New-Onset Breast Tenderness After Initiation of Estrogen Plus Progestin Therapy and Breast Cancer Risk

Carolyn J. Crandall, MD, MS; Aaron K. Aragaki, MS; Rowan T. Chlebowski, MD, PhD; Anne McTiernan, MD, PhD; Garnet Anderson, PhD; Susan L. Hendrix, DO; Barbara B. Cochrane, PhD, RN; Lewis H. Kuller, MD, DrPH; Jane A. Cauley, DrPH

Background: Estrogen plus progestin therapy increases breast cancer incidence and breast tenderness. Whether breast tenderness during estrogen plus progestin therapy is associated with breast cancer risk is uncertain.

Methods: We analyzed data from the Women’s Health Initiative Estrogen + Progestin Trial, which randomized postmenopausal women with an intact uterus to receive daily conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg (n=8506), or placebo (n=8102). At baseline and annually, participants underwent mammography and clinical breast examination. Self-reported breast tenderness was assessed at baseline and at 12 months. The incidence of invasive breast cancer was confirmed by medical record review (mean follow-up of 5.6 years).

Results: Of women without baseline breast tenderness (n=14,538), significantly more assigned to receive conjugated equine estrogens plus medroxyprogesterone vs placebo experienced new-onset breast tenderness after 12 months (36.1% vs 11.8%, \( P < .001 \)). Of women in the conjugated equine estrogens plus medroxyprogesterone group, breast cancer risk was significantly higher in those with new-onset breast tenderness compared with those without (hazard ratio, 1.48; 95% confidence interval, 1.08-2.03; \( P = .02 \)). In the placebo group, breast cancer risk was not significantly associated with new-onset breast tenderness (\( P = .97 \)).

Conclusions: New-onset breast tenderness during conjugated equine estrogens plus medroxyprogesterone therapy was associated with increased breast cancer risk. The sensitivity and specificity of the association between breast tenderness and breast cancer were similar in magnitude to those of the Gail model.

Trial Registration: clinicaltrials.gov Identifier: NCT00000611

Arch Intern Med. 2009;169(18):1684-1691
aged 50 to 79 years without a previous hysterectomy were recruited at 40 clinical centers largely via mass mailings between October 29, 1993, and December 31, 1998. The WHI used the following criteria to define postmenopausal: no vaginal bleeding for 6 months (12 months for 50- to 54-year olds), hysterectomy, or past use of postmenopausal hormone therapy. Women were required to cease any menopausal hormone therapy for 3 months before randomization. Before enrollment, all the women underwent clinical breast examination and mammography; abnormal findings required clearance before study enrollment. Interested WHI E + P Trial participants were also enrolled in the WHI Dietary Modification component that randomly assigned 48 835 postmenopausal women to a low-fat or a usual diet. All the participants provided written informed consent. The human subjects committee at each institution approved the study.

In the WHI E + P Trial, women were randomly assigned to receive a daily tablet containing conjugated equine estrogens, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (n=8506), or an identical-appearing placebo tablet (n=8102). Local dispensation of study medications was masked via medication bottles with unique bar codes. The following conditions required discontinuation of study medication use: breast cancer, endometrial abnormalities (hyperplasia not responsive to therapy, atypia, or cancer), deep venous thrombosis, pulmonary embolism, malignant melanoma, meningioma, a triglyceride level greater than 1000 mg/dL (to convert to millimoles per liter, multiply by 0.0113), institution of anticoagulant medication use for thrombophlebitis, or the use of nonstudy hormones (estrogen, progestin, androgen, tamoxifen, or raloxifene), although short-term (<3 months) vaginal estrogen use was allowed.

Safety monitoring and assessment of adherence to therapy occurred 6 weeks after initiation of therapy along with assessment of clinical outcomes at 6-month intervals. Annual mammography and clinical breast examination were required for continued administration of study medication. Participants were clinically monitored regardless of medication adherence. After mean follow-up of 5.6 years, the WHI Data and Safety Monitoring Board recommended stopping the WHI E + P Trial because the incidence of breast cancer exceeded a predesignated stopping boundary, and a global index supported the finding that overall risks exceeded overall benefits.

ASSESSMENT OF INVASIVE BREAST CANCER

Breast cancer outcomes were self-reported every 6 months using standardized questionnaires; breast cancer diagnoses were confirmed by local physician adjudicators who reviewed medical records and pathology reports. Subsequently, all breast cancer diagnoses were centrally adjudicated by trained coders using standards from the Surveillance, Epidemiology, and End Results system. Community physicians evaluated and treated breast abnormalities. When the study intervention ended, 359 invasive breast cancers were confirmed by means of central adjudication.

ASSESSMENT OF BREAST TENDERNESS

Breast tenderness was self-reported at baseline and at the 12-month follow-up visit via a symptom inventory based on questionnaire items related to menopausal hormone use and aging from national surveys and clinical trials. Participants rated the degree of bother from breast tenderness during the past 4 weeks using a 4-point Likert-type scale: symptom did not occur, symptom was mild (did not interfere with usual activities), symptom was moderate (interfered somewhat with usual activities), or symptom was severe (so bothersome that usual activities could not be pursued). We considered participants to have NOBT if they reported the absence of breast tenderness at baseline and the presence of breast tenderness (mild, moderate, or severe) at the first annual follow-up visit.

OTHER QUESTIONNAIRE MEASUREMENTS AND ANTHROPOMETRIC MEASURES

At baseline, breast cancer risk factors were assessed by using standardized self-report questionnaires. Participants were asked about medical and reproductive history, family medical history, cigarette smoking, alcohol use, race/ethnicity, education status, income, and physical activity. Energy expenditure from recreational physical activity was calculated from questionnaire items regarding physical activity frequency and duration. Menopausal hormone use before trial intervention was ascertained at baseline using an interviewer-administered questionnaire. Gail breast cancer risk score was calculated based on risk factors collected at baseline.

STATISTICAL ANALYSES

All primary analyses were based on the intention-to-treat principle. Baseline characteristics were compared in women with and without baseline breast tenderness using χ² tests of association. Statistical significance tests for baseline characteristics by NOBT were adjusted for age and treatment assignment. Relative risk (RR) of breast tenderness at the first annual follow-up visit was obtained from a generalized linear model using a log-link function. We assessed whether the occurrence of breast tenderness at annual follow-up differed according to the presence of breast tenderness at baseline. To do this, we used a generalized linear model with randomization group (conjugated equine estrogens plus medroxyprogesterone vs placebo) and baseline breast tenderness (yes vs no) as main effects, risk of breast tenderness at the first annual follow-up visit (yes vs no) as the outcome, and randomization group × baseline breast tenderness as the interaction term.

To examine the association between NOBT and invasive breast cancer risk in multivariate Cox models, we defined a time-dependent binary covariate X(t) equal to 0 for all women until the first annual follow-up visit and equal to 1 after the first annual follow-up visit if a woman reported breast tenderness at the first annual follow-up visit and had not reported breast tenderness at baseline. Survival time, t, was defined as the number of days after randomization to the first diagnosis of breast cancer and was censored at the time of a woman’s last documented follow-up contact or death. To allow better control for age, in addition to making a linear adjustment for age, we allowed the baseline hazard functions to vary by age group. Thus, each model allowed the baseline hazard function to vary by age group (50-54, 55-59, 60-69, or 70-79 years old) and WHI Dietary Modification trial randomization assignment and was adjusted for age (linear), ethnicity (white, black, American Indian, Asian Pacific Islander, or unknown), alcohol consumption (nondrinker, ≤1 drink daily, or >1 drink daily), cigarette smoking (never, past, or current), body mass index (linear and quartiles), energy expenditure from physical activity (metabolic equivalent hours per week, including walking and mild, moderate, and strenuous physical activity, linear and quartiles), parity (never pregnant, 1, 2, or ≥3), mother’s age at first birth (never pregnant or ≤20, 20-29, ≥30 years), duration of breastfeeding (never, ≤1 year, or >1 year), time since menopause (<5, 5-10, 11-15, or >15 years), Gail model breast cancer risk score (linear and quartiles), menopausal hormone


©2009 American Medical Association. All rights reserved.
therapy before trial participation (yes or no), and baseline breast tenderness. Potential confounders were chosen based on biological plausibility and findings from published studies. Multiple imputation was used to avoid deletion of observations with missing covariate values. Hazard ratio (HR) estimates are expressed as RR. The SAS PROC MI (SAS Institute Inc, Cary, North Carolina) was used to generate a set of 5 plausible values for the missing covariate data that we assumed were missing at random, and PROC MIANALYZE (SAS Institute Inc) was used to combine parameter estimates from the Cox models for valid statistical inference.

To assess the extent to which NOBT was a marker of the effect of conjugated equine estrogens plus medroxyprogesterone on the risk of invasive breast cancer, we compared the estimates of the conjugated equine estrogens plus medroxyprogesterone HR in models with and without NOBT. Using the method of Li et al, we estimated the proportion of the effect of conjugated equine estrogens plus medroxyprogesterone on breast cancer risk that was explained by NOBT. Using the incidence estimates of NOBT and the parameter estimates from a Cox proportional hazards model, this formula was used to calculate the proportion of the treatment effect explained by the surrogate marker, NOBT, divided by the overall effect of treatment. We calculated the sensitivity (true-positive rate) and specificity (1 minus false-positive rate) of NOBT as a predictor of breast cancer risk in women assigned to receive conjugated equine estrogens plus medroxyprogesterone. All statistical tests were 2-sided. \( P < .05 \) was considered statistically significant for tests of main effects. All statistical analyses were performed using a software program (SAS/STAT 9.1; SAS Institute Inc).

For the 16 608 women participating in this trial, demographics and breast cancer risk factors (including previous hormone exposure, family history, dietary intake, education, ethnicity, and Gail risk score) were similar in the hormone therapy and placebo groups. Women who reported baseline breast tenderness tended to be younger, heavier, black or Hispanic, lower alcohol consumers, less physically active, younger at first child's birth, more distant from menopause transition, at lower predicted breast cancer risk (Gail model), and more likely to have used menopausal hormone therapy, and Gail breast cancer risk score. Data were too sparse to allow for stratification of the breast tenderness–breast cancer association according severity (mild, moderate, or severe) of breast tenderness.

We used the criteria of Prentice to further explore the breast tenderness–breast cancer association. Before inclusion of randomization assignment, women with NOBT had a 37% higher risk of invasive breast cancer than did women without NOBT (HR, 1.37; 95% CI, 1.05-1.77; \( P = .02 \)) (data not shown). When treatment assignment and NOBT were included in the same Cox regression model, the magnitude of the increased risk of breast cancer in women with NOBT was modestly lowered (HR, 1.29; 95% CI, 0.99-1.70) (data not shown). Likewise, the magnitude of the HR associated with assignment to receive conjugated equine estrogens plus medroxyprogesterone was lowered and lost statistical significance after adjustment for NOBT (HR, 1.25; \( P = .04 \) before adjustment; and HR, 1.19; \( P = .11 \) after adjustment for NOBT) (data not shown).

Of women assigned to conjugated equine estrogens plus medroxyprogesterone therapy, NOBT had a sensitivity of 41%, a specificity of 64%, and a positive predictive value of 2.7% in predicting invasive breast cancer risk during the intervention period (mean, 5.6 years). The proportion of breast cancer risk conferred by conjugated equine estrogens plus medroxyprogesterone use that was...
Association for categorical variables and 2-sample tests for continuous variables.

Of the 16,608 WHI E + P Trial participants, information regarding baseline and year 1 breast tenderness was available for 15,177. Thus, this table excludes participants for whom information regarding breast tenderness was missing from the baseline visit (n=95), the year 1 visit (n=1,303), and both (n=33).

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CEE + MPA, daily conjugated equine estrogens (0.625 mg) plus medroxyprogesterone acetate (2.5 mg); MET, metabolic equivalent; WHI E, Women’s Health Initiative Estrogen Plus Progestin.

Compares baseline characteristics of participants without vs with baseline breast tenderness (ie, columns 2 and 3 vs columns 4 and 5) based on the χ² test of association for categorical variables and 2-sample tests for continuous variables.

Compares baseline characteristics of participants without vs with new-onset breast tenderness (ie, column 2 vs column 3) adjusted for age and treatment assignment. Tests of association for age and treatment assignment are unadjusted.

One thousand forty-five of the 16,608 WHI E + P Trial participants (6.29%) were current menopausal hormone therapy users at baseline, ie, they underwent a hormone therapy “washout period” to participate in the WHI E + P Trial.
Participants With NOBT

In participants in a large randomized controlled trial of menopausal hormone therapy, NOBT was a marker of future breast cancer risk. Of women assigned to the conjugated equine estrogens plus medroxyprogesterone group who were free of breast tenderness at baseline, those who reported NOBT at the first annual follow-up visit had a 48% higher risk of invasive breast cancer than did those who did not experience NOBT at the first annual follow-up visit. NOBT explained 24% of the breast cancer risk conferred by conjugated equine estrogens plus medroxyprogesterone therapy.

To our knowledge, no previous published studies have addressed whether there is an association between conjugated equine estrogens plus medroxyprogesterone–induced NOBT and breast cancer risk. However, an association between NOBT and breast cancer has biological plausibility. Three previous studies found that conjugated equine estrogens plus medroxyprogesterone–induced breast tenderness is associated with increased mammographic density, a risk factor for breast cancer that indirectly measures breast parenchymal tissue proliferation. Studies have linked estrogen plus progesterone therapy with increased breast cell proliferation. Thus, breast discomfort may be a clinical manifestation of increased proliferation that is manifest radiographically as increased breast density. However, in one study, mammographic density did not mediate the association between combination hormone therapy and breast cancer. The present study design does not permit us to directly test whether combined hormone therapy–induced breast tenderness represents increased breast cell proliferation. Because increases in the serum levels of estrone and estrone sulfate during conjugated equine estrogens plus medroxyprogesterone therapy are positively associated with increases in mammographic density, it is possible that conjugated equine estrogens plus medroxyprogesterone–induced increases in serum estrone or estrone sulfate levels could result in breast tenderness and increased breast cancer risk.

The emergence of endocrine symptoms in response to hormone-based interventions has recently been linked to breast cancer outcome in a large adjuvant breast cancer trial. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, patients with breast cancer who reported an increase in hot flashes and arthralgia symptoms after 3 months of therapy with tamoxifen or aromatase inhibitor had nearly half as many breast cancer recurrences compared with women who did not report such symptoms. Thus, systematic responses, such as the

**COMMENT**

explained by NOBT was 24% (95% CI, 6%-100%), as assessed using the method of Li et al.

---

**Table 2. Prevalence and Relative Risk (RR) of Breast Tenderness at the First Annual Follow-up Visit by Randomization Assignment in the WHI E + P Trial**

<table>
<thead>
<tr>
<th>Group</th>
<th>Women, No./Total No. (%)</th>
<th>CEE + MPAb</th>
<th>Placebo</th>
<th>RR (95% CI)c</th>
<th>P Valued</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3086/7808 (39.5)</td>
<td>1230/7646 (16.5)</td>
<td>2.40 (2.26-2.54)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>No breast tenderness at baseline</td>
<td>2477/6868 (36.1)</td>
<td>770/6555 (11.8)</td>
<td>3.07 (2.85-3.30)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Breast tenderness at baseline</td>
<td>599/695 (65.8)</td>
<td>448/859 (52.2)</td>
<td>1.26 (1.17-1.37)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CEE + MPA, conjugated equine estrogens (0.625 mg) plus medroxyprogesterone acetate (2.5 mg); CI, confidence interval; WHI E + P, Women’s Health Initiative Estrogen Plus Progestin.

a Includes 95 participants missing baseline breast tenderness data only, 1303 missing year 1 data, and 33 missing both baseline and year 1 data. N = 16,608.
b Percentage reporting breast tenderness at 12-month follow-up.
c The RR of breast tenderness at 12-month follow-up from a generalized linear model.
d P values for the main effect of treatment (boldface) and for the interaction between treatment assignment and baseline breast tenderness.

---

**Table 3. Annualized Rates and Multivariable-Adjusted Risk of Invasive Breast Cancer Owing to New-Onset Breast Tenderness at 12-Month Follow-up in the WHI E + P Trial**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Participants With NOBT</th>
<th>Participants With No NOBT</th>
<th>Hazard Ratio (95% CI)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>83 (3231)</td>
<td>209 (10 149)</td>
<td>1.29 (0.99-1.70)</td>
<td>.06</td>
</tr>
<tr>
<td>Placebo</td>
<td>15 (760)</td>
<td>111 (5769)</td>
<td>0.99 (0.59-1.66)</td>
<td>.97</td>
</tr>
<tr>
<td>CEE + MPA</td>
<td>68 (2471)</td>
<td>98 (4380)</td>
<td>1.48 (1.08-2.03)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CEE + MPA, conjugated equine estrogens (0.625 mg) plus medroxyprogesterone acetate (2.5 mg); CI, confidence interval; NOBT, new-onset breast tenderness; WHI E + P, Women’s Health Initiative Estrogen Plus Progestin.

a Annualized rates (unadjusted).
b Hazard ratios are from Cox proportional hazards models comparing risk of breast cancer in women with vs without NOBT. Cox proportional hazards models are adjusted for CEE + MPA randomization assignment, age, ethnicity, alcohol consumption, smoking, body mass index (linear and quartiles), physical activity (linear and quartiles), parity, mother’s age at first birth, breastfeeding, age at menopause, Gail model breast cancer risk score (linear and quartiles), and menopausal hormone therapy before trial participation. This table displays hazard ratios for women without baseline breast tenderness.
breast tenderness described in the present study, may represent integrated functions of biological interaction among the intervention, breast cancer, and the postmenopausal woman’s host response.

In the present study, the prevalence of NOBT in women assigned to the conjugated equine estrogens plus medroxyprogesterone group was 36%. Most randomized trials35-40 of conjugated equine estrogens plus medroxyprogesterone did not report the prevalence of NOBT at 1 year. The exception is the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, which asked participants at the first annual follow-up visit, "During the past week, including today, did any of these symptoms bother you or interfere with your life: breast sensitivity/tenderness (yes or no) and/or painful breasts (yes or no)"?41 In the PEPI trial, in women assigned to the conjugated equine estrogens plus medroxyprogesterone treatment arm who reported the absence of baseline breast symptoms, the prevalence of breast symptoms was 23% at the first annual follow-up visit.3 When we exclude WHI participants with mild breast symptoms was 23% at the first annual follow-up visit.3 When we exclude WHI participants with mild breast symptoms, more closely matching the PEPI trial assessment method, the prevalence of hormone therapy–associated NOBT is almost identical in the 2 trials (23% vs 23%). Thus, it is likely that heterogeneity regarding how questionnaires assess breast symptoms results in different prevalence estimates for hormone therapy–associated breast symptoms across studies.

Few characteristics explained who would develop NOBT. Although several characteristics were statistically significantly associated with NOBT (eg, ethnicity, cigarette smoking, and body mass index), the magnitude of their associations with breast tenderness was small. Risk factors for NOBT require further elucidation.

The sensitivity and specificity of NOBT for predicting invasive breast cancer risk in conjugated equine estrogens plus medroxyprogesterone users were similar to those of the Gail model. In the present study, based on mean follow-up of 5.6 years, NOBT had a sensitivity of 41%, a specificity of 64%, and a positive predictive value of 2.7% for predicting invasive breast cancer risk in women assigned to receive conjugated equine estrogens plus medroxyprogesterone. Using a 5-year risk of invasive breast cancer threshold of 1.67%, the Gail model had a sensitivity of 44% and a specificity of 66%.41 In another study,42 positive mammography findings had a positive predictive value of 6.6% for women aged 50 to 59 years and of 7.8% for women aged 60 to 69 years.

The present findings have potential clinical implications. The WHI E + P Trial has previously demonstrated that combined hormone therapy increases invasive breast cancer risk,2,43 mammographic breast density,44 and the frequency of mammograms with abnormalities that less reliably detect cancer.45 We report that an increase in breast tenderness, easily detected by physicians or patients, identifies a population at particular risk for breast cancer. These findings should be considered by women who experience NOBT while receiving combined hormone therapy and by their prescribing physicians to inform decisions regarding continued combined hormone therapy.

This study has limitations. The study questionnaire assessed breast tenderness annually. Thus, we may have underestimated breast tenderness, although this method of ascertainment probably resembles reporting of breast tenderness in a clinical setting. Also, although the rates of treatment discontinuation in the conjugated equine estrogens plus medroxyprogesterone treatment arm (42%) and of crossover from placebo to active therapy (11%) were relatively high,1 we believe that they tend to decrease the observed association between breast tenderness and breast cancer. Although women who developed NOBT had higher baseline Gail model breast cancer risk scores, the association between NOBT and future breast cancer risk persisted after adjustment for Gail risk score. Finally, the present results do not apply to other types or schedules of estrogen or progestogen therapy.

The strengths of this study include the large number of participants, the use of placebo controls, the comprehensive assessment of breast cancer risk factors, the rigorous assessment of breast cancer outcomes during several years of follow-up, the blinding of participants and investigators to treatment assignment, the requirement for annual mammography and clinical breast examination, and the serial prospective blinded assessment of breast tenderness in the placebo and treatment groups. To our knowledge, this study was based on the largest and longest randomized controlled trial of combination menopausal hormone therapy ever performed.

In conclusion, NOBT during conjugated equine estrogens plus medroxyprogesterone therapy may be a
Acquisition of data: Crandall, Aragaki, Chlebowski, McTiernan, Anderson, and Kuller.
Analysis and interpretation of data:

Correspondence: Carolyn J. Crandall, MD, MS, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles (Dr Crandall); Women's Health Initiative Clinical Coordinating Center (Mr Arakagi) and Division of Public Health Services (Drs McTiernan and Anderson), Fred Hutchinson Cancer Research Center, Seattle, Washington; Department of Hematology and Oncology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Dr Chlebowski); Department of Obstetrics and Gynecology, Wayne State University School of Medicine/Hutzel Women's Hospital, Detroit, Michigan (Dr Hendrix); Family and Child Nursing, University of Washington School of Nursing, Seattle (Dr Cochrane); and Department of Epidemiology, University of Pittsburgh, Pennsylvania (Drs Kuller and Cauley).

Accepted for Publication: June 12, 2009.

Author Affiliations: Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles (Dr Crandall); Women's Health Initiative Clinical Coordinating Center (Mr Arakagi) and Division of Public Health Services (Drs McTiernan and Anderson), Fred Hutchinson Cancer Research Center, Seattle, Washington; Department of Obstetrics and Gynecology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Dr Chlebowski); Department of Obstetrics and Gynecology, Wayne State University School of Medicine/Hutzel Women's Hospital, Detroit, Michigan (Dr Hendrix); Family and Child Nursing, University of Washington School of Nursing, Seattle (Dr Cochrane); and Department of Epidemiology, University of Pittsburgh, Pennsylvania (Drs Kuller and Cauley).

Correspondence: Carolyn J. Crandall, MD, MS, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, UCLA Medicine/GIM, 911 Buxton Ave, First Floor, Los Angeles, CA 90024 (ccrandall@mednet.ucla.edu).

Author Contributions: Mr Arakagi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Crandall, Hendrix, Cochran, and Kuller. Acquisition of data: Hendrix, Cochran, and Kuller. Analysis and interpretation of data: Crandall, Aragaki, Chlebowski, McTiernan, Anderson, Hendrix, and Cauley. Drafting of the manuscript: Crandall and Aragaki. Critical revision of the manuscript for important intellectual content: Crandall, Aragaki, Chlebowski, McTiernan, Anderson, Hendrix, Cauley, and Kuller. Statistical analysis: Aragaki and Anderson. Obtained funding: Chlebowski, Hendrix, and Kuller. Administrative, technical, and material support: Crandall, Hendrix, Cochrane, Kuller, and Cauley. Study supervision: Crandall, Chlebowski, McTiernan, Hendrix, and Cochrane.

Financial Disclosure: Dr Chlebowski receives consulting fees from or is on the paid advisory board of AstraZeneca, Eli Lilly and Company, Novartis International AG, Wyeth Pharmaceuticals, and Pfizer Inc and has received lecture fees from AstraZeneca and Novartis International AG.

Funding/Support: The WHI is funded by contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221 from the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. Dr Crandall's work was supported by research grant SK12 AG01004-08 from the National Institute on Aging, National Institutes of Health, and by the Tarlow-Eissner-Moss Research Endowment of the Iris Cantor–UCLA Women's Health Center. The active study drug and placebo were supplied by Wyeth-Ayerst Research Laboratories.

WHI Investigators: Program Office: National Heart, Lung, and Blood Institute, Bethesda, Maryland: Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller. Clinical Coordinating Centers: Fred Hutchinson Cancer Research Center: Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, and Anne McTiernan; Wake Forest University School of Medicine, Winston-Salem, North Carolina: Sally Shumaker; Medical Research Labs, Highland Heights, Kentucky: Evan Stein; University of California at San Francisco: Steven Cummings. Clinical Centers: Albert Einstein College of Medicine, Bronx, New York: Sylvia Wassertheil-Smoller; Baylor College of Medicine, Houston, Texas: Aleksandar Rajkovic; Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts: JoAnn Manson; Brown University, Providence, Rhode Island: Ann Louise R. Assaf; Emory University, Atlanta, Georgia: Lawrence Phillips; Fred Hutchinson Cancer Research Center: Shirley Beresford; George Washington University Medical Center, Washington, DC: Judith Hsia; Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California: Rowan T. Chlebowski; Kaiser Permanente Center for Health Research, Portland, Oregon: Evelyn Whitlock; Kaiser Permanente Division of Research, Oakland, California: Bette Caan; Medical College of Wisconsin, Milwaukee: Jane Morley Kitchin; MedStar Research Institute/Howard University, Washington, DC: Barbara V. Howard; Northwestern University, Chicago/Evanston, Illinois: Linda Van Horn; Rush Medical Center, Chicago: Henry Black; Stanford Prevention Research Center, Stanford, California: Marcia L. Stefanick; State University of New York at Stony Brook, Stony Brook: Dorothy Lane; The Ohio State University, Columbus: Rebecca Jackson; University of Alabama at Birmingham, Birmingham: Cora E. Lewis; University of Arizona, Tucson/Phoenix: Tamsen Bassford; University at Buffalo, Buffalo, New York: Jean Wactawski-Wende; University of California at Davis, Sacramento: John Robbins; University of California at Irvine: F. Allan Hubbell; University of California at Los Angeles: Howard Judd; University of California at San Diego, La Jolla/Chula Vista: Robert D. Langer; University of Cincinnati, Ohio: Margery Gass; University of Florida, Gainesville/Jacksonville: Marian Limacher; University of Hawaii, Honolulu: David Curb; The University of Iowa, Iowa City/Davenport: Robert Wallace; University of Massachusetts/Fallon Clinic, Worcester: Judith Ockene; University of Medicine and Dentistry of New Jersey, Newark: Norman Lasser; University of Miami, Florida: Mary Jo O'Sullivan; University of Minnesota, Minneapolis: Karen Margolis; University of Nevada, Reno: Robert Brunner; University of North Carolina, Chapel Hill: Gerardo Heiss; University of Pittsburgh: Lewis Kuller; University of Tennessee, Memphis: Karen C. Johnson; The University of Texas Health Science Center, San Antonio: Robert Brzyski; University of Wisconsin, Madison: Gloria S. Sarto; Wake Forest University School of Medicine: Denise Bonds; and Wayne State University School of Medicine/Hutzel Women's Hospital: Susan L. Hendrix.

(RePRINTED) ARCH INTERN MED/VOL 169 (NO. 18), OCT 12, 2009 WWW.ARCHINTERNMED.COM

©2009 American Medical Association. All rights reserved.
Additional Contributions: We thank the women who generously participated in the WHI E + P Trial and the WHI investigators and staff for their dedicated efforts.

REFERENCES


