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Breast Tenderness and Breast Cancer Risk in the Estrogen plus Progestin and Estrogen-Alone Women's Health Initiative Clinical Trials

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Abstract

Background—The associations between breast tenderness during use of conjugated equine estrogen (CEE) therapy with or without medroxyprogesterone (MPA) therapy and subsequent breast cancer risk are unknown.

Methods—We analyzed data from the Women's Health Initiative Estrogen plus Progestin (N = 16,608, 5.6 years intervention) and Estrogen-Alone (N = 10,739, 6.8 years intervention) clinical trials until trial close-out (Spring 2005). At baseline and annually, participants underwent mammography and clinical breast exam. Self-reported breast tenderness was assessed at baseline and 12 months. Invasive breast cancer was confirmed by medical record review.

Results—The risk of new-onset breast tenderness after 12 months was significantly higher among women assigned to active therapy than placebo (CEE alone vs. placebo risk ratio [RR] 2.15, 95% confidence interval [CI] 1.97–2.35; CEE + MPA vs. placebo RR 3.07, 95% CI 2.85–3.30). CEE + MPA doubled the risk of invasive breast cancer among women with baseline breast tenderness (hazard ratio [HR] 2.16, 95% CI 1.29–3.74), but had a smaller effect among women without baseline breast tenderness (HR 1.17; 95%CI 0.97–1.41). New-onset breast tenderness was associated with a higher risk of breast cancer among women assigned to CEE + MPA (HR 1.33, 95% CI 1.02–1.72, P=0.03), but not among women assigned to CEE alone (HR 0.98, 95% CI 0.62–1.53).

Conclusions—New-onset breast tenderness during use of CEE + MPA was associated with increased subsequent breast cancer risk. The association of CEE + MPA therapy with increased breast cancer risk was especially pronounced among women with baseline breast tenderness.

Keywords

breast tenderness; breast cancer; menopausal hormone therapy; conjugated equine estrogens; medroxyprogesterone acetate

Introduction

Breast tenderness is a common adverse effect of menopausal hormone therapy. Although studies vary in timing and methods of assessment of breast tenderness during menopausal hormone therapy, the incidence of breast tenderness in double-blind randomized controlled trials ranges from approximately 8% to 15% after initiation of conjugated equine estrogen therapy (CEE) alone [1,2], and from 9%–16% after initiation of CEE combined with medroxyprogesterone acetate (MPA) [3,2,4–6]. Little is known about the predictors of new-onset breast tenderness during use of CEE-containing therapy [7]. Traditional clinical teaching considers menopausal hormone therapy-associated breast tenderness to be an annoying adverse effect that may resolve with cessation[8] or alteration of menopausal hormone therapy dose or preparation[9,10], but little attention has been given to the biology underlying, or the potential clinical relevance of, menopausal hormone therapy-associated breast tenderness.

New-onset breast tenderness during CEE + MPA therapy may be a clinical correlate of increasing mammographic density, a strong breast cancer risk factor [11,12]. In a prior

study, women reporting new-onset breast tenderness during therapy 12 months after initiation of CEE and MPA had greater increases in mammographic density compared to women without new-onset breast tenderness [2].

Previously, using data from the Women's Health Initiative (WHI) Estrogen + Progestin Trial, we published results linking the new-onset of breast tenderness during CEE + MPA therapy with an increased risk of breast cancer over 5.6 years of follow-up [13]. We now report the results of our study regarding new-onset breast tenderness and subsequent breast cancer risk among women receiving CEE alone in the WHI Estrogen Alone Trial. The association between new-onset breast tenderness and breast cancer risk during therapy with CEE alone has not previously been examined. Because CEE + MPA and CEE alone have differential effects on breast cancer risk [14–17], and on mammographic density [18–20], it is possible that new-onset breast tenderness has differential associations with breast cancer risk among women taking CEE alone compared to women taking CEE + MPA.

The goals of this study were 1. To determine the association between new-onset breast tenderness and breast cancer risk among women taking CEE alone, and 2. To determine whether the association between new-onset breast tenderness and increased breast cancer risk in the CEE + MPA Trial persists over extended follow-up (until trial close-out with 180 additional breast cancer cases).

Methods

Design of the WHI Estrogen-Alone and Estrogen + Progestin Clinical Trials

Previous publications describe the eligibility criteria and recruitment methods [21,15,16]. For each of the two trials, postmenopausal women aged 50 to 79 years were recruited at 40 clinical centers between 1993 and 1998. The WHI Estrogen + Progestin Trial recruited 16,608 postmenopausal women without a previous hysterectomy [14]. The WHI Estrogen-Alone Trial recruited 10,739 postmenopausal women with previous hysterectomy [22]. Participation required cessation of any menopausal hormone therapy for 3 months before randomization [22,14]. Before enrollment, all participants underwent clinical breast examination and mammograms; abnormal findings required clearance prior to study enrollment [22,14]. Each institution obtained human subjects committee approval. Each participant provided written informed consent. The trials were registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier NCT00000611.

In the Estrogen + Progestin Trial, participants were randomly assigned to receive conjugated equine estrogens 0.625mg + medroxyprogesterone acetate 2.5 mg daily (n = 8506) or placebo (n = 8102). In the Estrogen-Alone Trial, participants were randomly assigned to receive conjugated equine estrogens 0.625 mg daily (n = 5310) or placebo (n = 5429).

Clinical outcomes were assessed at 6-month intervals. Participants were required to undergo annual mammography and clinical breast examination for continued administration of study medication. Participants were clinically monitored regardless of medication adherence. The Estrogen + Progestin Trial intervention was stopped after a mean follow-up of 5.6 years because the incidence of breast cancer exceeded a predesignated stopping boundary, and a global index supported the finding that overall risks exceeded overall benefits [16]. The Estrogen-Alone Trial intervention was stopped after a mean follow-up of 6.8 years due to increased risk of stroke and low likelihood of cardioprotection [15]. Following cessation of intervention, annual mammography and participant follow-up continued on the same schedule until trial close-out (Spring 2005).

Assessment of invasive breast cancer

Breast cancer diagnoses were ascertained every 6 months by questionnaire, confirmed by local physician adjudication of medical records and pathology reports, and centrally adjudicated by trained coders using standards from the Surveillance, Epidemiology, and End Results system [14,23]. When study intervention ended (6.8 years for the Estrogen-Alone Trial, 5.2 years for the Estrogen + Progestin Trial), the numbers of invasive breast cancers centrally confirmed were 360 (206 among women assigned to CEE + MPA, 154 among women assigned placebo) in the Estrogen + Progestin Trial, and 239 (104 among women assigned to CEE, 135 among women assigned to placebo) for the Estrogen-Alone Trial. Between the end of study intervention and trial close-out (Spring 2005), the numbers of additional invasive breast cancers that were centrally confirmed were 153 (87 among women assigned to CEE + MPA, 66 among women assigned to placebo) in the Estrogen + Progestin Trial, and 27 (13 among women assigned to CEE, 14 among women assigned to placebo) for the Estrogen-Alone trial.

Assessment of breast tenderness

At baseline and at 12-month follow-up, breast tenderness was assessed using self-assessment questionnaires [24,25]. Degree of bother from breast tenderness during the past 4 weeks was rated with a 4-point Likert-type scale as: symptoms 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 classified participants as having new-onset breast tenderness 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.

Other questionnaire-based measurements and anthropomorphic measurements

At baseline, participants were asked to fill standardized self-report questionnaires regarding breast cancer risk factors, medical and reproductive history, medication use (including previous menopausal hormone therapy use), prior breast biopsies, family medical history, previous hysterectomy and/or oophorectomy, cigarette smoking, alcohol intake, caffeine intake, menopausal vasomotor symptoms, race/ethnicity, education, income, and physical activity. Energy expenditure from recreational physical activity was estimated from the validated WHI Physical Activity Questionnaire [26–28].

Age at menopause was defined as the lowest of: 60 years, the age at which a woman had last had menstrual bleeding, the age at which a woman had undergone bilateral oophorectomy, or the age at which a woman had begun using postmenopausal hormone therapy [29]. Age at menopause was considered missing if ages at last menstrual bleeding, bilateral oophorectomy, and menopausal hormone therapy initiation were each unavailable. For women who had undergone hysterectomy without bilateral oophorectomy, age at menopause was defined as the lowest of: age 60, the age of onset of hot flashes or night sweats, the age at which she began taking menopausal hormone therapy, or the age at hysterectomy. Gail breast cancer risk score was calculated using baseline questionnaire information [30,31].

Using standardized protocols, baseline height and weight were directly measured for calculation of body mass index (BMI, weight in kilograms divided by height in meters squared).

Statistical analysis

All primary analyses were conducted on the intention-to-treat principle. Baseline characteristics were compared in women with and without new-onset breast tenderness at year 1 using χ^2 tests of association, and adjusting for age and treatment assignment. We

determined the relative risk of new-onset breast tenderness of any severity (mild, moderate, or severe) at 12-month follow-up by randomization assignment using generalized linear models with a log link function. We compared the magnitudes of associations between treatment assignment and risk of new-onset breast tenderness between the two trials using Chi-squared tests.

We used multivariate Cox proportional hazards models to examine the association between new-onset breast tenderness and invasive breast cancer. We included baseline breast tenderness (yes/no), breast tenderness at year 1 as a time-dependent binary covariate X(t), and a time-dependent interaction term. Survival time 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. Baseline hazard was stratified by age group (50–54, 55–59, 60–69, or 70–79 years-old) and randomization assignment in the WHI Dietary Modification Trial. We included the following variables based on biological plausibility and/or published studies: randomization assignment, 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), BMI (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, age at first birth, breastfeeding (never, ≤1 year, > 1 year), time since menopause (<5 or 5–<10 or 10–<15 or ≥15 years), Gail model breast cancer risk (linear and quartiles), bilateral oophorectomy (yes/no), and menopausal hormone therapy use prior to trial participation (yes/no) [7,6,32–42,25,43–47].

Multiple imputation was used to avoid deletion of observations with missing covariate values. Cox regression models were then fit for each of five imputed datasets, and the resulting regression parameter estimates were averaged for statistical inference. Data were too sparse to allow reliable sensitivity analysis among the subgroup of women who were adherent to (took ≥ 80% of) therapy.

All statistical tests were 2-sided. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS/STAT 9.2 (SAS Institute, Inc).

Results

At baseline, mean age of participants was 63.6 years. Seventy-five percent of participants were White. Forty-five percent of participants had BMI greater than 30. Characteristics linked with the reporting of new-onset breast tenderness at 12-month follow-up in the Estrogen-Alone Trial are displayed in Table 1. In the CEE and placebo groups combined, characteristics that were statistically significantly associated with new-onset breast tenderness included older age, treatment assignment (CEE versus placebo), lower BMI, greater years since menopause, and past use of estrogen therapy (Table 1). Characteristics associated with new-onset breast tenderness in the combined treatment groups of the Estrogen + Progestin Trial have been previously reported and were similar [13].

The prevalence of breast tenderness at baseline in the CEE-Alone Trial was 17.4% in women assigned to placebo and 16.8% in women assigned to CEE. The prevalence of breast tenderness at baseline in the CEE + MPA trial was 11.8 % in women assigned to placebo and 11.8 % in women assigned to CEE + MPA.

Women assigned to either of the active therapies were at higher risk of developing breast tenderness at Year 1 compared to women assigned to placebo, and the effect of CEE+MPA (relative risk [RR] 2.40; 95% confidence interval [95% CI] 2.26–2.54) was significantly larger (P_{het} <0.001) than the effect of CEE alone (RR 1.73; 95%CI 1.62–1.84) (Table 2).

The increased risk of breast tenderness at year 1 with active therapy vs. placebo was significantly modified by baseline breast tenderness (P-interaction < 0.001). Again, the effects differed between active therapies (P_{het} < 0.001), where the risk of new-onset breast tenderness tripled for CEE+MPA (RR 3.07; 95%CI 2.85–3.30) and doubled for CEE (RR 2.15; 95%CI 1.97–2.35) compared to placebo. Among women experiencing breast tenderness at baseline, the risk of breast tenderness at Year 1 was approximately 25% higher for both active therapies compared to placebo.

Published results of the WHI Hormone Trials have shown that the use of CEE + MPA increases the risk of invasive breast cancer, but use of CEE alone does not [14–17]. Subgroup analyses show that the effect of CEE + MPA was significantly modified by baseline breast tenderness (P_{int} = 0.03, Table 3), where CEE + MPA doubled the risk of invasive breast cancer among women with baseline breast tenderness (hazard ratio [HR] 2.16, 95% CI 1.29–3.74), but had a smaller effect among women without baseline breast tenderness (HR 1.17; 95%CI 0.97–1.41). Further stratification by prior hormone use (P_{int} = 0.04) showed that the impact of breast tenderness on the effect of CEE + MPA was especially pronounced among women with baseline breast tenderness who had not previously used menopausal hormone therapy (HR 2.29, 95% CI 1.21–4.56). Breast tenderness was only rarely moderate or severe in intensity, but the risk of breast cancer associated with CEE + MPA appeared to increase with severity of breast tenderness at baseline (P_{trend} = 0.02). There was no conclusive evidence that breast tenderness at baseline modified the effect of CEE (P_{int} = 0.37), even when results were further stratified by prior menopausal hormone therapy use (P_{int} = 0.13) or by severity of baseline breast tenderness (P_{trend} = 0.53).

Table 4 shows multivariable-adjusted associations between new-onset breast tenderness and the subsequent risk of invasive breast cancer. Before stratification by treatment assignment, new-onset breast tenderness was not statistically significantly associated with risk of breast cancer in the Estrogen-alone Trial or in the Estrogen + Progestin Trial. In the participants who were assigned to CEE + MPA, new-onset breast tenderness was associated with a statistically significantly increased breast cancer risk (hazard ratio 1.33, 95% confidence interval 1.02–1.72). In contrast, in the participants who were assigned to active therapy with CEE alone, new-onset breast tenderness was not statistically significantly associated with breast cancer risk (hazard ratio 0.98, 95% confidence interval 0.62–1.53).

Kaplan-Meier curves illustrate the temporal patterns of associations between new-onset breast tenderness and breast cancer risk for the active therapy arms of both trials (Fig. 1). The curves for women on with new-onset breast tenderness and without new-onset breast tenderness during CEE + MPA use do not appear to converge.

Discussion

The current study shows the potential relevance of breast tenderness symptoms prior to, and during administration of, menopausal hormone therapy. Among women with baseline breast tenderness, being assigned to CEE + MPA was associated with a doubling of the risk of invasive breast cancer compared to placebo. The increased risk of invasive breast cancer associated with use of CEE + MPA was attenuated among women without baseline breast tenderness. This effect modification could not be explained by prior menopausal hormone use, and appeared to increase with the severity of baseline breast tenderness. In contrast, the effect of CEE alone on breast cancer risk did not vary by the presence of breast tenderness before randomization.

Both CEE alone and CEE + MPA significantly increased risks of new-onset breast tenderness, but the effect of CEE + MPA was significantly greater than that of CEE alone. These results are intriguing, given similar effects of CEE alone and CEE + MPA on serum levels of estrone, estradiol, and sex hormone binding-globulin [48]. The development of new-onset breast tenderness after initiation of CEE + MPA, but not of CEE-alone, was associated with a statistically significantly higher subsequent risk of breast cancer.

The differential associations between new-onset breast tenderness and breast cancer risk among women assigned to active therapy in the CEE alone and CEE + MPA trials may be consistent with known differential effects of CEE and CEE + MPA on breast cancer risk, mammographic density, and breast tenderness. In the WHI, women assigned to CEE alone for a mean of 7.1 years had a 23% lower risk of breast cancer than women assigned to placebo at 10.7 years of follow-up ($P = 0.02$), whereas women assigned to CEE + MPA had a 24% ($P < 0.001$) higher risk of breast cancer than women assigned to placebo after a mean of 5.6 years of follow-up [15,17,14,16,49]. In addition, in prior studies from the Estrogen-Alone and Estrogen + Progestin Trials, mammographic breast cancer detection was not substantially compromised by use of CEE alone, but was comprised by use of CEE + MPA [22]. Moreover, the effects of CEE + MPA on mammographic density [20,18,19] and breast tenderness [2,25] are more pronounced than those of CEE alone.

An experience of breast tenderness could theoretically cause change in behavior, such as increased frequency of breast self-exam, or increased frequency of mammography, which could result in increased breast cancer diagnoses. We would have expected this change in behavior to similarly affect participants of both trials, and therefore this potential behavior change would not explain the differential associations of new-onset breast tenderness and breast cancer in the two trials.

Our study has several limitations. The occurrence of breast tenderness that resolved prior to the first annual visit would have led us to underestimate the incidence of breast tenderness. On the other hand, this ascertainment method probably mimics the way in which adverse effects are assessed in clinical settings. Also, discontinuation of CEE by some participants assigned to CEE may have led to an attenuation of the observed association of new-onset breast tenderness with breast cancer risk

Strengths of this study include the large number of participants, comprehensive assessment of breast cancer risk factors, rigorous ascertainment of breast cancer outcomes, blinding of participants and investigators to treatment assignment group, the requirement for annual mammography and clinical breast exam, the prospective blinded assessment of breast tenderness in the placebo and treatment groups, and longitudinal follow-up. To our knowledge, the WHI clinical trials were the largest and longest randomized controlled trials of menopausal hormone therapy ever performed.

In conclusion, among women assigned to CEE + MPA, but not among women assigned to CEE alone, the development of new-onset breast tenderness was associated with a significantly higher risk of breast cancer. The association of CEE + MPA therapy with increased breast cancer risk was especially pronounced among women with baseline breast tenderness. These findings highlight the complexity inherent in the use of surrogate risk markers to assess menopausal hormone therapy-associated breast cancer risk.

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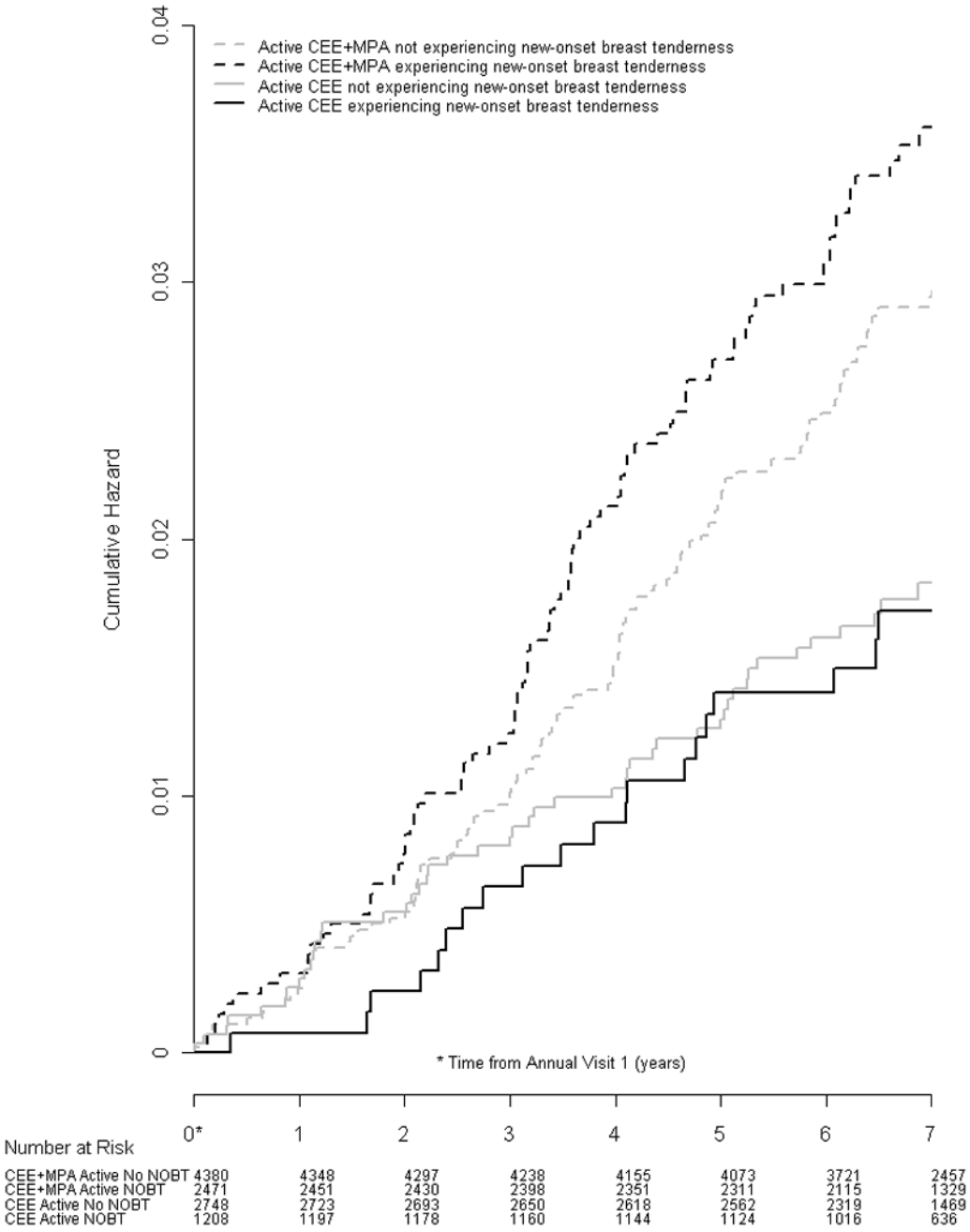

Figure 1.

Cumulative hazard of breast cancer according to presence vs. absence of new-onset breast tenderness in the active therapy arms of the WHI CEE + MPA and CEE-Alone trials.

Table 1

Baseline Characteristics of Participants in the WHI CEE-alone Trial by Breast Tenderness Status at Year 1 *

Characteristic	No tenderness at year 1 (N=6218)	Tenderness at year 1 (N=1793)	P†
Age at screening, mean (SD), y	63.9 (7.2)	64.6(7.2)	<0.001
Treatment assignment, No. (%)			<0.001
CEE Placebo	3463 (55.7)	575 (32.1)	
CEE Active	2755 (44.3)	1218 (67.9)	
Ethnicity, No (%)			0.06
White	4926 (79.2)	1382 (77.1)	
Black	794 (12.8)	260 (14.5)	
Hispanic	280 (4.5)	88 (4.9)	
American Indian	39 (0.6)	10 (0.6)	
Asian/Pacific Islander	97 (1.6)	24 (1.3)	
Unknown	82 (1.3)	29 (1.6)	
Daily alcohol intake, No. (%)			0.66
Non drinker	3086 (49.9)	913 (51.1)	
≤ 1 drink	2509 (40.5)	716 (40.1)	
> 1 drink	595 (9.6)	158 (8.8)	
Smoking status, No. (%)			0.27
Never	3165 (51.4)	919 (51.6)	
Past	2369 (38.5)	710 (39.9)	
Current	623 (10.1)	151 (8.5)	
Regular cups of coffee/day, No. (%)			0.41
None	2280 (37.0)	650 (36.5)	
1	917 (14.9)	266 (14.9)	
2	1253 (20.3)	393 (22.1)	
≥ 3	1712 (27.8)	472 (26.5)	
BMI (kg/m^2), No. (%)			0.03
< 25	1399 (22.6)	359 (20.2)	
25–<30	2168 (35.0)	626 (35.1)	
30–<35	1482 (23.9)	467 (26.2)	
35–<40	745 (12.0)	227 (12.7)	
≥40	396 (6.4)	102 (5.7)	
Quartiles of physical activity, MET h/wk, No. (%)			0.07
< 1.5	1458 (25.7)	447 (27.2)	
1.5 to 6.5	1517 (26.7)	446 (27.1)	
6.5 to 15.75	1390 (24.5)	417 (25.4)	
≥ 15.75	1311 (23.1)	333 (20.3)	
Parity, No. (%)			0.56

Characteristic	No tenderness at year 1 (N=6218)	Tenderness at year 1 (N=1793)	p†
Never pregnant/Never had term pregnancy	567 (9.2)	154 (8.6)	
1	482 (7.8)	129 (7.2)	
2	1248 (20.2)	377 (21.1)	
≥3	3883 (62.8)	1126 (63.0)	
Age at first birth, No, (%)			0.90
Never pregnant/never had term pregnancy	567 (10.1)	154 (9.7)	
< 20 years	1327 (23.5)	365 (23.1)	
20 – 29 years	3453 (61.2)	984 (62.2)	
≥ 30 years	291 (5.2)	80 (5.1)	
Age at menarche, No. (%)			0.04
<12 years	1455 (23.5)	387 (21.6)	
12–13 years	3281 (53.0)	1012 (56.6)	
≥14 years	1458 (23.5)	389 (21.8)	
Years since menopause, No. (%)			0.01
<5	354 (6.7)	89 (5.8)	
5–10	585 (11.1)	122 (7.9)	
11–14	847 (16.1)	232 (15.0)	
≥15	3474 (66.0)	1101 (71.3)	
Prior benign breast disease, No. (%)			<0.001
Never	4589 (81.8)	1263 (77.9)	
1 biopsy	755 (13.5)	255 (15.7)	
2+ biopsies	264 (4.7)	103 (6.4)	
Family history of female relative w/breast cancer, No. (%)	980 (16.7)	324 (19.3)	0.01
Bilateral oophorectomy, No. (%)	2374 (41.1)	701 (41.8)	0.69
Age when both ovaries removed, No.			0.17
< 40 years	598(25.4)	200 (28.8)	
40–49 years	1161 (49.4)	323 (46.5)	
50–54 years	355 (15.1)	95 (13.7)	
≥ 55 years	237 (10.1)	76 (11.0)	
Age at hysterectomy, No. (%)			0.14
< 40 years	2340 (37.9)	694 (38.9)	
40–49 years	2691 (43.6)	775 (43.4)	
50–54 years	648 (10.5)	182 (10.2)	
≥ 55 years	500 (8.1)	135 (7.6)	
Duration of breastfeeding, No. (%)			0.52
Never	2893 (47.3)	797 (45.3)	
≤ 1 year	2375 (38.8)	703 (39.9)	
> 1 year	850 (13.9)	260 (14.8)	
Quartiles of 5-year Gail model risk scores,			0.29

Characteristic	No tenderness at year 1 (N=6218)	Tenderness at year 1 (N=1793)	P†
No. (%)			
< 1.1	1583 (25.5)	442 (24.7)	
1.1 to < 1.44	1574 (25.3)	418 (23.3)	
1.44 to < 1.91	1547 (24.9)	453 (25.3)	
≥ 1.91	1514 (24.3)	480 (26.8)	
Pre-trial use of estrogen therapy, No. (%)			0.01
Never used	3310 (53.2)	951 (53.1)	
Past user	2097 (33.7)	657 (36.7)	
Current user	810 (13.0)	184 (10.3)	
Pre-trial use of estrogen + progesterone* therapy, No. (%)			0.72
Never used	5944 (95.6)	1715 (95.6)	
Past user	243 (3.9)	68 (3.8)	
Current user	31 (0.5)	10 (0.6)	

*Of the 10739 WHI CEE-alone trial participants, information regarding baseline and year 1 breast tenderness was available for 9620 participants. Thus, this table excludes participants for whom information regarding breast tenderness was missing from the baseline visit (n=86), the year 1 visit (n=1014), and both (n=19).

†Compares baseline characteristics of participants without vs with new-onset breast tenderness after adjustment for age and treatment assignment. Tests of association for age and treatment assignment are unadjusted.

*Self-reported at screening interview

Table 2

Prevalence and Relative Risk of Breast Tenderness at the First Annual Follow-up Visit in the WHI Hormone Therapy Trials [*]

	CEE-Alone							CEE+MPA							
	Active		Placebo				P-value[‡]	Active		Placebo				P-Value	P-Het[§]
Subgroup	N	(%)[**]	N	(%)	RR[†]	(95% CI)	(%)	N	(%)	N	(%)	RR	(95% CI)		
Active vs. placebo: All participants	**1771**	**(36.9)**	**1047**	**(21.4)**	**1.73**	**(1.62, 1.84)**	**<0.001**	**3086**	**(39.5)**	**1230**	**(16.5)**	**2.40**	**(2.26, 2.54)**	**<0.001**	**< 0.001**
Breast tenderness at baseline							<0.001							<0.001	<0.001
No	1218	(30.7)	575	(14.2)	2.15	(1.97, 2.35)		2477	(36.1)	770	(11.8)	3.07	(2.85, 3.30)		
Yes	537	(68.5)	462	(56.0)	1.22	(1.13, 1.32)		589	(65.8)	448	(52.2)	1.26	(1.17, 1.37)		

[*] N = 8011 for Estrogen-Alone Trial and N = 13,423 for the Estrogen + Progestin Trial

[†] Relative risk of breast tenderness at 12-month follow-up from a generalized linear model.

[‡] P-values for main effect of treatment (**boldface**) and for interaction between treatment assignment and baseline breast tenderness.

[§] Test of whether estimated RR differs between WHI Hormone Therapy Trials.

[**] Percent reporting breast tenderness at 12-month follow-up.

Table 3

Risk of Invasive Breast Cancer (Randomization through Close-Out according to baseline breast tenderness and prior menopausal hormone therapy in the WHI Hormone Trials

	CEE Trial							CEE+MPA Trial						
	CEE		Placebo					CEE+MPA		Placebo				
Subgroup	**N**	**(%)‡**	**N**	**(%)**	**HR***	**(95% CI)**	**P†**	**N**	**(%)**	**N**	**(%)**	**HR**	**(95% CI)**	**P**
Active vs. placebo: All participants	**117**	**(0.28)**	**149**	**(0.35)**	**0.81**	**(0.63, 1.03)**	**0.08**	**293**	**(0.43**	**221**	**(0.34)**	**1.25**	**(1.05, 1.49)**	**0.01**
Breast tenderness at baseline							0.37							0.03
No	91	(0.26)	125	(0.35)	0.75	(0.57, 0.98)		246	(0.41)	199	(0.35)	1.17	(0.97, 1.41)	
Yes	24	(0.34)	23	(0.31)	1.00	(0.56, 1.79)		45	(0.56)	20	(0.27)	2.16	(1.29, 3.74)	
Breast tenderness at baseline by prior MHT§							0.13							0.04
No breast tenderness/No prior MHT	42	(0.23)	75	(0.42)	0.56	(0.38, 0.82)		176	(0.40)	160	(0.38)	1.05	(0.85, 1.30)	
No breast tenderness/prior MHT	49	(0.29)	50	(0.29)	1.02	(0.69, 1.52)		70	(0.45)	39	(0.27)	1.63	(1.11, 2.44)	
Breast tenderness/No prior MHT	15	(0.40)	14	(0.39)	1.02	(0.49, 2.15)		31	(0.55)	13	(0.24)	2.29	(1.21, 4.56)	
Breast tenderness/prior MHT	9	(0.27)	9	(0.24)	1.09	(0.42, 2.80)		14	(0.58)	7	(0.32)	1.80	(0.74, 4.76)	
Severity of Breast tenderness at baseline							0.53							0.02
No breast tenderness	91	(0.26)	125	(0.35)	0.75	(0.57, 0.98)		246	(0.41)	199	(0.35)	1.17	(0.97, 1.41)	
Mild tenderness	20	(0.36)	18	(0.30)	1.14	(0.60, 2.17)		37	(0.54)	18	(0.28)	1.96	(1.13, 3.54)	
Moderate/severe tenderness	4	(0.27)	5	(0.37)	0.64	(0.16, 2.43)		8	(0.70)	2	(0.19)	4.55	(1.09, 30.82)	

*Hazard ratio from Cox proportional hazards models stratified by age, WHI Dietary Modification Trial treatment assignment, and subgroup.

†P-values for main effect of treatment **(boldface)** and for interaction between treatment assignment and subgroup.

‡Annualized percentage.

§MHT = menopausal hormone therapy

Table 4

Annualized Rates and Multivariable-Adjusted Risk of Invasive Breast Cancer Among women with and without New-Onset Breast Tenderness at 12-Month Follow-up in the WHI Estrogen-Alone and Estrogen + Progestin Trials

	CEE Trial							CEE+MPA Trial						
	Experienced new-onset breast tenderness		Did not experience new-onset breast tenderness					Experienced new-onset breast tenderness		Did not experience new-onset breast tenderness				
HT Trial Arm	Cases (N at risk)	(%)*	Cases (N at risk)	(%)	HR†	(95% CI)	P‡	Cases (N at risk)	(%)	Cases (N at risk)	(%)	HR	(95% CI)	P
All participants (Active and placebo)	42 (1779)	(0.34)	158 (6202)	(0.30)	1.04	(0.74, 1.48)	0.81	116 (3231)	(0.51)	301 (10149)	(0.35)	1.22	(0.97, 1.53)	0.09
Active	22 (1208)	(0.26)	62 (2748)	(0.26)	0.98	(0.62, 1.53)	0.92	93 (2471)	(0.53)	141 (4380)	(0.37)	1.33	(1.02, 1.72)	0.03
Placebo	20 (571)	(0.50)	96 (3454)	(0.34)	1.15	(0.70, 1.88)	0.57	23 (760)	(0.43)	160 (5769)	(0.34)	1.07	(0.70, 1.63)	0.76

*Annualized rates

†Hazard ratio from Cox proportional hazards models comparing risk of breast cancer among women with versus without new-onset breast tenderness. Cox proportional hazards models are adjusted for HT randomization assignment, age, ethnicity, alcohol consumption, smoking, body mass index (linear and quartiles), physical activity (linear and quartiles), parity, age at first birth, breast feeding, years of age at menopause, Gail model breast cancer risk (linear and quartiles), bilateral oophorectomy, menopausal hormone therapy use prior to trial participation. This table displays hazard ratios for women without baseline breast tenderness.

‡P-values for comparison of hazard ratios among women with new-onset breast tenderness and women without new-onset breast tenderness.