Published in final edited form as:
Menopause. 2010 ; 17(3): 462–470. doi:10.1097/gme.0b013e3181c29e68.

Predictors of Breast Discomfort among Women Initiating Menopausal Hormone Therapy

Carolyn J. Crandall, MD, MS[1], **Daniela Markovic, MS**[2], **Mei-Hua Huang, DrPH**[1], and **Gail A. Greendale, MD**[1]

[1] Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles

[2] Department of Biomathematics, David Geffen School of Medicine, University of California at Los Angeles

Abstract

Objective—To study the determinants of breast discomfort among postmenopausal women initiating menopausal hormone therapy (HT).

Methods—We analyzed questionnaire, anthropometric, and serum estrone data from the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI), a randomized trial comparing placebo, conjugated equine estrogen (CEE) alone, or CEE with a progestogen (continuous or cyclical medroxyprogesterone acetate or cyclical micronized progesterone) among postmenopausal women. HT users could join PEPI after stopping HT for 2 months. We modeled the relation between smoking, body weight, alcohol consumption, age, quitting HT to join PEPI, physical activity and alpha-tocopherol consumption and new-onset breast discomfort at 12-month follow-up among 662 participants without baseline breast discomfort.

Results—The associations of new-onset breast discomfort with weight and with strenuous exercise varied by treatment assignment. Among women assigned to CEE + progestogen, strenuous exercise was associated with a 49% lower odds of new-onset breast discomfort (OR 0.51, 95% CI 0.29–0.89, P = 0.02), whereas among women assigned to placebo or CEE alone, strenuous exercise was not significantly associated with new-onset breast discomfort. Surprisingly, among women taking CEE alone, each kilogram higher weight was associated with 6% lower odds of new-onset breast discomfort (P=0.04), whereas among women taking placebo, the association was in the opposite direction (P=0.04). Adjustment for estrone level had neglible effects on odds ratios. Alpha-tocopherol intake, age, smoking, and alcohol intake were not significantly associated with new-onset breast discomfort in adjusted analyses.

Conclusion—Strenuous exercise and higher body weight may decrease the odds of new-onset breast discomfort among postmenopausal women initiating HT.

Keywords

mastodynia; mastalgia; menopausal hormone therapy; estrogen therapy; breast pain

Corresponding Author: Carolyn J. Crandall, MD, MS, Associate Professor of Medicine, David Geffen School of Medicine at University of California, Los Angeles, UCLA Medicine/GIM, 911 Broxton Ave., 1st floor, Los Angeles, CA 90024, ccrandall@mednet.ucla.edu, Phone 310-794-8069, fax 310-794-0732, Asst. Ms. Laura Hidalgo, 310-794-2985.

Introduction

Cyclical breast discomfort is a common symptom among pre-menopausal women; it may interfere with sexual, physical, social, work, and school activities (1,2). However, the prevalence and determinants of breast discomfort among postmenopausal women are not well-understood. The prevalence of decreases significantly with age (3) and with completion of the menopause transition (4–6). In the Melbourne Women's Midlife Health Project, the menopause transition stage at which prevalence of breast discomfort changed the most was between the early and late perimenopause. The prevalence of breast discomfort was 21% lower in late perimenopause compared to early perimenopause (4).

The cyclic nature of breast discomfort among premenopausal women and the decline in prevalence of breast tenderness over the menopause transition suggest that changes in circulating sex steroid levels may influence the occurrence of breast discomfort. Moreover, breast discomfort is a recognized adverse effect of menopausal hormone therapy (HT) (3,7,8).

Certain factors may influence the occurrence of new-onset breast discomfort during administration of HT. First, factors that are associated with altered sex steroid metabolism might alter the odds of experiencing new-onset breast discomfort during administration of HT. For example, among women initiating oral HT, on-treatment estradiol level (9–16) and estrone level (9,14,15,17) increase to a lesser degree among smokers than non-smokers, possibly due to increased hepatic metabolism of estrogens among smokers (15). Similarly, through its influence on sex steroid metabolism (e.g. increased peripheral aromatization of androstenedione to estrone) and by increasing on-treatment estrogen levels during HT (18), higher weight may increase the risk of developing breast discomfort during HT. Finally, higher physical activity is associated with lower serum estrogen levels (19), and alcohol intake increases on-treatment estrogen levels during HT (17), suggesting that physical activity and alcohol intake levels may influence the effects of HT on breast discomfort.

Other factors may affect susceptibility to new-onset breast discomfort during HT. Inclusion of a progestogen regimen along with estrogen increases the risk of HT-associated breast discomfort (7,20–22). Also, alpha-tocopherol supplementation has been used by clinicians as a treatment for mastalgia and has been tested in randomized controlled trials of among premenopausal women with cyclic mastalgia (23,24). Whether alpha-tocopherol intake is associated with breast discomfort among postmenopausal women is unknown. Finally, because they have already been exposed to HT, recent users of HT may decrease susceptibility to new-onset breast discomfort upon HT re-initiation.

We analyzed baseline and 12-month data from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, a randomized controlled trial of placebo versus HT in postmenopausal women, to determine the associations between smoking, body weight, alcohol consumption, age, recent use of HT, alpha-tocopherol intake, and physical activity and change in serum estrone level. We then examined whether smoking, body weight, alcohol consumption, age, recent use of HT, alpha-tocopherol intake, and physical activity were associated with the new-onset of breast discomfort after initiation of HT, and whether these associations were mediated by change in serum estrone level.

Methods

Participants

We analyzed data from the Postmenopausal Estrogen/Progestin Intervention study (PEPI), a randomized controlled trial that has been described in detail previously (25). PEPI was

designed to compare the effects of placebo and several menopausal HT regimens on cardiovascular risk factors among postmenopausal women. Participants were recruited at seven centers: George Washington University, Washington, DC; Johns Hopkins University, Baltimore, MD; Stanford University, Stanford, CA; University of California, Los Angeles; University of California, San Diego; University of Iowa, Iowa City; and University of Texas Health Science Center, San Antonio. For inclusion, participants were required to be between 45 and 64 years-old and at least 1 year postmenopausal with a follicle-stimulating hormone level ≥ 40 mIU/mL. Women with a major contraindication to the use of estrogen or progestin therapy (such as breast cancer) were excluded (25). Women using HT at study recruitment were required to stop their privately-prescribed menopausal HT at least 2 months before their first screening visits ("quitting HT for PEPI").

Of the 1557 women screened for inclusion in PEPI, 875 met the inclusion criteria and were randomized to one of five treatment regimens. The treatment regimens were: placebo, conjugated equine estrogens 0.625 mg/d (CEE), daily CEE plus medroxyprogesterone acetate 10 mg/d for 12 days/month, daily CEE plus medroxyprogesterone acetate 2.5 mg/d continuously, and daily CEE plus micronized progesterone 200 mg/d for 12 days/month. Human research review boards at each study site approved the PEPI protocol. Informed consent was obtained from all participants.

Because the focus of the current analysis was to describe predictors of new-onset of breast discomfort according to whether women were assigned to and taking one of the four active regimens, we excluded 82 PEPI participants who reported having breast discomfort at baseline. Of the remaining 793 participants, 679 women took at least 80% of their assigned treatment at both 6-month and 12-month follow-up visits. At the 12-month follow-up visit, information was missing regarding breast symptoms for 4 participants, and was missing regarding alcohol and alpha-tocopherol intake for 1 participant. For an additional 12 participants, information was missing regarding other key covariates. Thus, 662 women comprised the final analytic sample for this study.

Questionnaire and Anthropometric Assessments

Information about age, ethnicity, cigarette smoking, alcohol use, physical activity level, ethnicity, age at menopause, smoking, reproductive history, hysterectomy, oophorectomy, and prior use of HT was obtained from standardized self-report questionnaires at baseline and 12-month follow-up (25).

For women who reported spontaneous menopause, age at menopause was based on self-reported age at last menstrual period. For women who had undergone bilateral oophorectomy, we assigned age at oophorectomy to be the age at menopause. Women who had hysterectomy without oophorectomy, women who reported removal of one ovary, and women who were uncertain how many ovaries were removed at time of hysterectomy, were considered to have uncertain age at menopause.

Adherence to treatment assignment was defined as taking at least 80% of study medication at both 6-month and 12-month follow-up visits (verified by pill count). We defined cigarette smokers as participants who reported current smoking at both baseline and 12-month follow-up.

Specific questions regarding breast discomfort were asked at baseline and 12-month follow-up: "During the past week including today, did any of these symptoms bother you or interfere with your life? Breast sensitivity/tenderness (yes or no), painful breasts (yes or no)". We classified women who reported one or more of these breast symptoms (sensitivity, tenderness, pain) as having "breast discomfort".

At 12-month follow-up, participants completed the Block Food Frequency Questionnaire assessing usual food intake over the past year (26,27). The Block questionnaire allowed quantification of average dietary alpha-tocopherol intake (mg/day) and average daily alcoholic beverage intake (gm/day) over the past 12 months.

At the 12-month follow-up visit, home, work, and leisure physical activity over the past 12 months were quantified using an intensity-based form (28,29) (Appendix). Examples of intensity levels were offered on the questionnaire (inactive=1, light=2, moderate=3, heavy=4). Because work activity was not applicable for 85 women, we focused on leisure and home physical activity in this analysis. In addition, the physical activity questionnaire at the 12-month follow-up visit asked “Do you regularly engage in strenuous exercise or hard physical labor? (yes or no)”.

At baseline and 12-month follow-up, using standardized techniques, weight (kg) and height were measured for calculation of body mass index (BMI, kg/m^2) (30).

Serum estrone assay

At baseline and at the 12-month follow-up visit, fasting blood samples were obtained between 7am and 10 am. Serum estrone level was measured by radioimmunoassay after organic solvent extraction and Celite column chromatography (31). Sensitivity of the assay was 4.0 pg/mL; intra- and inter-assay coefficients of variation were 6% and 9% respectively. Information regarding baseline or 12-month values of serum estrone was missing for 8 participants (4 women in the placebo group and 4 women in the CEE + progestogen group).

Statistical Analysis

As previously reported (7), reports of new-onset breast discomfort at 12 months among the 3 progestogen-containing treatment arms were similar to each other, and higher than those of CEE recipients (Table 1). Therefore, we grouped participants of the progestogen-containing arms together and considered treatment arm as a 3-level covariate: placebo, CEE alone, and progestogen-containing regimen (i.e. CEE plus progestogen).

We first used linear regression to determine the associations between change in serum estrone level (12 months-baseline) and each of the factors of interest: age, cigarette smoking, alpha-tocopherol intake, alcohol intake, quitting HT for PEPI, and physical activity. For the 4 women whose baseline estrone values were below the lower limit of detection, we assigned an estrone level of 2 pg/mL. (No 12-month estrone values were below the lower limit of detection.)

Using logistic regression, we first examined unadjusted associations between the new-onset of breast discomfort (yes/no) and each of the predictors of interest: age, cigarette smoking, alpha-tocopherol intake, alcohol intake, quitting HT for PEPI, and physical activity (3,16,19,32–52). Because the distribution of alcohol intake was skewed, we considered alcohol intake as a binary variable (daily # alcoholic drinks > median versus ≤ median). We evaluated alpha-tocopherol intake both as a binary variable (daily intake > median versus ≤ median) and as a continuous variable (mg/day). We evaluated body mass both as weight (kilograms) and body mass index (kg/m^2). The linearity of the relationship between weight and log odds of having breast discomfort was confirmed using restricted cubic splines regression separately in each arm. Physical activity score ([average of leisure score and home score] minus 1) was less strongly associated with new-onset breast tenderness than was the binary (yes/no) question relating to strenuous physical activity. Therefore, we used strenuous activity as the indicator of physical activity in the subsequent multivariable logistic regression analyses.

We used multivariable logistic regression to determine the association between each predictor and the new-onset of breast discomfort (yes/no) after simultaneous adjustment for the all of other covariates. Interaction terms were chosen *a priori* based on prior publications and biological plausibility as follows (7,9–22). To test whether effects of the predictors varied according to treatment assignment, interaction terms for treatment arm*physical activity, treatment arm*cigarette smoking, treatment arm*BMI, treatment arm*alcohol intake, and treatment arm*quitting HT for PEPI were considered for inclusion in multivariable logistic regression models. To select which interaction effects to retain in regression models, we used a backwards stepwise procedure with $P<0.1$ as the retention criterion for interaction effects and a threshold of $P<0.25$ for main effects. As a result of the model selection process, the following variables were included in the final multivariable logistic regression models: weight, strenuous exercise, quitting HT to join PEPI, and interactions of treatment assignment with weight, strenuous exercise, and quitting HT to join PEPI.

To explore whether change in serum estrone level from baseline to 12-month follow-up could explain associations between predictors and new-onset breast discomfort, we added change in log estrone to the multivariable logistic regression models that included the predictors that were significantly associated with new-onset breast discomfort.

In secondary analyses, we repeated our final models in the subgroup of participants for whom we had complete information regarding age at menopause (N = 505).

Sensitivity, specificity, and accuracy were computed under the logistic regression model using the receiver operating characteristic (ROC) curve analysis. Accuracy was defined as the unweighted average of the specificity and the sensitivity. For each subject we computed the predicted probability of reporting new-onset breast discomfort and the corresponding sensitivity, specificity, and accuracy. We examined the values of sensitivity and specificity that maximized the accuracy.

Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA, copyright 2002–2003). All statistical tests were 2-sided.

Results

In participants of the analytic sample, mean age was 57.1 years, mean alpha-tocopherol intake was 7.2 mg/d, mean alcohol intake was 6.0 gm/d (approximately 0.43 drinks/day because a drink of alcohol typically contains about 14 grams of alcohol (53)). Median BMI was 24.9 kg/m^2 (Table 1). Sixty-seven percent of the participants had low physical activity scores. Approximately 12% of the participants were current cigarette smokers (i.e. reported smoking at both baseline and 12-month follow-up). Approximately $1/3^{rd}$ of participants had quit menopausal hormone therapy to join PEPI (Table 1). As has been previously reported (7), new-onset breast discomfort was more common among women taking estrogen + progestogen (28.7%) compared to CEE alone (13.7%) or placebo (11.7%, Table 1).

Mean changes in serum estrone level from baseline to 12 months were as follows: placebo group −0.98 p/.ml, CEE-only 108.48 pg/mL, CEE + progestogen 101.46 pg/mL. Table 2 shows that increased weight was inversely associated with change in log serum estrone level. For each 10 kg higher weight, the serum estrone level declined by 0.08 pg/ml ($P<0.001$ for CEE-only and for CEE + progestogen groups). Strenuous exercise was marginally associated with increases in serum estrone level among women assigned to CEE + progestogen therapy ($p=0.06$).

Table 3 displays the odds of developing new-onset breast discomfort associated with each potential predictor in unadjusted (Model 1) and adjusted (Model 2) logistic regression models. In unadjusted models, among women assigned to estrogen + progestogen, strenuous exercise was associated with significantly decreased odds of new-onset breast discomfort (OR 0.53, 95% CI 0.30–0.91), Table 3, Model 1). Also, weight was inversely associated with new-onset breast discomfort among women assigned to CEE-only (OR 0.94, 95% CI 0.90–1.00). Other factors were not significantly associated with new-onset breast discomfort among women assigned to active therapy in unadjusted models.

However, in adjusted models, the associations of new-onset breast discomfort with weight, strenuous exercise, and quitting HT to join PEPI varied by treatment arm (P_{int} column). Therefore, we present separate odds ratio estimates for each treatment arm resulting from logistic regression models adjusted for weight, strenuous exercise, and quitting HT to join PEPI (Table 3, Model 2). In women taking CEE + progestogen, strenuous exercise was associated with a 49% lower odds of new-onset breast discomfort (OR 0.51, 95% CI 0.29–0.89), whereas in women taking placebo or CEE alone, strenuous exercise was not significantly associated with new-onset breast discomfort (Model 2). Among women taking CEE alone, each kilogram higher weight was associated with a 6% lower odds of new-onset breast discomfort among women assigned to CEE alone (OR 0.94, 95% CI 0.90–1.00) and (not statistically significant) among women assigned to CEE + progestogen (OR 0.99, 95% CI 0.97–1.01). In contrast, in women taking placebo, the association of weight with new-onset breast discomfort was in the opposite direction: each additional kilogram of weight was associated with 4% higher odds of new-onset breast discomfort (OR 1.04, 95% CI 1.00–1.09, Model 2). There was no significant association between quitting HT for PEPI and odds of new-onset breast discomfort in any treatment group. However, there was a suggestion of a lower odds of new-onset breast discomfort among women who had quit HT for PEPI compared with women who had not quit HT for PEPI among women who took CEE + progestogen (OR 0.66, P=0.08 in adjusted model and OR 0.64, P=0.06 in unadjusted model); in contrast, the odds of new-onset breast discomfort were (non-significantly) higher among placebo- and CEE-users who had quit HT for PEPI. These differences likely account for the statistical interaction between quitting HT for PEPI and use of CEE + progestogen during PEPI that was noted in Table 3, P_{int} column).

Weight was more strongly associated with breast discomfort than was BMI, but results of multivariable adjusted models using BMI instead of weight were qualitatively similar to those using weight (data not shown).

Adding log delta estrone level (12-month minus baseline) to the multivariable adjusted models had negligible effects on the odds ratio estimates for the main predictors (Table 3, model 3).

We performed a secondary analysis of participants for whom we had information regarding years since menopause. Information regarding years since menopause was missing or unknown in 158 of our 662 participants (23.8%), because they underwent hysterectomy prior to menopause but had at least one ovary left intact. Results of the multivariable analysis that was restricted the participants with known years since menopause yielded similar findings to those of the primary analysis (data not shown).

The sensitivity, specificity, and accuracy of the final model (adjusting for treatment arm, weight, strenuous exercise, quitting HT for PEPI, and interaction terms) in predicting new-onset breast discomfort were 79%, 49%, and 64%, respectively.

DISCUSSION

Among women initiating CEE + progestogen or CEE-only, higher weight was associated with significantly less on-treatment increase in serum estrone level; also, strenuous exercise was associated with marginally significantly greater increase in estrone level among women initiating CEE + progestogen therapy. Higher body weight was associated with decreased odds of new-onset breast discomfort, especially among women taking CEE alone. Strenuous exercise was associated with decreased odds of new-onset breast discomfort; the magnitude of reduction in odds among women taking CEE + progestogen was similar to that of women taking CEE alone.

Although measures of increased body mass have been associated with increased estrogen levels among postmenopausal women in prior studies (37,38,40–42,48,49,54–72), we found weight to be *inversely* correlated with on-treatment change in estrone level. In line with these findings, we found that higher body weight was associated with decreased odds of new-onset breast discomfort after HT initiation. Although the reduction in the odds of new-onset breast discomfort associated with higher body weight was not statistically significant in women taking CEE + progestogen, the magnitude of the odds ratio estimate was similar to that of women taking CEE alone, and the association of CEE + progestogen with new-onset breast tenderness was statistically significantly different from that of placebo. We did not expect these results because most circulating estrogen in postmenopausal women is produced by peripheral conversion of androgens (68), and obesity results in increased production of estrogen from androstenedione (57,60,73,74). Perhaps the decreased odds of new-onset breast discomfort that we observed with increasing body weight is due to chronic exposure to higher local estrogen production which in turn makes the breast less susceptible to effects of exogenous estrogen administration. To our knowledge only one prior study focused on the influence of body weight or related measures on breast pain during administration of CEE-containing regimens. After 1 year of treatment, BMI had no significant effect on changes from baseline in breast pain in the Women's HOPE trial, which included the same dosing and similarly-aged women as PEPI (75). The discrepancy across studies may be partially due to differing questions used to ascertain breast discomfort; the prior publication did not include details regarding the text of questions used to ascertain breast discomfort. Our use of weight as a continuous variable may have allowed enhanced sensitivity to detect associations of weight with new-onset breast discomfort; the prior study classified results according to a categorical method (BMI <25 kg/m^2 versus ≥ 25 kg/m^2). In contrast to the results in the active therapy groups, our findings among women in the placebo group were as hypothesized: weight was *not* inversely associated with change in estrone level, and increased weight was not associated with decreased odds of new-onset breast discomfort among women assigned to placebo.

Surprisingly, we found physical activity to be marginally associated with *increases* in estrone level among women assigned to CEE + progestogen therapy. Despite this finding, among women taking either CEE + progestogen or CEE alone, strenuous exercisers were approximately 50% less likely to experience new-onset breast discomfort after 12 months compared to women reporting no strenuous exercise. These results are in contrast with previously-reported influences of physical activity on circulating estrogen levels. A randomized controlled trial of combination home-based and facility-based physical activity intervention in postmenopausal women decreased serum estrone levels and free estradiol levels significantly compared to a control stretching intervention (19). Thus, the risk of developing new-onset breast discomfort among women initiating CEE-containing therapy may not correspond with, or act directly via, increases in serum estrone levels.

Women who quit HT to join PEPI may have had a lower odds of developing new-onset breast discomfort after initiation of CEE + progestogen, perhaps because breast tissue that is accustomed to effects of exogenous CEE + progestogen is less apt to become tender upon re-exposure.

Because adjustment for change in serum estrone had negligible effects on associations between strenuous exercise, quitting HT for PEPI, weight, and new-onset breast discomfort, the associations are unlikely to be explained by on-treatment change in serum estrone level. This may be because inter-individual differences in new-onset breast discomfort depend in large part on metabolism of sex steroids locally, i.e. on local metabolism in breast tissue which is not fully accounted for with adjustment for serum estrone level. All of the enzymes that convert circulating estrogen precursors into E_2 (3β-HSD, 17β-HSD, aromatase) are present in normal breast tissue, as is steroid sulfatase (which converts estradiol sulfate to estradiol) (76).

We did not find age or cigarette smoking to be a significant predictor of HT-associated breast discomfort, despite the lesser gains in serum estrone level experienced by smokers compared to non-smokers during HT (17). Randomized controlled trials of HT regimens other than ours have implicated older age to be positively associated (77,78) and smoking to be inversely associated (11) with risk of HT-associated breast discomfort. The use of different HT preparations(11,77,78), the earlier assessment of breast discomfort (e.g. at 10 weeks after HT initiation (78)), older age of participants(77), and higher numbers of women who smoke in prior studies may explain the discrepancy in results of the current study compared to prior studies. Moreover, we found no evidence that new-onset breast discomfort was influenced by dietary alpha-tocopherol intake among postmenopausal women assigned to CEE or CEE + progestogen therapy. Our results showing lack of association between alpha-tocopherol intake and new-onset breast discomfort are consistent with the lack of benefit of alpha-tocopherol in relieving cyclical breast discomfort in randomized controlled trials of premenopausal women (23,24).

Although a prior PEPI study of participants demonstrated that increases in serum estrone levels after 12-months of CEE-containing HT were 15% greater among women who drank more than 5.5 g/day of alcohol than among women who drank ≤5.5 g/day of alcohol (17), the current study does not support an influence of self-reported alcohol intake on the occurrence of HT-associated breast discomfort.

We appear to report a higher prevalence of new-onset breast discomfort compared to the large Women's Health Initiative Estrogen plus Progestin Clinical Trial, which reported a prevalence of 9.3% (3). However, the former report, which randomized postmenopausal women with an intact uterus to CEE 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily or placebo, quantified only moderate or severe breast tenderness, whereas we included women with any severity (mild, moderate, or severe) of breast tenderness in the current report. It is likely that heterogeneity regarding how questionnaires assess breast symptoms, and what degrees of severity are included in statistical analyses, result in different prevalence estimates for hormone therapy-associated breast symptoms across studies.

Strengths of our study include the exclusion of data from participants with baseline breast discomfort (optimizing the reliability of the estimate of new-onset breast discomfort), the ability to compare placebo, CEE alone, and CEE + progestogen, and the blinded method of collection of information regarding breast discomfort that was identically applied to all participants. Our study has limitations. Our assessments of alpha-tocopherol intake, alcohol intake, and physical activity levels may not have been as reliable as that which would have been afforded by prospectively-collected diaries.

CONCLUSIONS

In conclusion, strenuous exercise and higher body weight may decrease the odds of new-onset breast discomfort among postmenopausal women initiating CEE-containing HT. Determinants of new-onset breast discomfort during HT administration, and the mechanisms by which they act to induce breast discomfort, require further elucidation.

Acknowledgments

The authors thank the women who generously participated in the Postmenopausal Estrogen/Progestin Interventions Trial.

Financial support: Dr. Crandall's work was supported by NIA grant number AG1004. All authors received support from Public Health Service grant R01CA77708 (National Cancer Institute, Department of Health and Human Services.)

References

1. Ader DN, Browne MW. Prevalence and impact of cyclic mastalgia in a United States clinic-based sample. American journal of obstetrics and gynecology 1997 Jul;177(1):126–32. [PubMed: 9240595]
2. Ader DN, Shriver CD. Cyclical mastalgia: prevalence and impact in an outpatient breast clinic sample. Journal of the American College of Surgeons 1997 Nov;185(5):466–70. [PubMed: 9358091]
3. Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 2005 May;105(5 Pt 1):1063–73. [PubMed: 15863546]
4. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet Gynecol 2000 Sep;96(3):351–8. [PubMed: 10960625]
5. Bungay GT, Vessey MP, McPherson CK. Study of symptoms in middle life with special reference to the menopause. Br Med J 1980 Jul 19;281(6234):181–3. [PubMed: 6447529]
6. Davies EL, Gateley CA, Miers M, Mansel RE. The long-term course of mastalgia. Journal of the Royal Society of Medicine 1998 Sep;91(9):462–4. [PubMed: 9849515]
7. Crandall CJ, Karlamangla A, Huang MH, Ursin G, Guan M, Greendale GA. Association of new-onset breast discomfort with an increase in mammographic density during hormone therapy. Archives of internal medicine 2006 Aug 14–28;166(15):1578–84. [PubMed: 16908790]
8. Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ (Clinical research ed) 2008;337:a1190.
9. Jensen J, Christiansen C. Effects of smoking on serum lipoproteins and bone mineral content during postmenopausal hormone replacement therapy. American journal of obstetrics and gynecology 1988 Oct;159(4):820–5. [PubMed: 2972209]
10. Byrjalsen I, Haarbo J, Christiansen C. Role of cigarette smoking on the postmenopausal endometrium during sequential estrogen and progestogen therapy. Obstet Gynecol 1993 Jun;81(6): 1016–21. [PubMed: 8497343]
11. Bjarnason NH, Jorgensen C, Kremmer H, Alexandersen P, Christiansen C. Smoking reduces breast tenderness during oral estrogen-progestogen therapy. Climacteric 2004 Dec;7(4):390–6. [PubMed: 15799610]
12. Bjarnason NH, Christiansen C. The influence of thinness and smoking on bone loss and response to hormone replacement therapy in early postmenopausal women. J Clin Endocrinol Metab 2000 Feb;85(2):590–6. [PubMed: 10690860]
13. de Valk-de Roo GW, Netelenbos JC, Peters-Muller IR, Voetberg GA, van de Weijer PH, Bouman AA, et al. Continuously combined hormone replacement therapy and bone turnover: the influence of dydrogesterone dose, smoking and initial degree of bone turnover. Maturitas 1997 Dec 15;28(2):153–62. [PubMed: 9522323]

14. Geisler J, Omsjo IH, Helle SI, Ekse D, Silsand T, Lonning PE. Plasma oestrogen fractions in postmenopausal women receiving hormone replacement therapy: influence of route of administration and cigarette smoking. J Endocrinol 1999 Aug;162(2):265–70. [PubMed: 10425465]
15. Jensen J, Christiansen C, Rodbro P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. N Engl J Med 1985 Oct 17;313(16):973–5. [PubMed: 4047104]
16. Cassidenti DL, Vijod AG, Vijod MA, Stanczyk FZ, Lobo RA. Short-term effects of smoking on the pharmacokinetic profiles of micronized estradiol in postmenopausal women. American journal of obstetrics and gynecology 1990 Dec;163(6 Pt 1):1953–60. [PubMed: 2256508]
17. McDivit AM, Greendale GA, Stanczyk FZ, Huang MH. Effects of alcohol and cigarette smoking on change in serum estrone levels in postmenopausal women randomly assigned to fixed doses of conjugated equine estrogens with or without a progestin. Menopause (New York, NY) 2008 Mar–Apr;15(2):382–5.
18. Yasui T, Uemura H, Umino Y, Takikawa M, Saito S, Kuwahara A, et al. Serum estrogen level after hormone replacement therapy and body mass index in postmenopausal and bilaterally ovariectomized women. Maturitas 2005 Jan 10;50(1):19–29. [PubMed: 15590210]
19. McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004 Apr 15;64(8):2923–8. [PubMed: 15087413]
20. Greendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumaker S, Johnson S, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. Obstet Gynecol 1998 Dec;92(6):982–8. [PubMed: 9840563]
21. Carranza-Lira S, Garduno-Hernandez MP, Caisapanta DA, Aparicio H. Evaluation of mastodynia in postmenopausal women taking hormone therapy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2005 May;89(2):158–9. [PubMed: 15847887]
22. Girdler SS, O'Briant C, Steege J, Grewen K, Light KC. A comparison of the effect of estrogen with or without progesterone on mood and physical symptoms in postmenopausal women. Journal of women's health & gender-based medicine 1999 Jun;8(5):637–46.
23. Ernster VL, Goodson WH 3rd, Hunt TK, Petrakis NL, Sickles EA, Miike R. Vitamin E and benign breast "disease": a double-blind, randomized clinical trial. Surgery 1985 Apr;97(4):490–4. [PubMed: 3885456]
24. Meyer EC, Sommers DK, Reitz CJ, Mentis H. Vitamin E and benign breast disease. Surgery 1990 May;107(5):549–51. [PubMed: 2185569]
25. Espeland MA, Bush TL, Mebane-Sims I, Stefanick ML, Johnson S, Sherwin R, et al. Rationale, design, and conduct of the PEPI Trial. Postmenopausal Estrogen/Progestin Interventions. Controlled clinical trials 1995 Aug;16(4 Suppl):3S–19S. [PubMed: 7587218]
26. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A databased approach to diet questionnaire design and testing. Am J Epidemiol 1986 Sep;124(3):453–69. [PubMed: 3740045]
27. Block G, Dresser CM, Hartman AM, Carroll MD. Nutrient sources in the American diet: quantitative data from the NHANES II survey. I. Vitamins and minerals. Am J Epidemiol 1985 Jul;122(1):13–26. [PubMed: 4014190]
28. Greendale GA, Bodin-Dunn L, Ingles S, Haile R, Barrett-Connor E. Leisure, home, and occupational physical activity and cardiovascular risk factors in postmenopausal women. The Postmenopausal Estrogens/Progestins Intervention (PEPI) Study. Archives of internal medicine 1996 Feb 26;156(4):418–24. [PubMed: 8607727]
29. Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1995 Nov 1;142(9):889–903. 1978. discussion 887–8. [PubMed: 7572969]
30. Wood PD, Kessler G, Lippel K, Stefanick ML, Wasilauskas CH, Wells HB. Physical and laboratory measurements in the PEPI Trial Postmenopausal Estrogen/Progestin Interventions. Controlled clinical trials 1995 Aug;16(4 Suppl):36S–53S. [PubMed: 7587219]

31. Anderson DC, Hopper BR, Lasley BL, Yen SS. A simple method for the assay of eight steroids in small volumes of plasma. Steroids 1976 Aug;28(2):179–96. [PubMed: 973234]
32. Friedman AJ, Ravnikar VA, Barbieri RL. Serum steroid hormone profiles in postmenopausal smokers and nonsmokers. Fertil Steril 1987 Mar;47(3):398–401. [PubMed: 2951278]
33. Khaw KT, Tazuke S, Barrett-Connor E. Cigarette smoking and levels of adrenal androgens in postmenopausal women. N Engl J Med 1988 Jun 30;318(26):1705–9. [PubMed: 2967432]
34. Michnovicz JJ, Naganuma H, Hershcopf RJ, Bradlow HL, Fishman J. Increased urinary catechol estrogen excretion in female smokers. Steroids 1988 Jul–Aug;52(1–2):69–83. [PubMed: 2854668]
35. Schlemmer A, Jensen J, Riis BJ, Christiansen C. Smoking induces increased androgen levels in early post-menopausal women. Maturitas 1990 Jun;12(2):99–104. [PubMed: 2123959]
36. Cassidenti DL, Pike MC, Vijod AG, Stanczyk FZ, Lobo RA. A reevaluation of estrogen status in postmenopausal women who smoke. American journal of obstetrics and gynecology 1992 May; 166(5):1444–8. [PubMed: 1534446]
37. Tazuke S, Khaw KT, Barrett-Connor E. Exogenous estrogen and endogenous sex hormones. Medicine (Baltimore) 1992 Jan;71(1):44–51. [PubMed: 1549058]
38. Wu AH, Stanczyk FZ, Seow A, Lee HP, Yu MC. Soy intake and other lifestyle determinants of serum estrogen levels among postmenopausal Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev 2002 Sep;11(9):844–51. [PubMed: 12223428]
39. Bjornerem A, Straume B, Midtby M, Fonnebo V, Sundsfjord J, Svartberg J, et al. Endogenous sex hormones in relation to age, sex, lifestyle factors, and chronic diseases in a general population: the Tromso Study. J Clin Endocrinol Metab 2004 Dec;89(12):6039–47. [PubMed: 15579756]
40. Cauley JA, Gutai JP, Kuller LH, LeDonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol 1989 Jun;129(6):1120–31. [PubMed: 2729251]
41. Madigan MP, Troisi R, Potischman N, Dorgan JF, Brinton LA, Hoover RN. Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). Cancer Causes Control 1998 Mar;9(2):199–207. [PubMed: 9578297]
42. Wu F, Ames R, Evans MC, France JT, Reid IR. Determinants of sex hormone-binding globulin in normal postmenopausal women. Clinical endocrinology 2001 Jan;54(1):81–7. [PubMed: 11167930]
43. Copeland JL, Consitt LA, Tremblay MS. Hormonal responses to endurance and resistance exercise in females aged 19–69 years. J Gerontol A Biol Sci Med Sci 2002 Apr;57(4):B158–65. [PubMed: 11909881]
44. Matthews CE, Fowke JH, Dai Q, Leon Bradlow H, Jin F, Shu XO, et al. Physical activity, body size, and estrogen metabolism in women. Cancer Causes Control 2004 Jun;15(5):473–81. [PubMed: 15286467]
45. van Gils CH, Peeters PH, Schoenmakers MC, Nijmeijer RM, Onland-Moret NC, van der Schouw YT, et al. Physical activity and endogenous sex hormone levels in postmenopausal women: a cross-sectional study in the Prospect-EPIC Cohort. Cancer Epidemiol Biomarkers Prev 2009 Feb; 18(2):377–83. [PubMed: 19190137]
46. Gavaler JS, Love K, Van Thiel D, Farholt S, Gluud C, Monteiro E, et al. An international study of the relationship between alcohol consumption and postmenopausal estradiol levels. Alcohol Alcohol Suppl 1991;1:327–30. [PubMed: 1845556]
47. Gavaler JS, Van Thiel DH. The association between moderate alcoholic beverage consumption and serum estradiol and testosterone levels in normal postmenopausal women: relationship to the literature. Alcohol Clin Exp Res 1992 Feb;16(1):87–92. [PubMed: 1558307]
48. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995 Sep 6;87(17):1297–302. [PubMed: 7658481]
49. Nagata C, Kabuto M, Takatsuka N, Shimizu H. Associations of alcohol, height, and reproductive factors with serum hormone concentrations in postmenopausal Japanese women. Steroid hormones in Japanese postmenopausal women. Breast Cancer Res Treat 1997 Jul;44(3):235–41. [PubMed: 9266103]

50. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst 2001 May 2;93(9): 710–5. [PubMed: 11333294]
51. Onland-Moret NC, Peeters PH, van der Schouw YT, Grobbee DE, van Gils CH. Alcohol and endogenous sex steroid levels in postmenopausal women: a cross-sectional study. J Clin Endocrinol Metab 2005 Mar;90(3):1414–9. [PubMed: 15572431]
52. Rinaldi S, Peeters PH, Bezemer ID, Dossus L, Biessy C, Sacerdote C, et al. Relationship of alcohol intake and sex steroid concentrations in blood in pre- and post-menopausal women: the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control 2006 Oct;17(8):1033–43. [PubMed: 16933054]
53. National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much: a clinician's guide NIH Publication No. -7=3769. U.S. Department of health and human services; 2005.
54. Adami HO, Johansson ED, Vegelius J, Victor A. Serum concentrations of estrone, androstenedione, testosterone and sex-hormone-binding globulin in postmenopausal women with breast cancer and in age-matched controls. Ups J Med Sci 1979;84(3):259–74. [PubMed: 575585]
55. Kirchengast S. Interaction between sex hormone levels and body dimensions in postmenopausal women. Hum Biol 1994 Jun;66(3):481–94. [PubMed: 8026817]
56. Nisker JA, Hammond GL, Davidson BJ, Frumar AM, Takaki NK, Judd HL, et al. Serum sex hormone-binding globulin capacity and the percentage of free estradiol in postmenopausal women with and without endometrial carcinoma. A new biochemical basis for the association between obesity and endometrial carcinoma. American journal of obstetrics and gynecology 1980 Nov 15;138(6):637–42. [PubMed: 7192053]
57. Baglietto L, English DR, Hopper JL, Macinnis RJ, Morris HA, Tilley WD, et al. Circulating steroid hormone concentrations in postmenopausal women in relation to body size and composition. Breast Cancer Res Treat. 2008 May 29;
58. Rinaldi S, Key TJ, Peeters PH, Lahmann PH, Lukanova A, Dossus L, et al. Anthropometric measures, endogenous sex steroids and breast cancer risk in postmenopausal women: a study within the EPIC cohort. Int J Cancer 2006 Jun 1;118(11):2832–9. [PubMed: 16385576]
59. Lapidus L, Lindstedt G, Lundberg PA, Bengtsson C, Gredmark T. Concentrations of sex-hormone binding globulin and corticosteroid binding globulin in serum in relation to cardiovascular risk factors and to 12-year incidence of cardiovascular disease and overall mortality in postmenopausal women. Clin Chem 1986 Jan;32(1 Pt 1):146–52. [PubMed: 3940696]
60. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003 Aug 20;95(16):1218–26. [PubMed: 12928347]
61. Newcomb PA, Klein R, Klein BE, Haffner S, Mares-Perlman J, Cruickshanks KJ, et al. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995 May;6(3):318–21. [PubMed: 7619943]
62. Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas 1995 Feb;21(2):103–13. [PubMed: 7752947]
63. Overlie I, Moen MH, Morkrid L, Skjaeraasen JS, Holte A. The endocrine transition around menopause--a five years prospective study with profiles of gonadotropines, estrogens, androgens and SHBG among healthy women. Acta obstetricia et gynecologica Scandinavica 1999 Aug;78(7): 642–7. [PubMed: 10422913]
64. Lamar CA, Dorgan JF, Longcope C, Stanczyk FZ, Falk RT, Stephenson HE Jr. Serum sex hormones and breast cancer risk factors in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2003 Apr;12(4):380–3. [PubMed: 12692114]
65. Mahabir S, Baer DJ, Johnson LL, Hartman TJ, Dorgan JF, Campbell WS, et al. Usefulness of body mass index as a sufficient adiposity measurement for sex hormone concentration associations in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2006 Dec;15(12):2502–7. [PubMed: 17164376]

66. Castracane VD, Kraemer GR, Ogden BW, Kraemer RR. Interrelationships of serum estradiol, estrone, and estrone sulfate, adiposity, biochemical bone markers, and leptin in post-menopausal women. Maturitas 2006 Jan 20;53(2):217–25. [PubMed: 15913927]

67. Jensen J, Riis BJ, Hummer L, Christiansen C. The effects of age and body composition on circulating serum oestrogens and androstenedione after the menopause. Br J Obstet Gynaecol 1985 Mar;92(3):260–5. [PubMed: 3978055]

68. Judd HL, Lucas WE, Yen SS. Serum 17 beta-estradiol and estrone levels in postmenopausal women with and without endometrial cancer. J Clin Endocrinol Metab 1976 Aug;43(2):272–8. [PubMed: 950362]

69. Judd HL, Davidson BJ, Frumar AM, Shamonki IM, Lagasse LD, Ballon SC. Serum androgens and estrogens in postmenopausal women with and without endometrial cancer. American journal of obstetrics and gynecology 1980 Apr 1;136(7):859–71. [PubMed: 7361834]

70. Lee JS, Ettinger B, Stanczyk FZ, Vittinghoff E, Hanes V, Cauley JA, et al. Comparison of methods to measure low serum estradiol levels in postmenopausal women. J Clin Endocrinol Metab 2006 Oct;91(10):3791–7. [PubMed: 16882749]

71. Rod NH, Hansen AM, Nielsen J, Schnohr P, Gronbaek M. Low-risk factor profile, estrogen levels, and breast cancer risk among postmenopausal women. Int J Cancer 2009 Apr 15;124(8):1935–40. [PubMed: 19123466]

72. 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 Apr;89(4):1555–61. [PubMed: 15070912]

73. Shiraki M, Ito H, Fujimaki H, Higuchi T. Relation between body size and bone mineral density with special reference to sex hormones and calcium regulating hormones in elderly females. Endocrinologia japonica 1991 Aug;38(4):343–9. [PubMed: 1802674]

74. Speroff, L.; Fritz, MA. Clinical gynecologic endocrinology and infertility. 7. Philadelphia: Lippincott Williams & Wilkins; 2005.

75. Utian WH, Gass ML, Pickar JH. Body mass index does not influence response to treatment, nor does body weight change with lower doses of conjugated estrogens and medroxyprogesterone acetate in early postmenopausal women. Menopause (New York, NY) 2004 May–Jun;11(3):306–14.

76. Li Z, Luu-The V, Poisson-Pare D, Ouellet J, Li S, Labrie F, et al. Expression of enzymes involved in synthesis and metabolism of estradiol in human breast as studied by immunocytochemistry and in situ hybridization. Histol Histopathol 2009 Mar;24(3):273–82. [PubMed: 19130396]

77. Bellantoni MF, Harman SM, Cullins VE, Engelhardt SM, Blackman MR. Transdermal estradiol with oral progestin: biological and clinical effects in younger and older postmenopausal women. J Gerontol 1991 Nov;46(6):M216–22. [PubMed: 1834727]

78. Marsh MS, Whitcroft S, Whitehead MI. Paradoxical effects of hormone replacement therapy on breast tenderness in postmenopausal women. Maturitas 1994 Aug;19(2):97–102. [PubMed: 7968650]

Menopause. Author manuscript; available in PMC 2011 May 1.

Table 1

Selected characteristics of participants (N=662)

	Mean	Standard deviation	Median	Number	Frequency
Age, years	57.1	4.2	57.0		
Alpha-tocopherol intake mg/d*	7.2	4.6	6.3		
Cigarette pack-years at baseline among smokers	28.8	18.5	27.0		
Body mass index at baseline (kg/m^2)	25.8	4.4	24.9		
Weight at baseline (kg)	69.0	12.5	66.7		
Years since menopause†	6.6	2.7	6.4		
Alcohol intake over past year (gm/day)*	6.0	10.9	0.8		
Physical activity score over past 12 months‡					
<1.5 (low)				443	67.0%
1.5 to <3 (medium)				215	32.5%
≥3 (high)				4	0.6%
Strenuous exercise§				156	23.6%
Quitting menopausal hormone therapy to join PEPI**				206	31.0%
Recency of hormone use, months ††	6.1	10.5	4.7		
Cigarette smokers at both baseline and 12-month follow-up				78	11.8%
New-onset breast discomfort at 12-months‡‡				149	22.5%
Placebo				15	11.7%
Conjugated equine estrogen alone				16	13.0%
Conjugated equine estrogen + cyclical medroxyprogesterone				43	31.9%
Conjugated equine estrogen + continuous medroxyprogesterone				37	26.4%
Conjugated equine estrogen + cyclical micronized progesterone				38	27.9%

*Assessed at 12-month follow-up. In the subset of women reporting any alcohol use, mean intake was 9.5 g/d, SD was 12.5 g/d, and median intake was 5.4 g/d.

†For women with bilateral oophorectomy, menopause was considered to occur at the time of oophorectomy. There were 158 women for whom the number of years since menopause was not classifiable because they underwent hysterectomy without bilateral oophorectomy.

‡Physical activity score = ([leisure physical activity + home physical activity]/2) − 1. Based on self-assessment questionnaire.

[§] Self-report of engaging in strenuous exercise or hard physical labor (yes vs. no) assessed at 12-month follow-up.

[**] Women using menopausal hormone therapy at study recruitment were allowed to join the trial if they stopped privately-prescribed menopausal hormone therapy at least 2 months before the first screening visit.

[††] Months elapsed since menopausal hormone therapy use in those participants who stopped hormone therapy to join the PEPI trial (N=206).

[##] Women reporting breast sensitivity, tenderness, and/or breast pain at 12-month follow-up and absence of any of these symptoms at baseline.

Table 2

Associations between predictors of breast discomfort and change in log serum estrone level (12-month minus baseline)

	Beta coefficient	P value
Placebo		
Weight (per 10 kg increase)	0.003	0.79
Strenuous exercise	−0.48	0.23
Quit HT for PEPI	0.003	0.93
CEE-only		
Weight (per 10 kg increase)	−0.079	<0.001
Strenuous exercise	−0.023	0.76
Quit HT for PEPI	0.098	0.13
CEE + progestogen		
Weight (per 10 kg increase)	−0.082	<0.0001
Strenuous exercise	0.063	0.06
Quit HT for PEPI	0.016	0.61

Table 3

Predictors of new-onset breast discomfort stratified by assignment to placebo, CEE-only, or CEE + progestogen (N=662)

		Model 1*			Model 2†				Model 3‡		
Treatment group	**N**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**P_{int}§**	**OR**	**95% CI**	**P value**
Placebo											
Weight (kg)	128	1.03	1.00–1.07	0.07	1.04	1.00–1.09	0.04	N/A	1.05	1.00–1.09	0.03
Strenuous exercise (yes vs. no)	128	1.76	0.55–5.62	0.34	1.84	0.56–6.11	0.32	N/A	2.12	0.61–7.34	0.23
Quitting HT for PEPI**	128	1.38	0.44–4.38	0.58	2.30	0.63–8.39	0.21	N/A	1.98	0.51–7.68	0.32
Age	128	0.96	0.86 – 1.08	0.54							
Alpha-tocopherol mg/d	128	1.17	1.05–1.30	0.006							
Cigarette pack-years (among smokers)	20	0.88	0.66–1.17	0.37							
Alcohol intake††	128	0.35	0.10–1.15	0.08							
Cigarette smoking at baseline and 12 months	128	0.38	0.05–3.05	0.36							
Physical activity score medium or high‡‡	128	1.03	0.33–3.22	0.96							
CEE only											
Weight (kg)	123	0.94	0.90–1.00	0.04	0.94	0.90–1.00	0.04	0.003	0.95	0.89–1.00	0.06
Strenuous exercise (yes vs. no)	123	0.55	0.12–2.61	0.45	0.48	0.10–2.34	0.37	0.18	0.50	0.10–2.41	0.38
Quitting HT for PEPI	123	1.22	0.39–3.82	0.73	1.17	0.37–3.77	0.79	0.45	1.11	0.34–3.63	0.86
Age	123	0.95	0.84–1.08	0.44							
Alpha-tocopherol mg/d	123	1.04	0.96–1.13	0.33							
Cigarette pack-years (among smokers)	15	0.97	0.88–1.07	0.55							
Alcohol intake	123	0.53	0.18–1.55	0.24							
Cigarette smoking at baseline and 12 months	123	2.24	0.54–9.21	0.26							
Physical activity score medium or high	123	0.40	0.11–1.50	0.18							
CEE + progestogen											
Weight (kg)	411	0.99	0.98–1.01	0.47	0.99	0.97–1.01	0.21	0.01	0.99	0.97–1.01	0.50
Strenuous exercise (yes vs. no)	411	0.53	0.30–0.91	0.02	0.51	0.29–0.89	0.02	0.06	0.51	0.29–0.88	0.01
Quitting HT for PEPI (yes vs. no)	411	0.64	0.40–1.03	0.06	0.66	0.41–1.06	0.08	0.07	0.62	0.38–1.01	0.05
Age	411	1.01	0.96–1.07	0.66							

	Model 1*			Model 2†				Model 3‡		
Treatment group	**N**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**P_{int}§**	**OR**	**95% CI**	**P value**
Alpha-tocopherol mg/d	411	0.96	0.91–1.01	0.13							
Cigarette pack-years (among smokers)	51	1.03	0.99–1.07	0.10							
Alcohol intake	411	1.06	0.69–1.62	0.80							
Cigarette smoking at baseline and 12 months	411	0.76	0.37–1.55	0.45							
Physical activity score medium or high	411	0.65	0.40–1.04	0.07							

*Unadjusted odds ratio

†Multivariable logistic regression models using backwards selection, adjusting for weight, strenuous exercise, quit hormone therapy to join PEPI.

‡Multivariable logistic regression models adjusting for delta log estrone (12-months minus baseline) in addition to the covariates in Model 2.

§P value for interaction between main effect (weight, strenuous exercise, or quitting hormone therapy for PEPI) and treatment group (CEE only or CEE+ progestogen versus placebo reference group.

**Participants were required to cease hormone therapy for 2 months prior to the first screening visit.

††> median vs. ≤ median

‡‡Assessed at 12-month follow-up visit. Physical activity score = ([leisure physical activity + home physical activity]/2) −1. Low score <1.5, medium score 1.5 to >3, high score ≥ 3. Reference group is low score.

Appendix

Physical activity questionnaire items[1]

For *a* through *c* below, use the following as a guide to describe your activity level	
1. physical inactivity: The inactive person spends most waking hours sitting or standing quietly. Activities include working at a desk, reading, watching television, or other quiet pursuits. Usually does not walk more than a few minutes.	
2. light physical activity: This person usually walks more than 10 minutes at a time each day, leisurely rides a bicycle, fishes, bowls, golfs, or engages in light carpentry, light gardening, light industrial work, teaching, or light housework on a regular basis.	
3. moderate physical activity: This person participates in such activities as brisk walking, recreational or doubles tennis, or swimming; or works in such occupations as mail carrier, telephone repair, light building, and construction; or engages in housework and home repairs or moderate gardening.	
4. heavy physical activity: This person performs vigorous activity on a regular basis, including jogging, singles tennis, paddleball, or high-intensity aerobics; or engages in heavy activities, such as carrying heavy weight (20 lb or more), strenuous farm work, or strenuous gardening.	
Work physical activity	
Question a.	"Thinking about the things you usually did *at work* during the last 12 months, how would you describe the kind of physical activity you performed?
Response choices	Inactive, light, moderate, heavy, not applicable
Home physical activity	
Question b.	"Thinking about the things you usually did *in your home* during the last 12 months, how would you describe the kind of physical activity you performed?
Response choices	Inactive, light, moderate, heavy
Leisure physical activity	
Question c.	"Thinking about the things you usually did *in your leisure time* during the last 12 months, how would you describe the kind of physical activity you performed?
Response choices	Inactive, light, moderate, heavy
Strenuous activity	
	"Do you regularly engage in strenuous exercise or hard physical labor? (yes or no)".

[1] Physical activity score = ([average of leisure score and home score] − 1)