Menopausal Hot Flashes: A Review of Physiology and Biosociocultural Perspective on Methods of Assessment1,2

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Abstract
Hot flashes continue to be a troublesome problem for menopausal women the world over. After >50 y of research, we still do not understand the etiology and mechanism of hot flashes, nor do we know how estrogen, the major pharmaceutical treatment, works to reduce hot flashes. We are gaining insight into sociocultural complexities that may affect how and whether women report hot flashes. And we are becoming more sophisticated in our research tools (be it questionnaires, physiological monitors, or brain imaging techniques). New aspects of hot flash research, including neuroimaging and the study of genetic polymorphisms, when combined with increasingly nuanced ways of asking questions of culturally distinct populations, provide challenges but rich complexity from which a better understanding will emerge. J. Nutr. 140: 1380S–1385S, 2010.

Introduction
Hot flashes are one of the most common symptoms experienced by women around the world during the transition to and through menopause. Whereas prevalence rates tend to be higher in Western countries than, e.g., in Asian countries, rates vary widely and are likely influenced by a range of factors (1). In the U.S., hot flashes are one of the main reasons women at menopause seek medical help or look for dietary supplements and over-the-counter remedies for relief (2,3). In 2002, after publication of the results from the large NIH-funded Women’s Health Initiative study, which indicated that estrogen was harmful on a number of indices, many women stopped taking this hormone therapy (4) and for >30%, bothersome, often severe hot flashes returned (5). These women re-experienced hot flashes they thought they had left far behind. Yet, while women have complained of these “spells” of heat sensation from time immemorial and despite this considerable public health problem, at the start of the 21st century, we still do not understand the etiology or physiology, nor do we know how the most widely used pharmaceutical treatment to date, estrogen, works to relieve hot flashes.

This article aims to provide a brief overview of some aspects of the biology of hot flashes and methods used in research, given insights we now have into biosociocultural factors that influence how we observe and the phenomenon being observed. Emerging areas of research are also discussed.

Hot flashes: the phenomenon
The terms hot flash and hot flush are used interchangeably and are typically synonymous, referring to a sudden sensation of heat and sweating, most notably on the upper body. Hot flashes occur primarily and most intensively in peri- and postmenopausal women. They also may occur when estrogen drops suddenly and rapidly, such as after removal of the ovaries of premenopausal women, with chemically induced menopause, and also in breast cancer patients treated with selective estrogen receptor modifiers such as tamoxifen. Men can experience hot flashes, particularly when testosterone levels fall rapidly, such as in men with prostate cancer treated medically or surgically. In both women and men, these are situations where there is an abrupt drop in sex steroid hormones, resulting in hot flashes.

Hot flashes can occur day or night; when they occur at night, they are called night sweats. Each particular episode lasts between 3 and 10 min and can recur with varying frequency (6). Some women experience hot flashes hourly or daily, while for others they may occur only occasionally; a small percent of women report not having any hot flashes. Whether this is a

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matter of a threshold of perception or there are genetic, environmental, or lifestyle factors that preclude hot flashes is a subject of increasing interest.

Although for most women, hot flashes begin and have their peak occurrence during the peri- and early postmenopausal periods, typically when a woman is in her late 40s and early 50s, at times they may begin when menstrual cycles are still regular (6). The majority of women have hot flashes for a year or two, but ~15% may have them nonstop for 10, 20, or 30 y (6). And while every woman’s estrogen level decreases during the transition to and through menopause, it remains an enigma as to why some women’s bodies seem to adjust and hot flashes taper off, while others continue having hot flashes for many years. In addition, for some women whose hot flashes were treated successfully by estrogen, the hot flashes resume after cessation of estrogen treatment.

Physiological changes during a hot flash

Thermography provides a visual snapshot of the skin surface manifestation of the pattern of thermoregulatory changes during a hot flash and provides insights into underlying physiological changes (Supplemental Fig. 1). One can see the skin areas that warm during the hot flash (fingers, neck, face) and cool as the hot flash subsides.

Figure 1 graphically illustrates some of the primary physiological changes that occur during a hot flash (7). “Sensation” is a subjective rating of the sense of hot flash intensity on a scale of 0–10 (10 being the most intense). At the onset of a hot flash, there is a sudden increase in sweating. Heart rate increases to normal. During a hot flash, many of the easily observed physiological changes involve the thermoregulatory and vascular systems. This remains an area of incomplete research.

Clearly, estrogen plays some role as a mediator of hot flashes. Hot flashes occur as estrogen levels decline and they are alleviated for the most part by treatment with estrogen (9). Estrogen priming is likely important. Young women with low estrogen levels do not have hot flashes, but if given estrogen and then withdrawn from it, they will have hot flashes. And premenopausal women whose ovaries are removed most often experience hot flashes almost immediately. However, low estrogen levels alone do not explain the presence of hot flashes. Investigators have searched for correlations between estrogen levels and the occurrence of hot flashes in women with and without hot flashes as well as with individual hot flashes with conflicting results. Some population studies have demonstrated inverse relationships between estrogen levels and hot flashes (10,11), as have more recent studies (12). Others, including Freedman et al. (13), have not corroborated these results when small groups of symptomatic and asymptomatic women were compared.

There has been examination of the levels of circulating hormones, including sex steroids and gonadotropins, among others. Substances such as luteinizing hormone (14,15), B-endorphin, adrenocorticotropic hormone (16), and others show pulsatile activity that is temporally correlated with hot flash occurrence, but not causally related (7). Freedman et al. (17) have proposed, based on several studies, that elevated brain norepinephrine plays a role in the etiology of hot flashes. Examining the complex interactions of the multiple systems that are involved has not been substantively undertaken. Thus, at this time, there is no definitive determination of what it is that triggers individual hot flashes or explains why some women do or do not experience them.

Sociocultural issues in measuring hot flashes

Hot flashes occur worldwide, and starting in the 1970s, research documenting such occurrence increased substantially. A wide
distribution of the prevalence of hot flashes around the globe continues to be examined, with reports, particularly in Asian countries, of prevalence less than that in the US and other Western countries (1,18). Interest in understanding these differences has raised questions about whether these differences are due to genetic, cultural, environmental, or lifestyle factors such as diet and exercise.

Research in Japan has provided particular insight. Japanese women have a high dietary intake of soy (relative to Western countries) and it was hypothesized that this might explain why they have fewer hot flashes than women in the US, Canada, and Europe. Basic science research has established that isoflavones (compounds in soy and other plants) have estrogen-like activity (19). Interest in the relationship between the soy consumption of different populations and hot flash prevalence led to epidemiological studies comparing level of dietary soy intake and frequency of hot flashes in countries such as Japan, where an inverse association between soy intake and hot flashes has been demonstrated (20,21). Clinical studies of soy foods and soy isoflavones to treat hot flashes proliferated, with mixed results, although there was a tendency toward a beneficial effect (22).

However, it is now known that there are confounding factors that make this a more complex issue and might contribute to explaining the differing results among the clinical trials. The isoflavone daidzein is biotransformed by intestinal microflora to the active metabolite, equol. The presence of the particular bacterial species responsible for this conversion differs among people in different countries and thus some people are "equol producers" and some are not (19,23).

Further complexity may relate to a critical period for soy consumption relative to its beneficial health effects. This has come to light while trying to understand the observation of lower breast cancer rates in populations with high soy food consumption. Exposure during adulthood did not support these observations. Data are accumulating to support a protective effect of soy when it is consumed during early life (childhood/adolescence) with regard to breast cancer later in life (24). Soy foods are a staple in Asian cuisine and are consumed throughout life, suggesting their role in breast cancer prevention. Consumption of soy or genistein affects gene expression and activates estrogen receptor α, thereby affecting BRCA1 (25,26). Similarly, it is possible that consuming soy during puberty may affect whether one experiences hot flashes during menopause; initiating soy consumption or isoflavone supplementation at age 50 y may not have the same outcome of reducing hot flashes.

The Japanese experience
In the 1980s, Lock et al. (27) studied menopause among Japanese women and asked women about symptoms, including those typically experienced by American and Canadian women; they also asked the Japanese women (and their physicians) how they would describe this time of life and the symptoms they experienced. The respondents used a combination of 3 terms (sudden feeling of heat; feeling hot or flushed; rush of blood to the head) to encompass what Western women and physicians mean by the single term hot flash. The Japanese women reported fewer hot flashes than their Western counterparts. The researchers concluded that fewer Japanese women were experiencing hot flashes and night sweats.
Twenty years later, Melby (28) conducted a follow-up study in Japan, this time focusing on the more linguistically nuanced terminologies as she came to understand how Japanese women spoke about their sensations of heat and sweating during the menopausal years. Melby included Lock’s symptom list in her questionnaire but asked about hot flash terms separately, and found there was an increase in symptom reporting in the time since Lock’s study. There was an increase in those reporting each of the symptoms comprising the nuanced components hot flashes (Table 1) (28). Some of the explanation for increased symptom reporting may involve the globalization of the Western approach to and discussion of menopause. Zeserson (29) commented on the media’s impact on how women discuss and view their symptoms. In the case of hot flashes, Zeserson (29) noted that Japanese women began using the Americanized expression ‘botto furasshu’ and became conversant with the Western terminology of “hot flash,” having heard this in the media. As described earlier, there are a number of measurable physiological changes that constitute a hot flash.

Some women’s heart rate increases, some women sweat, while others flush and feel a sensation of heat. In Western countries, women describe whether they flush or sweat during a hot flash; they name this constellation of changes as a “hot flush” or “hot flash.” Japanese women describe an individual component of hot flash sensation if they experience it. In Traditional Chinese medicine (and its Kampo counterpart in Japan), a practitioner would identify the particular characteristic of an individual woman presenting with the Western diagnosis of hot flashes, whether she sweats (sweat effusion or fa re), has rapid heart patterns of symptoms. Thus, not all women with a Western diagnosis of menopausal hot flashes would receive the same suggested treatment. Western investigators, too, can apply these distinctions and stratify clinical trials to explore whether some treatments are more appropriate for certain subsets of women with specific patterns of symptoms.

Interestingly, Melby (31) administered to both men and women in Japan the same symptom questionnaire. Both groups reported shoulder stiffness (the most prevalent symptom reported by women) and men reported more night sweats than did the women (Table 2) (31). How do we determine which symptoms are influenced by cultural factors and expectations and which are a function of hormonal or other physiological change?

Do women of Japanese ancestry really have fewer hot flashes than western women or do they just not report them?

Theories have been offered to explain the differences in hot flash prevalence around the world, including genetics, physiology, expectation, lifestyle (soy foods, exercise), or other environmental factors. Brown et al. (32) looked elsewhere to examine whether part of the explanation for fewer hot flashes among Japanese-American women might involve a lack of reporting rather than a lack of occurrence of hot flashes. Their study, conducted in Hawaii, compared objectively measured hot flashes: physiology and sociocultural perspective 1383S

<table>
<thead>
<tr>
<th>Romanized Japanese symptom</th>
<th>English symptom</th>
<th>Females, n = 32</th>
<th>Males, n = 22</th>
<th>χ²  p</th>
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<tbody>
<tr>
<td>Katakori</td>
<td>Shoulder stiffness</td>
<td>43.8</td>
<td>40.9</td>
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<tr>
<td>Sutoresu</td>
<td>Stress</td>
<td>12.5</td>
<td>36.4</td>
<td>4.296 0.013</td>
</tr>
<tr>
<td>Kyuu na hakkans</td>
<td>Sudden perspiration</td>
<td>12.5</td>
<td>0.0</td>
<td>2.970 0.110</td>
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<tr>
<td>Inarinu</td>
<td>Irritability</td>
<td>6.3</td>
<td>27.3</td>
<td>4.566 0.033</td>
</tr>
<tr>
<td>Ne asse</td>
<td>Night sweats</td>
<td>6.3</td>
<td>13.6</td>
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<tr>
<td>Shirikin no shinchoe</td>
<td>Nervous tension</td>
<td>0.0</td>
<td>13.6</td>
<td>6.262 0.016</td>
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<tr>
<td>Kentaikan</td>
<td>Exhaustion</td>
<td>0.0</td>
<td>9.1</td>
<td>3.021 0.082</td>
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2 The nonparametric chi-square test was used to assess sex difference in symptoms experienced in the previous 2 wk and reported by >99% of the sample.
3 Significant at the 0.05 level (2-tailed).
4 Significant at the 0.10 level (2-tailed).
flashes (using the measure of skin conductance) with self-report in women of Japanese descent and European descent living in Hilo, Hawaii. They administered a postal questionnaire asking about symptoms experienced in the past 2 wk and followed that with 24-h objective monitoring with diary reporting in a subset of women. The postal survey indicated that Japanese women had fewer symptoms such as backache, hot flashes, night sweats, depression, and trouble sleeping (Fig. 3). However, the ambulatory monitor revealed no difference between the groups in the percentage of women exhibiting objective hot flashes (Fig. 4). There was a distinct difference between what was reported in the postal questionnaires and the ambulatory monitoring. Japanese-American women were significantly less likely to report hot flashes in the previous 2 wk, yet, they had the same frequency of objectively recorded hot flashes as the European-Americans. The authors concluded that fewer reported hot flashes in women of Japanese ancestry might be a consequence of reporting bias likely due to cultural perceptions of what is acceptable to discuss and report. The study of Brown et al. (33) highlights the value of objectively measuring hot flashes. There can be cultural differences in how and whether one reports hot flashes; diary use often underreports hot flashes such as those that occur during sleep or during a busy period when a hot flash is not noticed or goes unreported.

Clinical research has been hampered by the lack of a hot flash monitor that is accurate and easy-to-use in ambulatory subjects. Most of the portable monitors available for measuring skin conductance (or other physiological signals) are cumbersome to wear and have wires that do not facilitate ease of use. A new, miniature, wireless monitor, developed by Bahr Management in collaboration with researchers at the University of California, San Francisco, promises increased accuracy and ease of use (34,35).

Emerging areas of interest

Brain imaging techniques such as functional MRI are being used to examine brain function during hot flashes. Initial studies of brain activation during hot flashes have found that the insula and anterior cingulated cortex are activated during hot flashes (36). Better understanding of the neural control of hot flashes will provide further insight into mechanisms.

Another area of growing interest is the relationship between hot flashes and polymorphisms of genes involved in estrogen function, such as sex steroid metabolizing enzymes and estrogen receptors. Given that estrogen plays some role in the hot flash phenomenon, investigators are examining variation in genes coding for enzymes involved in estrogen synthesis and hormone interconversion for a possible role in the variance in observed circulating hormone levels (37). Genetic polymorphisms are also being studied in an attempt to explain observations of race/ethnic differences in hot flash prevalences (38), such as seen in the Study of Women Across the Nation in the US. Two studies indicate that there are certain race/ethnicity associations between polymorphisms for sex metabolizing hormones (39,40). This line of research is in its infancy but may provide new insights into the often conflicting and variable results of studies examining factors that might predict who most is at risk for hot flashes.

The study of equol for the treatment of hot flashes holds promise and clinical and basic science studies are underway in the US, Japan, and elsewhere. To better study soy, equol, or any herbal or pharmaceutical agent for the treatment of hot flashes, researchers need better measurement techniques, including better questionnaires that ask questions in a culturally sensitive context. More research on the basic underlying physiology and brain function during hot flashes is needed to better understand mechanisms that can lead to the design of treatments targeting these mechanisms.

Summary

Hot flashes remain a particularly bothersome problem for a majority of menopausal women in the US and elsewhere and a primary reason for which women in the menopausal years seek treatment. Yet, after >40 y of studying hot flash physiology, we still do not understand the etiology, nor do we understand how the most effective treatment to date, estrogen, works to reduce hot flashes. There has been substantial examination of and insight into cross-cultural differences, the nuances of linguistic expressions,
and dietary and other factors that are providing means of stratifying results to better understand the variability in responses. Newer research is focusing on brain function and genetic polymorphisms, both of which add new levels of complexity to what is obviously a very rich and compelling area for investigation. After so many years with insufficient research attention, the time and measurement tools are now ready for a more sophisticated examination of hot flashes. Any additional understanding of mechanism would provide valuable guidance for those wishing to study and develop new treatments for this age-old problem.

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Literature Cited