Factors That May Influence the Experience of Hot Flushes by Healthy Middle-Aged Women

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Abstract

Background: Interest in menopausal symptoms in general and hot flushes (HFs) in particular has grown in recent years. This is mostly due to increased awareness and the vast impact these symptoms have on women's lives. Despite the high prevalence of women who experience HFs, a definitive etiology for HFs is yet to be found. Our objective was to review the current literature dealing with associated factors for experiencing HFs and to provide a synthesized overview on this common and often debilitating condition.

Methods: We systematically searched the English-language literature in the PubMed database using relevant key words and included only those articles that contained information on associated factors for HFs in generally healthy midlife women.

Results: Both conflicting scientific results between studies documenting factors that influence HFs and the lack of validated measuring tools make it difficult to truly pinpoint associated factors for HFs. Nonetheless, we identified the following clusters of associated factors: the menopausal stages, sex steroid hormones, other endocrine agents, genetic polymorphisms, race/ethnicity, body mass index (BMI) and obesity, mood disorders, smoking, soy isoflavones and phytoestrogens, alcohol consumption, and physical activity.

Conclusions: No single associated factor was consistently identified as having a major role in experiencing HFs. More resources should be directed to develop a unified study system along with multivariable analyses to get a better understanding of this condition, which often imposes a tremendous social and personal toll on the women who experience it.

Introduction

MENOPAUSAL HOT FLUSHES (HFs) are usually defined as transient periods of intense sensations of heat, mainly in the upper part of the body, arms, and face. They are often followed by flushing of the skin and profuse sweating¹ and may be followed by a sense of anxiety and palpitations. The physiological changes that occur during HFs have been described in depth in several review articles.²⁻⁵ The most common belief is that HFs occur as a result of disturbance of the temperature-regulating mechanism located in the hypothalamus.³ This disturbance is thought to lead to a reduction in the thermoneutral zone (within which fluctuations of basal body temperature do not provoke compensatory vascular responses) so that even minor fluctuations in core body temperature reach the limits of the zone and initiate thermoregulatory response.³ HFs vary greatly among women and within women in the time when first experienced, frequency, intensity, and severity.⁶ It is estimated that during the next five decades, 27–37 million American women may experience

menopausal HFs, and these symptoms may be severe and difficult to tolerate in about 7 million menopausal women.⁶ HFs are reported more frequently and severely during the late menopausal transition stage and early postmenopausal years⁶ (as described in detail in the menopausal stages section). HFs can last from a few seconds to more than an hour and persist for 1 year in 95% of affected women and up to 5 years in 65% of affected women.⁶ Conflicting scientific results between studies documenting risk factors for HFs and the lack of validated measuring tools make it difficult to truly pinpoint risk factors for HFs. This review article summarizes the current literature concerning the most common factors that may influence the severity or incidence and timing of HFs among generally healthy midlife women.

Materials and Methods

A systematic search in the PubMed database was conducted in mid-2009 without limiting the publication date and by using the key words: hot flash, hot flush, vasomotor

symptoms (VMS, a term that is usually used to describe HFs and night sweat events), menopause, and not treatment. The last was added because the main purpose of this review article is to deal with factors that may influence the severity or incidence and timing of HFs that are experienced by generally healthy midlife women. The search yielded 432 abstracts. We excluded about 75% of those after following our predetermined exclusion criteria: articles whose main focus was not on factors associated with HFs in generally healthy midlife women (i.e., mainly dealt with etiology, treatment options, breast cancer patients, induced menopause, non-English articles). In this review, we included 111 published articles (49 cross-sectional, 23 longitudinal prospective, 11 experimental, 9 case-control, and 19 review studies) that were mainly generated from our original search, their references, and specific searches for issues that needed to be further explained.

We divided the main findings into the following categories: the menopausal stages, sex steroid hormones, other endocrine agents, genetic polymorphisms, race/ethnicity, body mass index (BMI) and obesity, mood disorders, smoking, soy isoflavones and phytoestrogens, alcohol consumption, and physical activity.

It is important to point out that our review deals with associated factors among generally healthy midlife women, excluding women taking various medications. Therefore, studies that report other associated factors, such as aromatase inhibitors and antiestrogenic drugs (e.g., tamoxifen that is taken by breast cancer patients), although significantly associated with HFs, were excluded from this review.

Results

The menopausal stages

Although women describe episodes similar to menopausal HFs at various stages of their reproductive life cycle,^{1,7} most women experience HFs during the menopausal stages.⁸ It is estimated that at some point during the menopausal transition, up to 80% of women will experience classic menopausal symptoms, including HFs.⁹ Several cross-sectional^{8,10} and longitudinal prospective^{11–13} studies, but not all, indicate that the late stages of menopause are associated with an increased risk of HFs.^{8,10–13} Part of the inconsistency in findings is explained by the fact that researchers have not used comparable terminology for menopausal stages when exploring the different associations between menopausal stages and HFs. Therefore, in 2001, the Stages of Reproductive Aging Workshop (STRAW) proposed conventional terminology for menopause stages. Later, the ReSTAGE Collaboration added supplementary definitions to reproductive aging,¹⁴ thus allowing a comparable distinction between reproductive aging and general aging events. Burger et al.¹⁴ summarized the proposed menopause nomenclature that since has been widely accepted and used by researchers and clinicians. The stages that are most relevant to this review are the late reproductive stage, characterized by no changes in menstrual cycle (follicular-stimulating hormone [FSH] levels may rise toward the end of this stage); the early menopausal transition stage, characterized by changes of ≥ 7 days in the menstrual cycle length; the late menopausal transition stage, characterized by ≥ 60 days of amenorrhea and FSH levels of ≥ 40 IU/L, which predict the final menstrual period; and the postmenopausal stage, ≥ 1 year of amenorrhea. These terms have

great importance in the study of HFs because of the strong associations that have been detected in a prospective longitudinal study between menopausal stages and HFs¹¹ and the fact that the menopausal stages are not interchangeable with chronological age.¹⁵

A vast majority of the data collected so far identifies the menopausal transition and postmenopausal stages as the main time points when women experience HFs. As a result of a longitudinal prospective study, Freeman et al.¹² reported that the risk of HFs increased throughout the menopausal transition and was greatest in postmenopausal women (odds ratio [OR] 2.87, 95% confidence interval [CI] 1.76–4.67, $p < 0.001$). In addition, VMS were most strongly related to the late menopausal transition stage in all racial/ethnic groups^{10,14,16,17} and nearly as strongly related to postmenopause, even after adjusting for covariates,^{10,12,18–22} as reported in several other published cross-sectional,^{10,16–18,20,22} longitudinal prospective,^{12,21} and review^{14,19} articles.

The menopausal stages can be used further in HF studies when the unique and similar endocrine characteristics of each stage are fully understood. For example, Hyde Riley et al.,²³ as a result of their cross-sectional study ($n = 755$ women), suggested that different modifiable factors are significant in the different menopausal stages in the context of HFs. More specifically, high BMI ≥ 25 kg/m² (OR 2.00, 95% CI 1.28–3.12 compared with women with a BMI of < 25 kg/m²) and alcohol use of 1–5 drinks per week (OR 0.52, 95% CI 0.31–0.86 compared with women who drank no alcohol) are correlated with women in their menopausal transition stage who experience HFs (after controlling for age, race, oral contraceptive use, hormone therapy use, and depression). Intake of at least one high-fat meal per day compared with intake of high-fat food weekly or less (OR 0.35, 95% CI 0.15–0.81) is correlated with fewer HFs in postmenopausal women (after controlling for age, race, oral contraceptive use, hormone therapy use, and depression).²³ Therefore, when performing analysis on factors that affect the incidence or severity of HFs, the nomenclature of the menopausal stages should be introduced along with other covariates in the final multivariate analysis. In summary, the menopausal stages (mainly the menopausal transition and postmenopause) are strongly associated with HFs, but there is still no single menopausal stage that has been identified as the critical time point for experiencing HFs.

Endocrinology

Sex steroid hormones. Numerous studies that evaluated risk factors for HFs have focused on sex steroid hormones, particularly estrogen. The focus on estrogen and HFs is likely due to the high prevalence of women who experience HFs (acutely or for several years) in association with dramatically decreased estrogen levels due to such various physiological conditions as bilateral oophorectomy³ or postpartum state, the involvement of estrogen in thermoregulatory homeostasis in the hypothalamus,²⁴ and the high success rate of estrogen-based treatments in easing HFs, as published in a review article of double-blind, randomized, placebo-controlled trials.²⁵ The association between HFs and lower levels of estradiol is fairly consistent.^{3,13,26–28} For example, Fentiman et al.²⁸ showed, in a cross-sectional study, that a decrease in symptom severity was correlated with high estradiol levels. This finding was also observed in other cross-sectional,^{26,27}

review,³ and longitudinal prospective¹³ studies. However, people who have abnormal gonadal function, such as Turner syndrome patients, were not reported as experiencing HFs. Additionally, women whose estrogen levels gradually decline rarely experience HFs^{29,30} (e.g., prepubertal girls, later postmenopausal years, hyperprolactinemia, postpartum Sheehan's syndrome, or other causes of pituitary insufficiency with gradual loss of ovarian function). In general, estrogen levels can vary between women for different reasons, such as reproductive aging (e.g., depletion of ovarian follicles) and other physiological factors that are part of a complex feedback-based system. The finding of Longcope³¹ that not all postmenopausal ovaries express aromatase (the enzyme that catalyzes the conversion of testosterone to estrogen) activity may explain other aspects of the differences in estrogen level (besides reproductive ones) and its possible outcomes in association with HFs. Nonetheless, the pathophysiological mechanism by which altered estrogen level plays a role in HFs is yet to be determined.

Schilling et al.,²⁶ in a cross-sectional study, investigated the associations among other sex steroid hormones, sex hormone-binding proteins, and HFs. The authors found that lower sex hormone-binding globulin (SHBG), estrone, and free estradiol index (FEI) levels and a higher ratio of total androgens/total estrogens levels were significantly associated with HFs. Androstenedione, testosterone, and dehydroepiandrosterone-sulfate (DHEA-S) were not associated with HFs. The lack of association between DHEA-S and testosterone and HFs may be partially explained by the fact that DHEA-S and testosterone levels remain relatively stable for most women during the menopausal transition and postmenopause stages.³² Testosterone levels likely remain stable during the later menopausal stages because ovarian stromal cells^{31,33,34} and adrenal glands³⁵ can synthesize and secrete hormones during this time, as was reported in studies using different (experimental,^{31,33} cross-sectional,³⁴ and longitudinal prospective³⁵) study designs. Despite the lack of association between HFs and testosterone, it is possible that testosterone has an effect on HFs only in symptomatic women. According to the findings of a cross-sectional study by Fentiman et al.,²⁸ women with higher testosterone levels experienced the more severe HF-related symptoms during the shift from the menopausal transition to the postmenopausal stage. Therefore, the role of testosterone in the pathogenesis of HFs should be further investigated.

Other endocrine agents. Other hormones that might play a role in the occurrence of HFs are the peptide hormones, inhibin A and B and FSH. Burger³² and Overlie et al.³⁶ confirmed previous observations that a fall in inhibin B and an increase in FSH are reliable markers of ovarian aging (mainly through the ovarian hypothalamic feedback system). More specifically, their results indicated that a decline in inhibin A levels preceded a decline in inhibin B levels and that 1 year before menopause, neither peptide hormone could be detected in serum. The researchers concluded that the disappearance of these peptide hormones is an important predictor of approaching menopause. Moreover, Sammel et al.³⁷ showed, in a longitudinal prospective study, that FSH levels could predict entry into each stage of menopause. Freeman et al.,^{12,38} in longitudinal prospective studies, found significant associations between HFs and lower levels of inhibin B,

higher levels of FSH (which may also be a result of lower levels of inhibin B), and fluctuating levels of estradiol after adjusting for menopausal stage.

Casper and Yen³⁹ demonstrated in an experimental study that HF episodes were always coupled to luteinizing hormone (LH) pulses, but not all LH pulses were accompanied by HFs. This result, along with the finding that elimination of LH pulses using an LH-releasing hormone analog, did not abate HFs, indicates that pulsatile LH release by the pituitary is not causally related to menopausal HFs.^{3,39}

Another peptide hormone that may be associated with HFs is anti-müllerian hormone (AMH). However, no studies have directly tested whether AMH is associated with HFs. Generally, AMH inhibits FSH-dependent follicle growth in a time-dependent manner; therefore, Hale and Burger,⁴⁰ in their review article, suggested that AMH may be a reliable indicator of the reproductive stage, as its levels appear to be a stable biomarker of the remaining ovarian follicles.

An additional area of interest that has been described in a limited number of publications is the association between thyroid hormone levels and HFs. Sowers et al.⁴¹ hypothesized that altered thyroid hormone levels could potentially contribute to variations in levels of other hormones that are commonly associated with the menopause transition. The researchers analyzed data from the Study of Women's Health Across the Nation (SWAN) and found no association between thyroid-stimulating hormone (TSH) levels or other reproductive hormones and HFs. The authors noted that it might be better to measure triiodothyronine (T₃) and thyroxine (T₄) and assess their association with HFs. The results of Sowers et al.⁴¹ were supported by Rojas et al.,⁴² who conducted a cross-sectional study on Hispanic women in Puerto Rico and found no significant difference in thyroid hormone levels between women in premenopausal and postmenopause stages. In contrast, support for a potential association between thyroid hormones and HFs is given by Badawy et al.,⁴³ who reported marked improvement in menopausal-like symptoms (including HFs) after treatment of thyroid dysfunction. Because of the numerous interactions of thyroid hormones with most body systems and their major role in metabolism, the relationship between thyroid hormones and the pathogenesis of HFs requires further investigation.

Genetic polymorphisms

As previously mentioned, several studies indicate that some hormone levels are associated with HFs.^{11,26,28,38} Thus, researchers hypothesized that genetic variation in hormone biosynthesis and metabolizing enzymes might play a role in the variability of HFs. To date, the literature describing associations between genetic polymorphisms and HFs is limited. Published reports, mainly from cross-sectional studies or using data originally collected in a longitudinal prospective study design, have focused on single nucleotide polymorphisms (SNPs) that mainly involve genes that encode estrogen receptors (ESRs) and genes that encode the enzymes of the estrogen biosynthesis and metabolic pathway (CYP450).

In a cross-sectional study, Malacara et al.⁴⁴ found a weak association between a polymorphism in the ESR1 gene and HFs, and Crandall et al.,⁴⁵ in their longitudinal prospective study, found no association between ESR1 (rs2234693 PvuII)

and VMS. Additionally, Sowers et al.,⁴⁶ after a longitudinal prospective study, indicated that women with a genetic polymorphism in the ESR1 gene may have a greater likelihood for more advanced ovarian aging than other women, suggesting a possible role of the polymorphism in the timing of the menopausal stages. As HFs are strongly associated with later menopausal stages, the polymorphism in the ESR1 gene should be further assessed for potential associations with HFs. Additionally, Crandall et al.⁴⁵ reported that the presence of the ESR1 (rs9340799 XbaI AG genotype) was significantly and negatively related to VMS reporting in Caucasian women with a BMI <25 and significantly associated with a 2.6-fold increase in VMS reporting in Caucasian women with a BMI ≥ 30 , compared with the AA genotype ($p < 0.0001$ for interaction with BMI).

As for ESR2, Takeo et al.⁴⁷ found, in a cross-sectional study, a strong relationship between a cytosine-adenine (CA) repeat polymorphism in the ESR2 gene and the risk of menopausal symptoms. The researchers suggested that a short CA repeat in the ESR2 gene results in a less active receptor that may, in turn, decrease androgen production by adrenal glands or the ovaries. The decrease in androgen production might lead to the lower levels of endogenous estrogens, which have been reported to be associated with HFs.^{3,29}

Other associations have been examined between polymorphisms in the genes in the estrogen metabolic and biosynthesis pathway and HFs. Massad-Costa et al.⁴⁸ found no association between HFs and a polymorphism in the CYP17 α MspA1 gene. Visvanathan et al.⁴⁹ examined polymorphisms in the following genes: CYP17 α MspA1, CYP1A1, and CYP1B1. Only the polymorphism in the CYP1B1 gene (rs1056836) had a significant association with the severity, frequency, and duration of HFs. Because the association was independent of estradiol and estrone levels (similar to the report by Lurie et al.⁵⁰), the authors suggested that a potential increase in the degradation of estradiol and estrone to catechol estrogens (due to the polymorphism in the CYP1B1 gene) might act directly on the hypothalamus to alter vasomotor tone and thus elicit HFs. This hypothesis, however, has not been verified. In a more recent cross-sectional study, Schilling et al.²⁶ focused on genetic polymorphisms in the CYP1B1 (rs1056836), 3 β HSD, CYP19, and COMT genes. The authors concluded that women who carried the examined polymorphisms in CYP1B1 and 3 β HSD had a significantly greater risk of experiencing HFs (any/moderate or severe, respectively) compared with women who did not carry the selected polymorphisms. Moreover, there was a statistically significant trend for a higher risk of HFs with the number of polymorphisms carried. Women who carried polymorphisms in both 3 β HSD and CYP1B1 had a higher risk of experiencing any HFs (p for trend = 0.02), moderate or severe hot flashes (p for trend = 0.006), or HFs that occur at least weekly (p for trend = 0.02) compared with women who did not carry both polymorphisms, pointing toward a possible additive effect of the SNPs. Similarly, Woods et al.⁵¹ reported that women with two CYP19 11r alleles had significantly more days of HFs during the middle and late menopausal transition and postmenopause than those with one or no allele. In contrast, Schilling et al.²⁶ did not find any association between selected polymorphisms in the CYP19 or COMT genes and HFs. These differences in results might stem from differences in study design (e.g., the tested populations and analysis assumptions,

such as including menopausal stage in the analysis). To date, no specific polymorphisms have been identified as specific biomarkers for the risk of experiencing HFs. Multifactorial statistical analysis that combines hormone levels and genetic polymorphisms in the aforementioned genes as covariates and HFs may assist in elucidating the pathogenesis of HFs.

Crandall et al.⁴⁵ identified race/ethnic-specific associations between reporting VMS and specific polymorphisms for sex steroid-metabolizing enzymes and ESR1. African American women with the heterozygous CYP1B1 (rs1056836) guanine-cytosine (GC) genotype had lower odds of reporting VMS compared with those with the cytosine-cytosine (CC) genotype. In Chinese women only, the presence of the CYP1A1 (rs2606345) adenine-cytosine (AC) genotype was associated with lower odds of VMS compared with the CC genotype.⁴⁵ Caucasian women who possessed the heterozygous 17 β HSD polymorphisms (rs615942 thymine-guanine [TG], rs592389 TG, and rs2830 AG) had significantly lower odds of reporting VMS than did women with homozygous genotypes.⁴⁵ In summary, several landmark epidemiological studies that performed extensive investigations of the relationship among environmental factors, ethnicity, and genetic polymorphism further support the notion that HFs have a multifactorial pathogenesis.

Race/ethnicity

Several studies have reported racial differences in the prevalence of HFs. These racial dissimilarities in the prevalence of HFs are partially because of heterogeneity in the tendency to report symptoms among a spectrum of socioeconomic groups. Specifically, African American women consistently report being more likely to experience HFs than Caucasian women.^{10,27,52–54} In SWAN, a multiethnic, longitudinal study that was conducted on a large cohort ($n = 16,065$) of the U.S. population, the following distribution of experiencing HFs among ethnic groups was found: African American (46%), Hispanic (36%), Caucasians (31%), Chinese (21%), and Japanese (18%) women.²⁰

In recent years, there has been an increased interest in HFs across cultures worldwide and in whether cultural and geographical differences can solely explain differences in prevalence of HFs. According to a cross-sectional study by Miller et al.,²⁷ racial/ethnic differences in HFs are due to racial/ethnic differences in obesity, smoking, and low estrogen levels. Freeman and Sherif's systematic review⁵⁵ indicates that VMS are highly prevalent in most societies, and, interestingly, HF prevalence patterns are more associated with the menopausal stages than with regional variation.

Previous studies found that Asian women have a reduced risk of reporting HFs compared with other racial groups.^{18,29} It has been hypothesized that this difference stems from dietary differences between Asian and Caucasian women (soy or phytoestrogen-based diet) and cultural differences. A cross-sectional study by Brown et al.⁵⁶ supports the possible associations of cultural differences and HFs. This study compared both reported (questionnaire) and objective (measured by chest and neck skin conductance) HFs among Japanese American and European American women. The results indicate that Japanese American women are less likely than European American women to report HFs on questionnaires, although no significant difference was present in

the likelihood of measured HF between groups. However, Ishizuka et al.⁵⁷ studied a nonclinical random community-based sample of Japanese women ($n=1,169$, mean age 50 years) and found a higher prevalence of HF (36.9%) than in a previous report on Japanese women (9.5%).⁵⁸ This increased prevalence is partially explained by westernization and medicalization of menopause in Japan and the increased attention given to it in the media.⁵⁹ Although the prevalence of HF has increased in Japan, however, it is still lower than in most Western populations.^{16,27,59} These findings, along with those from other studies, such as SWAN,^{10,27,52,60} allude to an important observation that race/ethnicity may not independently explain HF prevalence, as no statistically significant association was found between ethnicity/race and HF after adjustments for such covariates as lifestyle, BMI, smoking, menopausal status, and health-related quality of life.

Body mass index and obesity

Many studies indicate that obesity and higher BMI are associated with HF, but the evidence for this association is inconclusive. Two main theories have been developed in an attempt to explain the association between obesity and HF. The thermoregulatory model is based mainly on collected data that obese people have a reduced heat tolerance. It theorizes that adipose tissue has a strong insulating capacity, which inhibits heat dissipation, resulting in a higher tendency for VMS events in order to release the heat.^{61,62} In contrast, the thin hypothesis states that women with greater body fat or higher mean body weight will have a reduced risk of VMS because of potentially higher estrogen concentrations (androstenedione is aromatized into estrone in adipose tissue).^{63,64} The latter model is questioned by the findings of a case-control study by Gallicchio et al.⁶⁵ and a cross-sectional study by Schilling et al.,⁶⁶ who found significantly lower levels of estrogen in obese women (BMI ≥ 35 kg/m², BMI >30 kg/m², respectively) compared with normal-weight midlife women (BMI <25 kg/m²). Similarly, other studies indicate that higher BMI^{10,52,54,65,67,68} and a higher percentage of body fat^{63,69} are associated with increased odds of reporting VMS. Although there is greater evidence in support of the thermoregulatory model than the thin hypothesis, it cannot solely explain the pathogenesis of HF. Additional studies are needed.

Mood disorders

Studies have found that depression occurs more commonly during the menopausal transition in women who have HF compared with those who do not experience HF.^{70–74} Woods et al.,⁷⁵ while describing their longitudinal prospective study, suggested that the late menopausal transition represents a vulnerable time for depressed mood as well as HF and sleep disturbances. One of the many findings from SWAN was that a relatively high percentage (40.5%) of the midlife participants reported feeling depressed within the past 2 weeks of the survey,⁷⁶ but it is unclear from this study if depressive mood was a risk factor for HF. Freeman et al.⁷⁷ conducted a 10-year follow-up study of women who at baseline did not report HF or depressed mood. The results of this study indicated that depressive symptoms are more likely to precede HF in women who report both symptoms. For women who had

depressed moods, that is, high Center for Epidemiologic Studies-Depression (CES-D) scores before HF (and after adjusting for all other risk factors in the model), the odds of having HF at a subsequent assessment were three times greater compared with not having depressed moods (OR 3.06, 95% CI 1.43–6.58, $p=0.004$). In addition, both depressed mood and HF occurred in the early stages of the menopausal transition, and both were associated with early hormone changes. Women who first reported depressed mood had an individual increase in their FSH levels, whereas the onset of HF was independently associated with increased FSH levels and decreased levels of inhibin B. As described earlier, these changes are among the earliest markers of ovarian aging in the transition to menopause and have a strong association with HF. Finally, Thurston et al.⁷⁸ analyzed, in a prospective cohort study, the associations among HF, major depression, and physical activity. They found that although physical activity was not significantly associated with HF, women with a history of major depression had a decreased risk of VMS if they exercised.

There is less consistent evidence for the relationship between the menopausal transition and increased risk of other mood disorders.²⁴ Most of the associations between mood disorders and HF can be explained by other primary factors that are being experienced during the menopausal transition, such as sleep disturbances and altered hormone levels. In several studies, anxiety has been linked to HF. Freeman et al.⁷⁷ reported that women with moderate anxiety were nearly three times more likely to report HF and women with high anxiety were five times more likely to report HF than women without anxiety. Anxiety also remained strongly associated with HF after adjusting for menopause stage, depressive symptoms, smoking, BMI, estradiol levels, race, age, and time. Pursuing this further, it was found by means of a predictive model that anxiety levels significantly predicted HF.⁷⁷

Life events as other possible effectors on mental health were explored in association with HF in a limited number of studies. Thurston et al.,⁷⁹ in a longitudinal prospective study, found that childhood abuse or neglect was associated with an increased tendency to report HF in adulthood. Park et al.⁸⁰ concluded in their case-control study that mental workload under time pressure might be a risk factor for menopausal HF (although the overall performance of most people was not affected by them). In conclusion, although mental disorders showed some associations with HF, such conditions might be better studied in conjunction with at least two other primary factors while trying to determine the pathogenesis of HF.

Cigarette smoking

The positive relationship between HF and smoking is one of the most consistent associations found to date.^{10,54,68} This association has been described in detail by Greendale and Gold in their review article.⁸¹ However, the mechanism by which cigarette smoking is associated with HF has not been elucidated. Several mechanistic hypotheses have been suggested. First, it is proposed that cigarette smoking may decrease estrogen or androgen levels by interacting with enzymes along the estrogen biosynthesis and metabolic pathway (CYP450 enzymes), particularly aromatase. Aromatase is responsible for metabolism of the chemicals in

cigarette smoke as well as for metabolism of estrogen.^{29,82–85} Second, it is proposed that the chemicals in cigarette smoke may reduce estrogen levels by inducing mutations or destroying ovarian follicles (a process that might induce early menopause by accelerated depletion of ovarian reserve).^{86,87} Finally, it is hypothesized that smokers have a lower BMI or weight than nonsmokers, which is why these women are at a higher risk of HFs (according to the thin hypothesis).^{29,88,89} It also has been suggested that the chemicals in cigarette smoke may indirectly alter estrogen metabolism by reducing body weight. However, Gallicchio et al.⁹⁰ reported in their case-control study that the observed association between cigarette smoking and HFs is probably not due to changes in endogenous estrogen levels and that the mechanism likely involves hormones other than just estrogen.

Cochran et al.⁹¹ tested this hypothesis specifically in a cross-sectional study and found that compared with nonsmokers, current smokers had a significantly higher androgen/estrogen ratio, higher androstenedione levels, and lower progesterone levels than nonsmokers. As in other studies, former and current smokers had increased odds of experiencing HFs. Interestingly, this association was not attenuated when adding hormones to the smoking-HFs model. It was concluded that some of the alterations in hormone levels and ratios were an additional consequence of smoking rather than a cause of HFs (including progesterone levels, which were significantly lower in smokers). A similar conclusion is indicated by the results of Sammel et al.,³⁷ who found, in a longitudinal prospective study, that current smoking increased the likelihood of entry into each menopausal stage. Thus, in addition to a potential direct effect of cigarette smoking on the risk of development of HFs, smoking may indirectly induce HFs by accelerating ovarian aging.^{86,87} Cochran et al.⁹¹ found a significant association between cigarette smoking (current/former smokers) and increased levels of androstenedione. They described a potentially permanent effect of nicotine on adrenal gland activity that may cause increased androstenedione levels. Gallicchio et al.⁹⁰ indicated that women who were passively exposed to cigarette smoke had similar risks of developing HF as active smokers. In summary, there is solid evidence for the toxic effects of cigarette smoking. The fact that smokers have an increased risk for HFs is fairly consistent, but the mechanism and the specific role of the chemicals in cigarette smoke in the pathogenesis of HFs need to be further studied.

Soy isoflavones and phytoestrogens

Soy isoflavones and phytoestrogens in the diet have attracted researchers' attention because of their estradiol-like effects and the alleged relative lower prevalence of HFs among populations whose diet is rich in these compounds, for example, Asian women. However, no significant long-term association has been found between consumption of soy isoflavones and HFs. Sievert et al.⁹² reported no significant association between high soy intake and VMS in Hawaiian women in their cross-sectional study. This finding supports other recent studies on soy and phytoestrogens.^{55,93,94} A recent experimental study by D'Anna et al.⁹⁵ discusses the effects of the phytoestrogen genistein. They reported a short-term positive effect (up to 1 year) of genistein in reduction of HFs. The role of soy isoflavones and phytoestrogens in the

etiology of HFs might be clearer once more conclusive information is gathered on estrogenic compounds in general.

Alcohol consumption

A relatively small percentage of women describe alcohol consumption as a trigger for their HFs when compared with other reported triggers (stress/emotional situations 59%, external heat 44%, confining space 38%, alcohol 20%, and caffeine 17%).⁹⁶ Researchers who have studied the associations between alcohol consumption and HFs, however, have obtained ambiguous results. For example, in a cross-sectional study by Hyde Riley et al.,²³ consumption of 1–5 alcoholic drinks per week was associated with a reduced risk of menopausal HFs in women compared with women who drank no alcohol (OR 0.35, 95% CI 0.15–0.81) after controlling for age, race, oral contraceptive use, hormone replacement therapy use, and depression. A possible explanation comes from the findings of a cross-sectional study conducted by Gavalier and Van Thiel,⁹⁷ who reported increased estradiol levels as a function of weekly drinks in 128 normal postmenopausal women.

Conversely, Freeman et al.,⁵² in a longitudinal prospective study of 436 African American and Caucasian premenopausal women aged 34–47 years, found a statistically significant association between alcohol intake (number of drinks per week) and having any HFs (OR 1.1, $p = 0.002$). Similarly, Schwingl et al.,⁸⁸ in a cross-sectional study ($n = 334$) on African American and Caucasian postmenopausal women, suggested that those who had ever consumed alcohol recalled more HFs during their menopausal transition than did nondrinkers (OR 1.3, $p = 0.13$, after adjustment for relevant covariates). One potential explanation for the association between HFs and moderate alcohol consumption is that some alcoholic beverages contain estrogen-like compounds that might increase estrogen levels in women's serum.^{98–100} In a cross-sectional study conducted by Schilling et al.,¹⁰¹ moderate alcohol consumption (up to 2 drinks a day) was associated with a reduced risk of any, severe, and frequent HFs in midlife women, but the association of HFs with alcohol use was not reported as likely to include changes in sex steroid hormone levels. Thus, the relationship between alcohol consumption and HFs might be circumstantial or confounded by other variables, such as smoking. Therefore, any questionnaires on HFs and further statistical analysis should include relevant modifiable factors that will be tested for possible confounding effects. Lastly, it is noteworthy that some of the studies are based on surveys in which alcohol use is not questioned in detail.

Physical activity

Physical activity has been suggested as a potential method of easing VMS. Studies that have examined the relation between self-reported levels of exercise^{102–104} or exercise interventions^{102,105} and VMS have been inconclusive. After a cross-sectional study, Romani et al.¹⁰⁶ suggested there is a positive relation between physical activity and moderate or severe HFs, but no relation between physical activity and the reporting of any HFs, daily HFs, or HFs experienced for >1 year. Other investigations suggest that physical activity has no relation to¹⁰⁵ or decreases the risk^{102,107} of HFs. Furthermore, Whitcomb et al.¹⁰⁴ evaluated, in a cross-sectional study, the association of patterns of physical activity during ages

35–40 and immediately before the last menstrual period with occurrence, frequency, and severity of HFs in a population-based sample. This study indicated that frequent physical activity by midlife women may be associated with a risk of greater severity and frequency of menopausal HFs compared with women reporting minimal activity. Nonsignificant ORs were observed in comparisons of the moderately active with the minimally active women. According to the authors, these findings stand in contrast to a case-control study¹⁰⁸ and several cross-sectional^{20,102,109} studies that observed decreased HFs with increasing activity,^{20,102,108,109} and it was suggested that differences have arisen because of the timing of physical activity, study design, and measuring methods. The authors also proposed that it is possible that chronic elevations of β -endorphin caused by frequent exercise may interfere with normal thermoregulation later in life during menopause. The inconclusive evidence about the association between physical activity and HFs needs to be further studied even if it might not be a leading factor in the pathogenesis of HFs.

Conclusions

HFs have been studied for many decades, but their etiology is yet to be discovered. It is likely that the pathogenesis of HFs consists of complex multifactorial interactions of environmental and genetic predisposing conditions and a fragile balance between several hormonal feedback loops. To date, the most consistent risk factors that have been found in association with HFs are later menopausal stages, smoking, lower levels of estrogen, higher FSH levels, lower levels of inhibin A and B, race/ethnicity, and higher BMI.

As pointed out by Kronenberg in 1990,⁹⁶ the investigation into the pathogenesis of HFs has encountered numerous obstacles. The comparison between most studies on HFs is difficult as a result of contradictions and inconsistency in study design and analysis. Additionally, similar to the investigation of many conditions, an animal model with end point variables that can be objectively measured and reproduced is missing, although some progress in this area has been made in recent years. Albertson and Skinner¹¹⁰ developed a novel animal model in the ewe that can detect small changes in peripheral skin temperature and, thus, potentially can be used in studies of HF pathology. Similarly, Freedman and Wasson¹¹¹ invented a miniature hygrometric HF recorder that should be useful in clinical trials and for research on the determinants of HFs.

In conclusion, the step toward genetic and biochemical characterization of potential biomarkers for HFs is an encouraging development, but is far from approaching the finish line in HF research. More resources should be used to develop a unified study system that will allow investigation of this condition, which often imposes a tremendous social and personal toll on the women who experience it.

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Disclosure Statement

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