid cancer, pancreatic cancer, or renal cell carcinoma vary depending on tumor characteristics (Mohyi et al., 1997).

Although all of the risk factors are associated with hot flashes, whether all of the populations at risk experience hot flashes in the same manner is unclear. Physiologic changes occurring with hot flashes have been studied mainly in healthy women (Aktan et al., 1998; Freedman, 1989, 1998; Kronenberg, 1990; Kronenberg et al., 1984) and to a lesser extent in breast cancer survivors (Carpenter et al., 1999; Carpenter, Gilchrist, et al., 2004). Similarly, qualitative descriptions of hot flashes have been obtained only from healthy women and breast cancer survivors (Carpenter, Johnson, et al., 2002; Finck et al., 1998; Knobf, 2001; Kronenberg, 1994). Therefore, researchers do not know whether all of the groups identified earlier experience a singular symptom or variations of a symptom. Further descriptive work in the heterogeneous groups is needed to address the issue fully.

Prevalence

Although a wealth of information is available on the prevalence and severity of hot flashes in healthy women, less is available in the context of cancer. In the latter context, hot flashes have been studied most widely in breast cancer survivors. Hot flashes and other menopausal symptoms in patients with breast cancer attracted national attention in the 1990s, when physicians and researchers convened the Boar's Head Conference to review existing evidence and issue clinical practice recommendations that subsequently were published (Swain, Santen, Burger, & Pritchard, 1999a, 1999b, 1999c, 1999d, 1999e, 1999f). Hot flashes have been studied to a lesser degree in women taking breast cancer chemopreventive agents, men with prostate cancer, and people with carcinoid tumors.

In regard to breast cancer, surveys indicate that 65% of survivors experience hot flashes, with a majority reporting the symptom to be severe (Carpenter et al., 1998; Carpenter, Johnson, et al., 2002; Couzi, Helzlsouer, & Fetting, 1995). In addition, population-based data indicate that breast cancer survivors are six times more likely to report hot flashes than age-matched controls (Harris, Remington, Trentham-Dietz, Allen, & Newcomb, 2002). As many as 51% of women diagnosed with breast cancer experience hot flashes prior to taking endocrine therapy, with significantly more women reporting hot flashes after three months of therapy (tamoxifen or nonsteroidal aromatase inhibitors) (Morales et al., 2004). Other reports have found that as many as 81% of women taking tamoxifen for breast cancer prevention experienced hot flashes (Day et al., 1999).

In men with prostate cancer and patients with carcinoid syndrome, the prevalence of hot flashes is similarly high. When 35 men taking luteinizing hormone-releasing hormone agonists for three months as neoadjuvant therapy for prostate cancer were studied, 69% reported having hot flashes during the treatment, with 11% reporting that hot flashes continued even after the medication was stopped (Schow et al., 1998). In other studies, 76% of men reported hot flashes after orchiectomy for prostate cancer, with 32% reporting the symptom to be severe (Charig & Rundle, 1989), and 74% of men receiving androgen-ablating therapies reported hot flashes (Spetz, Hammar, Lindberg, Spangberg, & Varenhorst, 2001). Similarly, 85%–90% of patients with carcinoid syndrome may report hot flashes (Schnirer, Yao, & Ajani, 2003). The studies suggest that hot flashes are a prevalent and severe symptom in the context of at least some cancers. Additional descriptive research may be helpful in elucidating the prevalence and severity of hot flashes in other cancer populations.

Impact

Hot flashes can interfere with compliance with life-saving medications. Women at high risk for breast cancer have been reported to decline tamoxifen as a chemopreventive agent, at least in part, because of concerns about hot flashes and other side effects (Bober, Hoke, Duda, Regan, & Tung, 2004). In addition, 4% of breast cancer survivors discontinue tamoxifen prior to the recommended five-year interval as a result of intolerable hot flashes (Morales et al., 2004).

The negative impact of hot flashes on quality of life has been established in women with breast cancer and men with prostate cancer. In breast cancer survivors, hot flashes have been linked to mood disturbance (e.g., depression, tension, anger), fatigue, confusion, negative affect, disruption in daily activities, poorer sleep quality, and poorer physical health (Carpenter, Johnson, et al., 2002; Stein, Jacobsen, Hann, Greenberg, & Lyman, 2000). Similarly, in Swedish and Japanese men with prostate cancer, hot flashes negatively affected quality of life (Nishiyama, Kanazawa, Watanabe, Terunuma, & Takahashi, 2004; Spetz, Zetterlund, Varenhorst, & Hammar, 2003). The impact of hot flashes in other populations is likely to be similar, although the notion merits further study. The high prevalence and negative impact of hot flashes support the importance of understanding, assessing, and managing the symptom in people with cancer.

Physiologic Mechanisms

The exact physiologic mechanisms underlying hot flashes are unknown. Although hot flashes have been believed to be centrally mediated events (Freedman, 2000b, 2001), at least one animal study suggested that they may be centrally and peripherally mediated (Acs et al., 2001). The following discussion reviews various mechanisms of hot flashes from human and animal studies, including thermoregulation and gluconeuroendocrine involvement. In addition, the potential role of genetics and classical conditioning in the physiologic occurrence of hot flashes is examined.

Thermoregulation

The thermoregulatory system is disrupted in healthy women who experience hot flashes (Freedman, 2000b, 2001). The thermoregulatory null zone is the threshold between sweating (high end) and shivering (low end). In women without hot flashes, the null zone is about 0.4°C. This means that temperature fluctuations of as much as ± 0.4°C do not cause sweating or shivering in women without hot flashes. However, in women with hot flashes, the interthreshold zone disappears. Therefore, temperature fluctuations quickly can lead to sweating or shivering—the sensation of a hot flash. One avenue for hot flash treatment, therefore, is to restore the thermoregulatory null zone.

The conclusions about thermoregulation were developed from a series of studies in healthy women performed in

a temperature- and humidity-controlled laboratory. First, Freedman, Norton, Woodward, and Cornelissen (1995) demonstrated that hot flashes were most likely to occur around the time of day when core temperature was highest. Ten naturally postmenopausal, healthy women participated in the study. Hot flashes were measured using validated sternal skin conductance monitoring. Temperature was measured every 30 seconds using an ingested radiotelemetry pill (CorTemp™, HQ Inc., Palmetto, FL). Core temperatures and hot flashes were found to exhibit a circadian (24-hour) pattern for the group as a whole and for individual women. Hot flashes peaked in frequency at 1825 hours, whereas core temperature peaked slightly earlier at 1529 hours (Freedman et al., 1995). Subsequently, with the same measurement methodologies, small elevations in core temperature were found to precede 24 of 37 hot flashes (65%) recorded in 8 women (Freedman & Woodward, 1996) and 22 of 29 hot flashes (76%) recorded in 14 women (Freedman, 1998). Core temperature elevations began about 17 minutes before each hot flash (Freedman, 1998). The findings led to the conclusion that hot flashes could be explained at least partially if the temperature elevations preceding hot flashes occurred in a reduced thermoregulatory null zone. Subsequently, 12 postmenopausal women experiencing hot flashes were compared to 8 postmenopausal women without hot flashes (Freedman & Krell, 1999). Women with symptoms exhibited a significantly smaller thermoregulatory null zone than those without symptoms.

A portion of the findings by Freedman and his colleagues were replicated in women with breast cancer. Following the discovery that hot flashes in 19 postmenopausal women with breast cancer did not exhibit the same circadian pattern as in healthy women (Carpenter, Gautam, Freedman, & Andrykowski, 2001), a detailed study of hot flashes and core temperature was performed (Carpenter, Gilchrist, et al., 2004). Nine breast cancer survivors were monitored for 24 hours in a temperature- and humidity-controlled room. Unlike in the Freedman studies of healthy women (Freedman, 1998, 2000a, 2000b; Freedman & Krell, 1999; Freedman & Woodward, 1996), hot flashes in the breast cancer survivors were not more likely to occur when core temperatures were highest, and neither temperature nor hot flashes exhibited a circadian pattern (Carpenter, Gilchrist, et al.). In addition, although temperature elevations preceded hot flashes in the breast cancer group, the timing of the elevations differed from those found previously in healthy women (Carpenter, Gilchrist, et al.). The flattened circadian pattern and faster temperature responses prior to hot flashes found in the breast cancer survivor group most likely were related to the high daily frequency at which the hot flashes were experienced.

Gluconeuroendocrine Involvement

Alterations in glucose transport across the blood-brain barrier have been theorized to be a trigger mechanism for menopausal hot flashes. Specifically, hot flashes are believed to be counter-regulatory attempts to increase cerebral blood flow and cerebral glucose levels (Dormire & Reame, 2003). To evaluate the hypothesis, 10 healthy women with hot flashes were randomized to normal saline or glucose infusion. Significantly more hot flashes were documented using sternal skin conductance monitoring during the fasting condition (normal saline, mean serum glucose = 86 mg/dl) as compared to glucose infusion (dextrose, mean serum glucose = 135 mg/dl) (Dormire & Reame). Further work in this area is under way.

Norepinephrine, a catecholamine that is released in response to sympathetic nervous system activation (e.g., in response to stress, activity, or exercise) (Guyton & Hall, 2000) has been implicated in hot flashes. Norepinephrine decreases the thermoneutral zone in animals and possibly in women with hot flashes (Freedman & Krell, 1999). Pharmaceutical agents that inhibit norepinephrine (e.g., clonidine) alleviate hot flashes (Freedman & Dinsay, 2000; Goldberg et al., 1994; Loprinzi et al., 1998; Nagamani, Kelver, & Smith, 1987), whereas agents that stimulate norepinephrine (e.g., yohimbine) cause hot flashes (Freedman & Krell).

Although strong evidence also implicated reduced serotonin in the etiology of hot flashes (Berendsen, 2000; Stearns et al., 2002), the mechanism underlying serotonin involvement is unclear. Data from ovariectomized rats have indicated that activation of serotonin 2A receptors restores thermoregulatory dysfunction associated with estrogen withdrawal (Sipe et al., 2004). Low serotonin has been observed in women after spontaneous or surgical menopause (Blum et al., 1996; Gonzales & Carrillo, 1993). Although carcinoid tumors are associated with high peripheral serotonin levels, central serotonin levels presumably are low (Mohyi et al., 1997; Schnirer et al., 2003). A study found elevated peripheral serotonin concentrations in perimenopausal women that were positively correlated with hot flashes, but changes in central serotonin concentrations were not measured (Chen, Lu, Huang, Xin, & Ye, 2002).

Estrogen plays a direct role in the thermoregulatory null zone and affects serotonin. Estrogen replacement therapy has been shown to raise the sweating threshold in humans, thus demonstrating at least one way it may be effective in decreasing hot flashes (Freedman & Blacker, 2002). Similarly, estrogen reduced spontaneous fluctuations in core temperatures that occurred after ovariectomy in rhesus monkeys, a species that regulates body temperature similarly to humans (Bellino & Wise, 2003), and in ovariectomized sheep (MacLeay et al., 2003). However, the role of estrogen in hot flashes is complex. Estrogen replacement also restores serotonin concentrations (Blum et al., 1996; Gonzales & Carrillo, 1993), and estradiol augments serotonergic activity in postmenopausal women (Halbreich et al., 1995). Estrogen appears to affect serotonin metabolism through direct effects on serotonin neurons that regulate genes involved in serotonin synthesis, transport, and signaling (Bethea, Mirkes, Shively, & Adams, 2000; Lu & Bethea, 2002).

Estrogen also may act peripherally to ameliorate hot flashes. In one study, ovariectomized rats received 12 weeks of estradiol, medroxyprogesterone, or both (Acs et al., 2001). Norepinephrine-induced vascular tone was significantly impaired in the ovariectomized rats compared to control rats. In addition, estradiol, but not medroxyprogesterone alone or in combination with estradiol, restored vascular reactivity. The findings suggest that estrogen may act peripherally to prevent hot flashes by restoring vascular tone.

Calcitonin gene-related peptide (CGRP) has been linked to hot flashes. CGRP, a neuropeptide found centrally and peripherally, has diverse biologic effects, including vasodilation and sweating. In castrated male rats, CGRP causes skin temperature elevations (Yuzurihara et al., 2003, 2004) that can be suppressed with testosterone or estradiol replacement therapy (Yuzurihara et al., 2004). Women with hot flashes have higher urinary excretion rates of CGRP prior to suc-

cessful hot flash treatment (Wyon, Lindgren, Lundeberg, & Hammar, 1995) and compared to women with no hot flashes (Wyon, Frisk, Lundeberg, Theodorsson, & Hammar, 1998). Increases in plasma CGRP during hot flashes in women and castrated men with prostate cancer also have been noted (Chen, Hirai, Seimiya, Hasumi, & Shiraki, 1993; Valentini et al., 1996; Wyon, Spetz, Hammar, Theodorsson, & Varenhorst, 2001; Wyon, Spetz, Theodorsson, & Hammar, 2000).

Genetics

Interest in linking genetic factors with hot flashes is increasing. Data from the Seattle Midlife Women's Health Study indicated that genetic polymorphisms were associated with subjective hot flash severity in healthy women. Less severe hot flashes were reported by women with the CYP 19 7r allele, and more severe hot flashes were reported by women with the CYP 19 7r(–3) allele compared to women with other CYP 19 alleles (Woods, Mitchell, Viernes, Janssen, & Farrin, 2004). Similarly, polymorphisms in estrogen receptor alpha (ERα) were associated with hot flash severity in patients with breast cancer. A sample of 71 patients with breast cancer was followed prior to starting tamoxifen and then 1, 4, 8, and 12 months later. Prior to starting tamoxifen, premenopausal women with the ESR2-02 AA genotype were less likely to report hot flashes in a diary. One month after starting tamoxifen, premenopausal women with the ERα XbaI TT genotype were less likely to report hot flashes. In addition, premenopausal women with the ERα XbaI TT genotype reported less increase in hot flashes over time compared to those with the CC or CT genotypes (Jin et al., 2004).

Classical Conditioning

Although classical conditioning has been posited to play a role in the physiologic occurrence of cancer treatment-related symptoms such as nausea, vomiting, and psychological distress (Matteson, Roscoe, Hickok, & Morrow, 2002; Sabbioni, Bovbjerg, Jacobsen, Manne, & Redd, 1992), its role in the occurrence of hot flashes has not been studied. The tenets of classical conditioning suggest that, when an unconditioned stimulus results in an unconditioned response and both are paired with an additional stimulus, the unconditioned response eventually can become conditioned to occur with the additional stimulus (conditioned stimulus) (Matteson et al.). For example, when chemotherapy results in nausea or vomiting and both occur in the presence of a nurse, the sight of the nurse alone (without chemotherapy) can cause nausea and vomiting (Matteson et al.; Sabbioni et al.). Similarly, everyday factors may become conditioned stimuli for hot flashes. For example, if a woman experiences a hot flash at the same time her alarm clock rings in the morning, the alarm clock alone has the potential to elicit hot flashes on subsequent mornings, according to classical conditioning. Understanding the role of classical conditioning in hot flashes may help in the selection of treatment options. Treatments previously shown to be effective for classically conditioned responses include anxiolytics and various behavioral techniques such as systematic desensitization, relaxation, and hypnosis (Matteson et al.).

Measurement Issues

Current measurement of hot flashes is complicated by two primary factors: (a) Hot flashes can be conceptualized and operationalized as an objective and a subjective phenomenon and (b) subjective and objective measurements are concordant in some settings and discordant in others. This section explores hot flash measurements and discusses data directly comparing objective and subjective measurements. National developments and their potential contributions to hot flash measurement also are described.

Objective Measurements

Objective measurements of hot flashes have been developed in the past 30 years. In the late 1970s, increases in skin and core temperatures initially appeared to correspond to the occurrence of subjectively reported hot flashes (Meldrum et al., 1979; Molnar, 1975, 1979; Tataryn, Meldrum, Lu, Frumar, & Judd, 1979). Skin temperatures of the finger (Meldrum et al.; Molnar, 1975, 1979; Tataryn et al., 1979), cheek (Molnar, 1975, 1979), and toe (Molnar, 1975, 1979) were evaluated, as well as core temperatures of the vagina (Molnar, 1979), rectum (Molnar, 1975), and esophagus (Kronenberg et al., 1984). Several of the early reports indicated that increases in peripheral and core temperatures preceded most menopausal hot flashes.

In the 1980s and 1990s, sternal skin conductance proved to be a more precise measurement of hot flashes than skin or core temperatures (de Bakker & Everaerd, 1996; Tataryn et al., 1980). In two reports, changes in temperature were noted in the absence of hot flashes (de Bakker & Everaerd; Freedman & Krell, 1999). In another study, sternal skin conductance changes were found to precede changes in skin (finger) and core (tympanic) temperatures and return to baseline more quickly than skin temperatures (Tataryn et al., 1980). Based on the later research, sternal skin conductance monitoring came to be considered the gold standard for objective measurement of hot flash occurrence in healthy women (Freedman, 1989; Tataryn et al., 1981) and women with breast cancer (Carpenter et al., 1999; Carpenter, Monahan, & Azzouz, 2004). However, sternal skin conductance is not an appropriate measurement of subjective hot flash severity or distress (Carpenter, Azzouz, Monahan, Storniolo, & Ridner, in press).

Skin conductance is a measurement of the skin's ability to conduct electricity and is the reciprocal of skin resistance (Cacioppo, Tassinary, & Berntson, 2000). Although skin conductance on the palms of the hands and soles of the feet can be widely affected by anxiety and other emotional states (Cacioppo et al.), readings from the sternal site appear to be more stable and unaffected by emotion. When a constant voltage current is applied to the sternum between two electrodes, skin conductance increases as sweat gland activity increases during a hot flash. Thus, rapid increases in sternal skin conductance can be used to measure hot flash occurrence (Carpenter et al., 1999; Freedman, 1989). Skin conductance values can vary based on the number of active sweat glands, sweat gland activity, the contact area of the electrodes, and the electrodermal gel that is used (Cacioppo et al.). Although measurement standards have been proposed to handle the latter two factors (Dormire & Carpenter, 2002; Freedman, 1989), damage to the number and activity of sweat glands as a result of local radiation therapy may interfere with skin conductance readings. Thus, in the context of cancer, sternal skin conductance monitoring may not be an appropriate measurement of the occurrence of hot flashes for all individuals.

Although sternal skin conductance is considered the gold standard for hot flash measurement in women, the accuracy

and precision of the measurement in men have not been demonstrated. Differential sweating rates and patterns between men and women have been noted (Bar-Or, 1998; Kaciuba-Uscilko & Grucza, 2001) and may interfere with using the measurement in men. Thus, the utility of sternal skin conductance monitoring as a measurement of hot flash occurrence in men with prostate cancer or men with carcinoid syndrome is unclear and warrants future study.

Subjective Measurements

Subjective measurements of hot flashes vary in format. For example, cancer researchers have used prospective daily diaries (Carpenter, Wells, et al., 2002; Cohen, Rousseau, & Carey, 2003; Sloan et al., 2001), daily summaries (Hammar, Frisk, et al., 1999), recalled averages over a given amount of time (Clover & Ratsey, 2002), and questionnaires (Carpenter, 2001). With the various formats, patients may be asked to record hot flash occurrence (frequency) (Carpenter, Wells, et al.), provide a rating of hot flash severity or distress (Carpenter, Wells, et al.; Cohen et al.; Thompson & Reilly, 2003), or rate the disruption in mood and daily life that is caused by hot flashes (Carpenter, 2001). The self-report measurements are consistent with conceptualizing a hot flash as a subjective phenomenon.

Paper hot flash diaries may be problematic. Poor compliance and a phenomenon called hoarding have been noted (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002). That is, rather than entering data at the time an event occurs, subjects tend to save all their entries for the end of the day or simply do not complete their entries. In one study, paper diaries were outfitted with photoelectric sensors to examine whether patients completed diaries at set times throughout the day as they had been instructed to do (Stone et al.). Although diaries appeared to have been filled out, photoelectric sensor data indicated that only 11% of entries were made at the time points indicated. The findings suggest that paper hot flash diaries may not provide the most accurate information about hot flashes.

Comparing Objective and Subjective Measurements

Several comparisons between objective and subjective hot flash measurements have been published. In laboratory studies, daytime and nighttime concordance rates have been reported. Daytime laboratory studies have demonstrated high concordance between subjective and objective measurements of hot flash occurrence in healthy women and breast cancer survivors. In laboratory settings, 95%–98% of subjectively reported hot flashes corresponded to objectively documented hot flashes among healthy women (Freedman, 1989; Tataryn et al., 1981). Unpublished data suggest that concordance rates among breast cancer survivors in a daytime laboratory study were similarly high (Carpenter, 2000). However, results from nighttime laboratory studies were less positive. In one study, 24 breast cancer survivors participated in a nighttime study of hot flashes and sleep (Savard et al., 2004). Subjective estimates of nighttime hot flashes showed no relation to objectively monitored nighttime hot flashes (Savard et al.). Objectively measured hot flashes were shown to be associated with greater nighttime wake time and total number of sleep stage changes on polysomnographic measures (Savard et al.). The results suggest two things: Hot flashes disrupt sleep even if not reported subjectively, and correspondence between measurements in controlled environments is high only when women are awake.

Concordance between measurements also has been reported for ambulatory studies. In ambulatory studies, breast cancer survivors have underreported hot flash frequency when self-reports were compared to objective hot flash monitoring. In one study, 18 breast cancer survivors were asked to estimate hot flash frequency (retrospective recall) and then record hot flashes prospectively using a diary and electronic event marker while wearing an objective hot flash monitoring device for 24 hours (Carpenter et al., 1999). The number of hot flashes women estimated having was significantly smaller than the number that was recorded prospectively using the diaries, event markers, and monitor. In addition, only 59% of objectively recorded hot flashes were reported subjectively, with fewer hot flashes being reported subjectively at night in particular. In another study, 55 breast cancer survivors provided two 24-hour periods of data, one week apart, at baseline before being randomized for an intervention study (Carpenter, Monahan, et al., 2004). Results indicated that 50% or more of objectively recorded hot flashes were not reported subjectively (Carpenter, Monahan, et al.). Underreporting can be a substantial problem in clinical practice and research. When a hot flash is not reported, the occurrence of that hot flash is not documented; thus, ratings of severity and bother for that hot flash are not provided. Therefore, underreporting of hot flashes may contribute to measurement error in frequency, severity, and bother.

Whether the lack of agreement between subjective and objective hot flash measurements is related to a reporting issue or a perception issue is difficult to disentangle. Some data have suggested that women may not report every hot flash that occurs. In one study, 35% of 18 breast cancer survivors reported problems with subjectively recording hot flashes in paper diaries or with an event button (Carpenter et al., 1999). Problems included having no free hands to record a hot flash because of certain daytime activities and being too tired to care about recording hot flashes at night (Carpenter et al., 1999). On the other hand, some studies have suggested that hot flashes that are not reported are not perceived (Sloan et al., 2001). For example, perhaps all or at least some hot flashes are so mild that they are not perceived by women as having occurred at all and thus are not reported. The fact that agreement between measurements is highest when women are paying attention to their hot flashes in a controlled environment and lowest when they are sleeping or otherwise distracted by the context of their everyday environments suggests that attention or perception may play a role in hot flash reporting. However, researchers cannot study perception of hot flashes, only reported hot flashes. Further study of factors that account for the discrepancy between subjective and objective measurements is warranted.

Figure 1 depicts the earlier discussion about conceptualizing and operationalizing hot flashes. When hot flashes are conceptualized as physiologic events (circle on the left), objective methods such as sternal skin conductance monitoring should be used. However, such methods only provide information on the occurrence of a hot flash. When hot flashes are conceptualized as reported events (circle on the right), subjective measurements can be used to obtain data on occurrence (frequency), severity, bother, and duration. As described earlier, because researchers cannot assume that hot flashes that are not reported are not perceived, a need exists to differentiate perceived hot flashes (circle in the middle) from reported hot flashes (circle on the right).

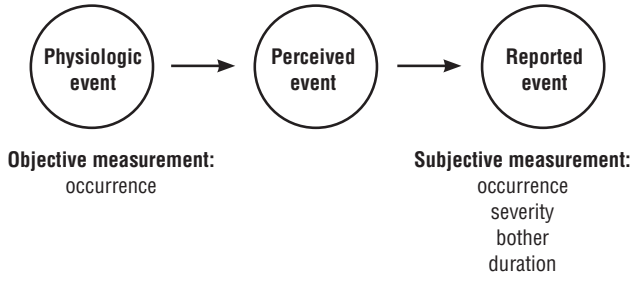

Figure 1. Conceptualizing and Operationalizing Hot Flashes

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National Developments

Two national developments related to hot flash measurement recently have occurred. The National Center for Complementary and Alternative Medicine, in combination with other offices and institutes at the National Institutes of Health, held a workshop on hot flash measurement in January 2004 (Miller & Li, 2004). Conference participants publicly acknowledged difficulties in measuring hot flashes and subsequent problems in building the evidence base for appropriate and effective treatments. The workshop noted that measurement problems can interfere with understanding the underlying physiology of hot flashes, subsequently interfering with selection or creation of potentially effective interventions. In addition, errors associated with current measurement tools, such as hot flash diaries, may interfere with accurately documenting intervention efficacy. The workshop is likely to have an impact on research funding opportunities and policy related to hot flash assessment and treatment at the national level.

A second national development related to hot flash measurement was a September 2004 request by the National Center for Complementary and Alternative Medicine for applications to improve measurement tools for sternal skin conductance and hot flashes. The funding mechanism was for Small Business Innovation Research that allows medical device manufacturers and other small businesses the opportunity to develop new technologies. Exciting new developments in hot flash measurement should be forthcoming as a result of the funding.

Summary

In the context of cancer, a diverse group of men and women diagnosed with or at high risk for cancer appears to be at risk for hot flashes and their negative impact on treatment compliance and quality of life. Although the symptom is recognized in a variety of oncology populations, it has not been studied equally across populations. Additional work is needed to understand more fully whether a hot flash is a singular phenomenon across the diverse groups affected. Although hot flashes appear to be caused by a complex interplay of thermoregulatory, gluconeuroendocrine, genetic, and behavioral factors (Freedman, 1998; Freedman & Krell, 1999; Freedman et al., 1995; Kronenberg, 1990, 1994; Lomax & Schonbaum, 1993; Rosenberg & Larsen, 1991), additional, unknown factors likely are involved (Freedman, 1998; Freedman & Krell; Lomax & Schonbaum; Rosenberg & Larsen). Further research is needed to expose the mechanisms and guide selection and testing of novel treatments. In addition, measurement of hot flashes should be considered carefully. Sternal skin conductance monitoring should be used when precise measurements of hot flash frequency are required. However, subjective diaries, rating scales, and questionnaires appear to be more appropriate for assessing other dimensions, such as severity and intensity, bother and distress, and disruption in quality of life. National developments suggest that, in the future, additional measurement devices may be available to account for problems in currently existing measures.

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