Published in final edited form as:
Obstet Gynecol. 2011 May ; 117(5): 1095–1104. doi:10.1097/AOG.0b013e318214f0de.

Duration of Menopausal Hot Flushes and Associated Risk Factors

Ellen W. Freeman, PhD[1], **Mary D. Sammel, ScD**[2], **Hui Lin, MS**[3], **Ziyue Liu, PhD**[2,4], and **Clarisa R. Gracia, MD**[1]

[1]Department of Obstetrics/Gynecology, School of Medicine, University of Pennsylvania, Philadelphia, PA

[2]Center for Clinical Epidemiology and Biostatistics, School of Medicine, University of Pennsylvania, Philadelphia, PA

[3]Center for Research in Reproduction and Women's Health, School of Medicine, University of Pennsylvania, Philadelphia, PA

[4]Division of Biostatistics, Department of Medicine, Indiana University, Indiana, IN

Abstract

OBJECTIVE—To estimate the duration of moderate-to-severe menopausal hot flushes and identify potential risk factors for hot flush duration.

METHODS—The Penn Ovarian Aging Study cohort was followed for 13 years. Hot flushes were evaluated at 9-month to 12-month intervals through in-person interviews. The primary outcome was the duration of moderate to severe hot flushes, estimated by survival analysis (N=259). Potential risk factors included menopausal stage, age, race, reproductive hormone levels, body mass index (BMI) and current smoking. A secondary analysis included women who reported any hot flushes (N=349).

RESULTS—The median duration of moderate to severe hot flushes was 10.2 years and was strongly associated with menopausal stage at onset. Hot flushes that commenced near entry into the menopause transition had a median duration >greater than 11.57 years; onset in the early transition stage had a median duration of 7.35 years (95% CI 4.94, 8.89), P<0.001); and onset in the late transition to postmenopausal stages had a median duration of 3.84 years (95% CI: 1.77, 5.52), P<0.001. The most common ages at onset of moderate-to-severe hot flushes were 45–49 years (median duration 8.1 years; 95% CI 5.12, 9.28). African American women had a longer duration of hot flushes than white women in adjusted analysis.

CONCLUSIONS—The median duration of hot flushes considerably exceeded the time frame that is generally accepted in clinical practice. The identified risk factors, particularly menopausal stage,

Corresponding author: Dr. Ellen W. Freeman, Department of Obstetrics/Gynecology, 3701 Market Street, Suite 820 (Mudd), Philadelphia, PA 19104; Tel: 215-662-3329; FAX: 215-349-5521; freemane@mail.med.upenn.edu.

Financial Disclosure: Dr. Freeman has received research support from Forest Laboratories, Inc., Wyeth, Pfizer, and Xanodyne Pharmaceuticals. She has also received honoraria for consulting and presentations from Wyeth, Forest Laboratories, Inc., Pherin Pharmaceuticals, and Bayer Health Care.

The other authors did not disclose any potential conflicts of interest.

race, and BMI, are important to consider in individualizing treatment and evaluating the risk to benefit ratio of hormones and other therapies.

INTRODUCTION

Relief for hot flushes, a predominant symptom of menopause (1), is among the most common reasons for clinical visits of mid-life women and a major cost in health care expenditures (2–4). Hot flushes are associated with poor sleep (5, 6), depressed mood (7, 8), decreased quality of life (9, 10), may worsen depressive symptoms and signal the onset or relapse of a major depressive episode (11, 12). Hot flushes may possibly mark underlying vascular changes that are associated with subclinical cardiovascular disease (13, 14), increased aortic calcification among users of hormone therapy (15), greater incident coronary heart disease (16) and may be a risk factor for poor bone health (17).

The peak prevalence of hot flushes occurs approximately one year after menopause (18), but the overall duration of hot flushes is unclear. Clinical guidelines indicate that the duration of hot flushes for most women is about 6 months to 2 years (19). However, the *average* duration of hot flushes was more than 5 years in the Melbourne Women's Midlife Health Project (20), and the median duration was 4 years in a meta-analysis of 10 previous hot flush studies (18), with 10% of the women reporting hot flushes 12 years after the final menstrual period.

Increased information about the duration of hot flushes is important for the clinical management of menopausal symptoms. Clinicians need to make evidence-based decisions about the duration of symptoms in order to counsel patients more effectively about the risk/benefit ratios of treatments. This is particularly important for treatment with hormone therapy, inasmuch as informed decisions about the duration of therapy are not possible without accurate estimates of the duration of the symptoms and knowledge of co-factors that influence symptom duration.

The purpose of this study was to estimate the duration of moderate-to-severe hot flushes in a population-based cohort of late reproductive age women and identify risk factors associated with hot flush duration. We hypothesized that menopausal stage at the onset of hot flushes predicted the duration of hot flushes. A secondary analysis was conducted to include all women who reported hot flushes, including mild hot flushes.

METHODS

Cohort and sample size

The cohort of 436 women was identified by random-digit dialing, stratified to obtain equal numbers of African American and white women (218 in each group), and followed from 1995 to 2009. At enrollment, the participants were ages 35–47 years, premenopausal with regular menstrual cycles in normal range (22–35 days) for the previous three cycles, had an intact uterus and at least one ovary. Exclusion criteria included current use of hormonal contraception, hormonal therapies, psychotropic medications; pregnancy or breast-feeding; serious health problems known to compromise ovarian function such as diabetes mellitus or liver disease; breast or endometrial cancer; and alcohol or drug abuse in the past year.

The present study evaluated 259 women in the cohort who did not report hot flushes in interview at baseline but did experience moderate to severe hot flushes between Assessment 2 and Assessment 14. An additional 90 participants reported only mild hot flushes in this interval and were included in the secondary analysis that evaluated a total of 349 women. Fifty-five women reported no hot flushes in the entire study interval and were not included

in the analyses of hot flush duration (see Table 1). The remaining 32 women in the cohort had data only in Assessment 1 (at study enrollment) and were not included in this study.

Study design

The cohort was followed for 13 years. The start point at Assessment 2 was the first follow-up assessment, conducted 9 months after cohort enrollment, and was the first assessment with ratings of the severity of hot flushes. Subsequent assessments were conducted at approximately 9- month intervals for the first five years of the study and then annually for the next 9 years, with a 2-year gap between assessments 10 and 11. At each assessment, there were two in-home visits to collect study data and blood samples for hormone assays. All visits were timed to the early follicular phase (days 1–6 of the menstrual cycle) and were conducted in two consecutive menstrual cycles or 1 month apart in non-cycling women (yielding a possible maximum of 26 hormone samples per participant in this study). The study was approved by the Institutional Review Board of the University of Pennsylvania and all participants provided written informed consent.

Data collection

At each assessment, trained research interviewers obtained structured interview and questionnaire data, blood samples for the hormone assays and anthropometric measures (height, weight, waist and hip circumference). The study was described to participants as a general women's health study. The structured interview questionnaire focused on overall health, and participants also completed a set of validated self-report measures to assess health and other behavioral variables of the study.

Identification of hot flushes

The primary outcome variable was the duration of moderate to severe hot flushes. The duration of hot flushes was calculated for each woman from her first report of *moderate or severe* hot flushes to her last observed assessment of moderate or severe hot flushes. The participants were queried about hot flushes at each assessment, using a validated menopausal symptom list that was embedded in the structured interview questionnaire (21). The questions asked whether hot flushes or night sweats occurred in the past month, whether hot flushes occurred in the past year (asked at Assessments 12–14), and the severity of reported hot flushes (severity ratings were 0, none; 1, mild; 2, moderate; 3, severe). Moderate or severe hot flushes were defined as those rated 2 or 3 by the participants. The cessation of hot flushes was defined as no moderate or severe hot flushes for at least one year. Because the interview questions queried only the past 30 days at Assessments 2 – 11, two consecutive assessments with no report of moderate/severe hot flushes were required for the cessation of hot flushes in this interval.

Other study variables

Menopausal stage was determined at each assessment using the menstrual date at the assessment (visits were conducted within the first six days of bleeding) and the two previous menstrual dates reported in the interview. Other confirmatory data were obtained from the daily symptom diaries that participants recorded for one menstrual cycle at each assessment and other interview data that included the number of menstrual periods between assessments, menstrual cycle length, and the number of bleeding days.

Stages of the menopause transition were adapted from the consensus statement of the Stages of Reproductive Aging Workshop (STRAW) (22) to capture early changes in bleeding patterns. Significant associations between these stages and reproductive hormones changes were reported previously (23, 24). The stages were as follows: 1) premenopausal: regular

menstrual cycles in the 22–35 day range; 2) late premenopausal: a change >=7 days either direction in the participant's own cycle length observed at one study assessment; 3) early transition: changes in cycle length >= 7 days either direction from the participant's baseline at enrollment and observed for a least two consecutive menstrual cycles in the study or 60 days amenorrhea; 4) late transition: 90 days to 11 months amenorrhea; 5) postmenopause: >=12 months amenorrhea excluding hysterectomy.

Hormones were measured in the Clinical and Translational Research Center of the University of Pennsylvania. Assays were conducted in batches that included 4 visits per subject to reduce the within-subject variability due to assay conditions. All assays were performed in duplicate and repeated if values differed by >15%. Estradiol and follicle stimulating hormone (FSH) were measured by radioimmunoassay using Coat-A-Count commercial kits (Diagnostic Products, Los Angeles, CA). Inter- and intra assay coefficients of variation were less than 5%. Inhibin b was measured by ELISA using the commercial kit from Diagnostic Systems Laboratories (Webster, TX). The sensitivity of the assay was 7 pg/mL (range 5–531 pg/mL). The inter and intra coefficients of variation were >5% and 7.3%, respectively. For the first 10 assessments, Dr. Patrick Sluss, PhD, Massachusetts General Hospital, Boston performed the inhibin b assays with a solid-phase sandwich ELISA (Diagnostic Systems Laboratories, Inc., Beckman Coulter, Houston, TX) based on the use of plates coated with a monoclonal antibody specific for the alpha-subunit for detection (25, 26). The limit of measurement for the assay was 15 pg/mL (CV=20%). The assay was controlled in triplicate using samples with mean concentrations of 155.3, 316.3, and 919.3 pg/mL, with interassay CVs of 11.6, 7.6 and 9.7%, respectively.

Other covariates were selected for their significance in previous studies and the goals of this study and were obtained at the study visits: age, race (African American or white), currently employed (yes, no), education >= high school, more than high school), body mass index (calculated as weight in kilograms divided by the square of height in meters), current smoking (yes, no), alcohol use daily (yes, no). The measures of depressed mood (CES-D) (27), anxiety (28), and perceived stress (29) provided continuous scores for analysis, with higher scores indicating more symptoms.

Statistical analysis

Statistical analyses were performed using Kaplan-Meier curves (30), log-rank tests (31) and Cox proportional hazards models (32) to compare duration of hot flushes among menopausal stages and age groups. Proportionality of hazards was evaluated by evaluating plots of transformed hazard estimates and smoothed residuals (33, 34) and identified no violations of model assumptions.

The primary analysis included all women who reported moderate or severe hot flushes in the study interval. A secondary analysis included all women who reported any hot flushes in the same study interval. We used the value of each covariate at the time of first report of moderate/severe hot flushes in order to emulate the clinical setting. The mean of 4 hormone measurements immediately preceding the onset of hot flushes for each participant was utilized and transformed to the natural log value to reduce the influence of large values. Mean hormone values are expressed in the report as the geometric mean (back-transformed from the natural log values) with 95% confidence intervals (CI). Hot flush duration was censored at times of reported hormone use, pregnancy and breast-feeding; observations of hot flushes at the last available assessment (Assessment 14 or the point of dropout if sooner) were also considered censored. Of the 259 women who comprised the primary study sample, 50 were considered censored from the point of discontinuation in the 13-year study interval (17 in years 2–5; 16 in years 6–9; 17 in years 10–13). Reasons for discontinuation were

deceased (n=11), medical problems (n=7), withdrew consent (n=6), moved from the area (n=2), no reason given (n=8) and lost to follow-up (n=16).

Each covariate was evaluated individually; those meeting the significance level of P<=0.15 were then included in multivariable models to identify their independent contributions after adjusting for the presence of all other variables. The final selection of covariates used a backward elimination strategy and was guided by whether the variable was associated with the response variable at P<=0.05 or its inclusion in the model modified other significant associations by 15% or more.

A sensitivity analysis of the primary outcome (duration of moderate/severe hot flushes) was conducted, omitting 24 women who indicated hot flushes in daily diaries that were collected at Assessment 1. The results for the remaining 235 women who had no moderate/severe hot flushes at Assessment 1 were nearly identical to the results for the 259 women that are presented in this report.

The study variables were compared among groups at baseline, using chi-square or F tests as appropriate for the data. All analyses were conducted using the SAS V9.2 statistical package (SAS Institute, Cary, NC). Statistical tests were 2-sided, with p values <=0.05 considered significant.

RESULTS

At the study baseline, the mean (SE) age was 42.2 (0.18) years, 91% were pre- or late premenopausal and 9% were in the early transition stage. Age, menopausal status, race, hormone measures, BMI and alcohol use did not differ among the hot flush severity groups (Table 1). The moderate/severe hot flush group had significantly higher baseline scores on measures of depressed mood, anxiety and stress; fewer were employed, education levels were lower, and more were smokers. Thirty-four percent of white participants and 49% of African Americans were smokers (chi-square = 5.58; df=1, P=0.02). Smoking did not differ by menopausal stage at the onset of hot flushes. At hot flush onset, 44% in the premenopausal group were smokers compared with 46% in the early transition group and 35% in the late transition/postmenopause group (chi-square = 2.23; df=2, P=0.33).

Duration of hot flushes

The median duration of moderate/severe hot flushes was 10.2 years. Thirty-seven percent of the women who reported moderate/severe hot flushes (96/259) reported hot flush cessation in the study interval (i.e., no moderate/severe hot flushes for at least one year), while the remaining women continued to report moderate/severe hot flushes.

The duration of hot flushes was strongly associated with menopausal stage at hot flush onset (P<0.001, Figure 1). The median duration of moderate/severe hot flushes for women who reported onset in the pre-/late premenopausal stage was >11.25 years, and only 21% in this group reported cessation in the study interval (Table 2). Median duration when onset was in the early transition stage was 7.35 years, with 51% reporting cessation in the study interval. When onset was in the late transition or postmenopause stage, the median duration was 3.84 years, with 52% reporting cessation during the follow-up interval.

The most common age at onset of moderate/severe hot flushes was 45–49 years (35%); 30% were ages 40–44 years, 21% were over age 50, and 14% were <40 years. Age at onset was inversely associated with duration of hot flushes (P<0.001) (Table 2). The median duration of hot flushes was longest when onset occurred at ages <40 years (11.57 years) and decreased with onset at older ages: 11.25 years duration with onset at ages 40–44 years; 8.1

years duration with onset at ages 45–49 years; and 3.8 years duration with onset at >=50 years of age.

Hormone levels

Mean hormone levels were significantly associated with the duration of hot flushes in unadjusted analyses. Higher levels of FSH and lower levels of inhibin b and estradiol indicated a greater likelihood of hot flush cessation (P<0.001, P<0.001 and P=0.08, respectively; Table 3). Higher FSH levels remained a significant predictor of cessation of hot flushes after adjusting for all other variables in the multivariable model (P=0.003).

Significant predictors of hot flush duration in adjusted analysis

Menopausal stage at onset of moderate/severe hot flushes was the strongest predictor of duration after adjusting for the presence of all other variables in the model (P<0.001) (Table 4). When the onset of hot flushes was in the pre-/late premenopause stages, the duration was longer compared to onset in the late transition or postmenopause stages (HR 5.14; 95% CI 2.70, 9.77; P<0.001). We then investigated whether the proportion of women with severe hot flushes was smaller in the earlier stages of the transition by comparing the proportion of women with severe hot flushes at onset in each menopausal stage. The proportion of severe hot flushes at onset was similar at each menopausal stage, with no significant association between hot flush severity and menopausal stage. At onset in the pre-/late premenopausal stage, 24% reported severe hot flushes; at onset in the early transition stage, 35% reported severe hot flushes; at onset in the late transition/postmenopausal stage: 20% reported severe hot flushes (chi-square = 4.29; df=2, P=0.12).

Other independent predictors of the duration of moderate/severe hot flushes in adjusted analysis were age (the younger the age at onset, the longer the duration, P=0.02); race (African American women had longer duration of hot flushes than white women, P=0.02); and BMI (non-obese women had longer duration of hot flushes than obese women, P=0.003).

Figure 2 shows the influence of age, race and BMI on the estimated duration of moderate/severe hot flushes for the early onset and late onset groups. For example, African American, non-obese women who were early starters (hot flush onset in the pre-/late premenopausal stage) had an estimated duration of over 10 years regardless of age at onset (Figure 2A). In contrast, white, non-obese women who were *late* starters (onset in late transition/postmenopausal stages) and age >=45 years at onset had an estimated duration of about 4 years (Figure 2B).

Of the remaining study variables, significant *unadjusted* associations with hot flush duration were observed for depressed mood (P=0.005), anxiety (P=0.006), stress (P=0.04) and current employment (P=0.008), but none were significantly associated with the duration of hot flushes in the multivariable model. Smoking, alcohol use and number of children had no association with duration of hot flushes in either adjusted or unadjusted models.

Current smoking was not associated with the duration of hot flushes in unadjusted analysis (HR 0.83, 95% CI: 0.55 – 1.25, P=0.36) but was examined in the final multivariable model to determine whether it was a confounder of the other risk factor associations with the duration of hot flushes. In the multi-variable model, smoking remained non-significant (P=0.41), and model results were nearly identical to those shown (Table 4).

Secondary analysis for any hot flushes

The analyses were repeated to include all women who reported any hot flushes (mild, moderate, severe) in the study interval (N=349), from the first report of any hot flushes to cessation of any hot flushes. By including mild hot flushes in the analysis, the median duration increased to 11.6 years. The duration of any hot flushes was associated with menopausal stage (P<0.001), age (P<0.001), and anxiety (P=0.006) in unadjusted analysis (data not shown). Mean hormone levels were associated with hot flush duration: FSH (P<0.001), inhibin b (P<0.001), estradiol (P=0.09), with hazard ratios similar to those shown for the unadjusted analysis in Table 3. Menopausal stage was the only significant predictor of duration of any hot flushes after adjusting for age, anxiety and each hormone separately in the multivariable model (P<0.001).

DISCUSSION

In this 13-year follow-up of hot flushes in a randomly-identified, population-based cohort, the median duration of moderate/severe hot flushes was 10.2 years, well beyond the duration considered in clinical guidelines (19). When women who reported mild hot flushes were included, the median duration of hot flushes increased to 11.6 years.

Previous reports indicated that the duration of hot flushes increased with the length of the follow-up (18, 20). However, the present results indicate that it is not simply the length of follow-up but the menopausal stage at onset that more accurately identifies hot flush duration. Women who reported onset of moderate/severe hot flushes as they entered the menopause transition had a duration greater than 11 years; in contrast, women whose onset of moderate/severe hot flushes was in the late transition or postmenopausal stages had a median duration of approximately 4 years. It is noteworthy that a 4-year median duration is consistent with the results of a meta-analysis of 10 hot flush studies that enrolled women who were generally older than the present cohort and were likely in stages closest to menopause when they were observed in studies (18).

As indicated in this study, the initiation of hot flushes is highly variable in relation to menopausal stage, but we know of no biological explanation for this. While hot flushes appear to originate in the central nervous system and are linked with a lowered thermoregulatory setpoint, their pathophysiology is not well understood (35, 36). Possibly women who report hot flushes in the late premenopause or earliest transition stages have greater sensitivity to hormone fluctuations or perception of symptoms, but this has not been demonstrated. In a previous report from this cohort, anxiety predicted hot flushes and the most anxious women had the most severe hot flushes (37). However, another study that compared anxiety scores between women with hot flushes and women with no hot flushes found significantly higher anxiety in peri- and postmenopausal women but not in the premenopausal women with hot flushes (38). Clear relationships between anxiety, initiation of hot flushes and biological mechanisms in the same women remain unknown. Age at hot flush onset was a strong predictor of hot flush duration. It is noteworthy that the great majority of women (79%) were under age 50 when they reported the onset of moderate/severe hot flushes, with 45–49 years the most common ages. The younger the age at onset, the longer the median duration of hot flushes. Hot flush duration was about 8 years when onset occurred in the 45–49 year age group compared to under 4 years when onset occurred at ages >=50 years.

Race was a significant predictor of hot flush duration in the multivariable model that adjusted for BMI, with African American women having a longer duration of hot flushes than white women. These findings extend previous information that indicated African

American women were more likely to report hot flushes than other racial groups (39–44)), but the reasons for racial differences remain unclear.

Obesity was significantly associated with the duration of moderate/severe hot flushes, but there was no significant interaction between obesity and race. Overall, obese women had a shorter duration of hot flushes compared to non-obese women. *Non-obese* African American women had the longest duration of moderate/severe hot flushes, followed by non-obese white women. Obese white women had the shortest duration, followed by obese African American women. These data suggest that the shorter duration of hot flushes among obese women may be associated with the well-recognized changes in estrogen metabolism that occur with ovarian senescence, when the contribution of estradiol from fat becomes dominant and obese women have higher estradiol levels than do non-obese women. We and others have previously reported a *postmenopausal* shift in the BMI effect, where obese women have lower estradiol levels premenopause (and earlier onset of hot flushes) but higher estradiol levels postmenopause compared to non-obese women (45, 46).

Although a number of studies have reported that women who smoke are more likely to report hot flushes, possibly due to the antiestrogenic effects of smoking (43, 47, 48), current smoking had no significant association with the *duration* of hot flushes in this cohort. Whether hot flushes commenced very early or in the late stages of the menopause transition also was not significantly associated with smoking.

Several strengths of this study include the prospective assessment of hot flushes and menopausal stage in a randomly-identified cohort over the entire menopause transition. Another strength is the use of survival analysis, although this method may over-estimate hot flush duration due to interval evaluation of hot flushes in the long follow-up interval. The annual assessments of hot flushes could potentially overestimate the duration by one year. On the other hand, while we believe that we evaluated the first onset of moderate/severe hot flushes, hot flush duration would be underestimated if hot flushes occurred prior to the study.

It is possible that hot flushes were due to conditions other than menopause, although the participants were generally in good physical health, and the strong associations of hot flushes with menopausal stages provide evidence of their association with reproductive aging. The study did not include women using hormone therapy, and studies to determine the effect of hormone therapy on hot flush duration are needed. Finally, the participants represent African American and white urban women in the U.S., and the results cannot be generalized to women in non-similar areas or other racial groups.

The findings indicate that the median duration of moderate/severe hot flushes considerably exceeds the time frame that is generally accepted in clinical practice. Indeed, a sizable number of women experienced hot flushes in the early stages of the menopause transition and about 80% were younger than age 50 at hot flush onset. This information is important for the clinical management of hot flushes. Perhaps treatments for vasomotor symptoms should be targeted more commonly to younger, irregularly menstruating women, although it must be recognized that traditional HT may not be the ideal choice for this population, given, for example, the problems of breakthrough bleeding and the need for contraception. Other treatments for hot flushes need to be evaluated, particularly for women who have not reached menopause. Race and BMI also significantly influenced the duration of hot flushes and are important considerations in individualizing treatment, particularly when the predicted duration of hot flushes is substantially longer than the length of hormone therapy that is currently recommended.

Acknowledgments

Supported by grants from the National Institutes of Health: RO1-AG-12745 (Dr. Freeman, Principal Investigator) and RR024134 (Clinical and Translational Research Center).

References

1. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Granger AL, Fehnel SE, et al. Frequency and severity of vasomotor symptoms among peri- and postmenopausal women in the United States. Climacteric. 2008; 11:32–43. [PubMed: 18202963]
2. Guthrie JR, Dennerstein L, Taffe JR, Donnelly V. Health care-seeking for menopausal problems. Climacteric. 2003; 6:112–117. [PubMed: 12841881]
3. Hoerger TJ, Downs KE, Lakshmanan MC, Lindrooth RC, Plouffe L Jr, Wendling B, et al. Healthcare use among U.S. women aged 45 and older: total costs and costs for selected postmenopausal health risks. J Womens Health Gend Based Med. 1999; 8:1077–1089. [PubMed: 10565666]
4. Owens GM. Gender differences in health care expenditures, resource utilization, and quality of care. J Manag Care Pharm. 2008; 14:2–6. [PubMed: 18439060]
5. Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. Semin Reprod Med. 2010; 28:404–421. [PubMed: 20845239]
6. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause. 2003; 10:19–28. [PubMed: 12544673]
7. Bromberger JT, Kravitz HM, Matthews K, Youk A, Brown C, Feng W. Predictors of first lifetime episodes of major depression in midlife women. Psychol Med. 2009; 39:55–64. [PubMed: 18377672]
8. Woods NF, Smith-DiJulio K, Percival DB, Tao EY, Mariella A, Mitchell S. Depressed mood during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. Menopause. 2008; 15:223–232. [PubMed: 18176355]
9. Avis NE, Ory M, Matthews KA, Schocken M, Bromberger J, Colvin A. Health-related quality of life in a multiethnic sample of middle-aged women: Study of Women's Health Across the Nation (SWAN). Med Care. 2003; 41:1262–1276. [PubMed: 14583689]
10. Nappi RE, Lachowsky M. Menopause and sexuality: prevalence of symptoms and impact on quality of life. Maturitas. 2009; 63:138–141. [PubMed: 19464129]
11. Reed SD, Ludman EJ, Newton KM, Grothaus LC, LaCroix AZ, Nekhlyudov L, et al. Depressive symptoms and menopausal burden in the midlife. Maturitas. 2009; 62:306–310. [PubMed: 19223131]
12. Stahl SM. Vasomotor symptoms and depression in women, part I. Role of vasomotor symptoms in signaling the onset or relapse of a major depressive episode. J Clin Psychiatry. 2009; 70:11–12. [PubMed: 19222980]
13. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, Hess R, Matthews KA. Hot flashes and subclinical cardiovascular disease: findings from the Study of Women's Health Across the Nation Heart Study. Circulation. 2008; 118:1234–1240. [PubMed: 18765392]
14. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control: a link to cardiovascular risk? Menopause. 2010; 17:456–461. [PubMed: 20042892]
15. Thurston RC, Kuller LH, Edmundowicz D, Matthews KA. History of hot flashes and aortic calcification among postmenopausal women. Menopause. 2010; 17:256–261. [PubMed: 20042895]
16. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007; 297:1465–1477. [PubMed: 17405972]
17. Crandall CJ, Tseng CH, Crawford SL, Thurston RC, Gold EB, Johnston JM, et al. Association of menopausal vasomotor symptoms with increased bone turnover during the menopausal transition. J Bone Miner Res. 2010

18. Politi MC, Schleinitz MD, Col NF. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. J Gen Intern Med. 2008; 23:1507–1513. [PubMed: 18521690]
19. North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause. 2004; 11:11–33. [PubMed: 14716179]
20. Col NF, Guthrie JR, Politi M, Dennerstein L. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. Menopause. 2009; 16:453–457. [PubMed: 19188852]
21. Freeman EW, Sammel MD, Liu L, Martin P. Psychometric properties of a menopausal symptom list. Menopause. 2003; 10:258–265. [PubMed: 12792299]
22. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric. 2001; 4:267–272. [PubMed: 11770182]
23. Freeman EW, Sammel MD, Gracia CR, Kapoor S, Lin H, Liu L, et al. Follicular phase hormone levels and menstrual bleeding status in the approach to menopause. Fertil Steril. 2005; 83:383–392. [PubMed: 15705379]
24. Gracia CR, Sammel MD, Freeman EW, Lin H, Langan E, Kapoor S, et al. Defining menopause status: creation of a new definition to identify the early changes of the menopausal transition. Menopause. 2005; 12:128–135. [PubMed: 15772558]
25. Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, et al. The relative role of gonadal sex steroids and gonadotropin-releasing hormone pulse frequency in the regulation of follicle-stimulating hormone secretion in men. J Clin Endocrinol Metab. 2008; 93:2686–2692. [PubMed: 18445673]
26. Welt CK, Taylor AE, Fox J, Messerlian GM, Adams JM, Schneyer AL. Follicular arrest in polycystic ovary syndrome is associated with deficient inhibin A and B biosynthesis. J Clin Endocrinol Metab. 2005; 90:5582–5587. [PubMed: 16030174]
27. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.
28. Zung WWK. A rating instrument for anxiety disorders. Psychosomatics. 1971; 12:371–379. [PubMed: 5172928]
29. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983; 24:385–396. [PubMed: 6668417]
30. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–481.
31. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966; 50:163–170. [PubMed: 5910392]
32. Cox DR. Regression models and life-tables. J R Stat Soc Series B. 1972; 34:187–220.
33. Kleinman, DG.; Klein, M. Survival analysis: a self-learning text. 2nd ed.. New York (NY): Springer-Verlag; 2005. p. 140
34. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Stat Med. 1995; 14:1707–1723. [PubMed: 7481205]
35. Freedman RR. Physiology of hot flashes. Am J Hum Biol. 2001; 13:453–464. [PubMed: 11400216]
36. Loprinzi CL, Barton DL. On hot flash mechanism, measurement, and treatment. Menopause. 2009; 16:621–623. [PubMed: 19436222]
37. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T. The role of anxiety and hormonal changes in menopausal hot flashes. Menopause. 2005; 12:258–266. [PubMed: 15879914]
38. Juang KD, Wang SJ, Lu SR, Lee SJ, Fuh JL. Hot flashes are associated with psychological symptoms of anxiety and depression in peri- and post- but not premenopausal women. Maturitas. 2005; 52:119–126. [PubMed: 16186074]
39. Simpkins JW, Brown K, Bae S, Ratka A. Role of ethnicity in the expression of features of hot flashes. Maturitas. 2009; 63:341–346. [PubMed: 19592184]
40. Appling S, Paez K, Allen J. Ethnicity and vasomotor symptoms in postmenopausal women. J Womens Health. 2007; 16:1130–1138.

41. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health. 2006; 96:1226–1235. [PubMed: 16735636]

42. Thurston RC, Bromberger JT, Joffe H, Avis NE, Hess R, Crandall CJ, et al. Beyond frequency: who is most bothered by vasomotor symptoms? Menopause. 2008; 15:841–847. [PubMed: 18521049]

43. Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstet Gynecol. 2007; 110:230–240. [PubMed: 17666595]

44. Thurston RC, Sowers MR, Chang Y, Sternfeld B, Gold EB, Johnston JM, et al. Adiposity and reporting of vasomotor symptoms among midlife women: the study of women's health across the nation. Am J Epidemiol. 2008; 167:78–85. [PubMed: 17881385]

45. Freeman EW, Sammel MD, Lin H, Gracia CR. Obesity and reproductive hormone levels in the transition to menopause. Menopause. 2010; 17:718–726. [PubMed: 20216473]

46. Randolph JF Jr, Sowers M, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. J Clin Endocrinol Metab. 2004; 89:1555–1561. [PubMed: 15070912]

47. Dennerstein L, Smith AM, Morse C, Burger H, Green A, Hopper J, et al. Menopausal symptoms in Australian women. Med J Aust. 1993; 159:232–236. [PubMed: 8412889]

48. Sievert LL, Obermeyer CM, Price K. Determinants of hot flashes and night sweats. Ann Hum Biol. 2006; 33:4–16. [PubMed: 16500807]

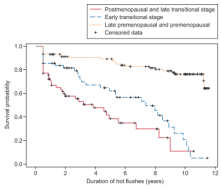

Figure 1.
Kaplan-Meier estimates of hot flush duration by menopausal stage and symptom onset. Log rank P<.001.

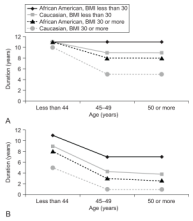

Figure 2.

A: Hot flush duration (in years) by age, race, and body mass index (BMI) for early onset (premenopausal or late premenopausal) of hot flushes. B: Hot flush duration (in years) by age, race, and body mass index (BMI) for late onset (late transitional or postmenopausal) of hot flushes.

Table 1

Variables at Study Baseline Compared Between Hot Flash Groups

Variable	**Moderate-Severe Hot Flashes n=259[2]**	**Mild Hot Flashes n=90[2]**	**No Hot Flashes n=55[2]**	**P Value[1]**
	N (%)	**N (%)**	**N (%)**	
Menopausal Stage				0.665
Premenopausal	164 (65)	59 (69)	43 (80)	
Late premenopausal	60 (24)	21 (24)	7 (13)	
Early/late transition	27 (11)	6 (7)	4 (7)	
Race				0.519
African American	128 (51)	38 (44)	27 (49)	
White	124 (49)	49 (56)	28 (51)	
Current smoking	108 (43)	26 (30)	14 (25)	0.013
Alcohol ∃ daily	33 (13)	6 (7)	4 (7)	0.180
Education				<0.001
# HS	124 (49)	27 (31)	15 (27)	
> HS	128 (51)	60 (69)	40 (73)	
Currently employed	197 (78)	78 (90)	47 (85)	0.043
Number of children				0.237
0	36 (14)	11 (13)	14 (25)	
1–2	122 (48)	46 (53)	25 (45)	
∃ 3	94 (37)	30 (34)	16 (27)	
Variable	Moderate-Severe Hot Flashes n=259	Mild Hot Flashes n=90	No Hot Flashes n=55	P Value[1]
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Age, yrs	42.4 (41.9, 42.8)	42.4 (41.7, 43.1)	41.3 (40.5, 42.2)	0.072
BMI, kg/m	29.4 (28.4, 30.4)	28.9 (27.4, 30.4)	27.0 (25.3, 28.7)	0.065
Depressed mood, (CES-D)	16.9 (15.6, 18.1)	13.5 (11.6, 15.3)	11.8 (9.2, 14.4)	<0.001
Anxiety, (Zung)	36.3 (35.3, 37.3)	32.8 (31.2, 34.4)	30.2 (28.4, 32.0)	<0.001
Stress, (PSS)	21.9 (20.9, 22.9)	19.5 (18.0, 21.1)	18.2 (15.7, 2.07)	0.003
Estradiol, pg/mL	34.9 (32.1, 37.9)	35.7 (31.7, 40.3)	36.4 (30.4, 43.6)	0.894
FSH, mIu/mL	7.3 (6.8, 7.9)	7.5 (6.7, 8.4)	7.4 (6.6, 8.3)	0.899
Inhibin b, ng/mL	59.8 (54.5, 65.8)	63.1 (73.1, 54.4)	70.7 (84.6, 59.1)	0.268

[1] P values are for chi-square test (class variables) or F test (continuous variables).

[2] Numbers that do not add to total are due to skipped assessments and 3 subjects censored due to pregnancy at Period 2 only.

Table 2

Duration of Moderate/Severe Hot Flashes Over 13-Year Follow-up Compared by Menopausal Stage and Age at Onset

Menopausal Stage	Onset of hot flashes N	Observed end N (%)	Continuing/ unknown N (%)	Median duration (yrs) (95% CI)	HR (95% CI)	P Value
Pre-, late premenopausal	121	25 (21%)	96 (79%)	> 11.25	----	----
Early transition	63	32 (51%)	31 (49%)	7.35 (4.94, 8.89)	4.62 (2.69, 7.95)	<0.001
Late transition, postmenopausal	75	39 (52%)	36 (48%)	3.84 (1.77, 5.52)	7.24 (4.18, 12.55)	<0.001
Age (years)						
< 40	36	7 (19)	29 (81)	>11.57 (11.21,---)	0.20 (0.09, 0.45)	<0.001
40–44	78	21 (27)	57 (73)	11.25 (10.07, ---)	0.40 (0.23, 0.67)	<0.001
45–49	90	44 (49)	46 (51)	8.1 (5.12, 9.28)	Ref	----
∃ 50	55	24 (44)	31 (56)	3.8 (1.65, 6.71)	1.82 (1.08, 3.09)	0.025

[1]HR = hazard ratio:The likelihood of hot flashes ending compared to the reference group. HR greater than 1 indicates greater likelihood of hot flashes ending (shorter duration of hot flashes); HR less than 1 indicates greater likelihood of hot flashes continuing (longer duration of hot flashes).

Table 3

Associations of Hormones with Median Duration of Moderate/Severe Hot Flashes[1]

	Unadjusted			Adjusted[2]		
Hormone	**Hazard Ratio[3]**	**95% CI**	**P Value**	**Hazard Ratio**	**95% CI**	**P Value**
Estradiol, pg/mL	0.80	0.62, 1.03	0.08	0.82	0.64, 1.05	0.110
FSH, mIu, mL	1.74	1.41, 2.15	<0.001	1.47	1.14, 1.90	0.003
Inhibin b, ng/mL	0.51	0.40, 0.66	<0.001	0.74	0.54, 1.02	0.068

[1] Hormones are natural log values.

[2] Adjusted for age, race and BMI; menopausal stage not included in the adjusted model due to high correlation with the hormone.

[3] HR greater than 1 indicates greater likelihood of hot flashes ending; HR less than 1 indicates greater likelihood of hot flashes continuing.

Table 4

Association of Study Variables with Duration of Moderate to Severe Hot Flashes from the Final Multivariable Model

	Hazard Ratio[1]			Hazard Ratio[1]		
Variable	**Unadjusted**	**95% CI**	**P Value**	**Adjusted**	**95% CI**	**P Value**
Menopausal Stage			<0.001[2]			<0.001[2]
Pre-, late premenopausal	Reference	---	---	Reference	---	---
Early transition	4.62	2.69, 7.95	<0.001	3.26	1.78, 5.97	<0.001
Late transition; postmenopausal	7.24	4.18, 12.55	<0.001	5.14	2.70, 9.77	<0.001
Age (yrs)			<0.001[2]			0.02[2]
# 39	0.20	0.09, 0.45	<0.001	0.33	0.14, 0.78	0.01
40–44	0.40	0.23, 0.67	<0.001	0.52	0.30, 0.91	0.02
45–49	Reference	---	---	Reference	---	---
∃ 50	1.83	1.08, 3.09	0.03	1.00	0.54, 1.87	0.99
Race						
African American	Reference	---	---	Reference	---	---
White	1.41	0.94, 2.11	0.09	1.73	1.11, 2.68	0.02
BMI						
<30	Reference	---	---	Reference	---	---
∃ 30	1.92	1.27, 2.90	0.002	1.94	1.25, 3.02	0.003
Estradiol, mean	0.80	0.62, 1.03	0.08	0.82	0.64, 1.05	0.11

[1] HR greater than 1 indicates greater likelihood of hot flashes ending; HR less than 1 indicates greater likelihood of hot flashes continuing

[2] Wald chi-square for overall test