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Breast Tenderness after Initiation of Conjugated Equine Estrogens and Mammographic Density Change

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Abstract

Background—We examined the association between new-onset breast tenderness and change in mammographic density after initiation of conjugated equine estrogens (CEE).

Methods—We analyzed baseline, year 1, and year 2 data from 695 participants of the Women's Health Initiative Estrogen + Progestin (daily CEE 0.625 mg + medroxyprogesterone acetate 2.5 mg [MPA] or placebo) and Estrogen-Alone (CEE 0.625 mg or placebo) trials who participated in the Mammogram Density Ancillary Study. Using multivariable repeated measures models, we analyzed the association between new-onset breast tenderness (i.e. absence of baseline tenderness

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and presence of tenderness at year 1 follow-up) and change from baseline in percent mammographic density.

Results—Active therapy increased the odds of new-onset breast tenderness (CEE + MPA vs. placebo risk ratio [RR] 3.01, 95% confidence interval [95% CI] 1.96-4.62; CEE vs. placebo RR 1.70, 95% CI 1.14-2.53). Among women assigned to CEE + MPA, mean increase in mammographic density was greater among participants reporting new-onset of breast tenderness than among participants without new-onset breast tenderness (11.3% vs. 3.9% at year 1, 9.4% vs. 3.2% at year 2, $P < 0.001$). Among women assigned to CEE alone, increase in mammographic density at year 1 follow-up was not significantly different in women with new-onset breast tenderness compared to women without new-onset breast tenderness (2.4% vs. 0.6% at year 1, 2.2% vs. 1.0% at year 2, $P = 0.30$).

Conclusions—The new-onset of breast tenderness after initiation of CEE + MPA, but not CEE alone, is associated with greater increases in mammographic density.

Keywords

Mammographic density; breast density; breast tenderness; mastalgia; mastodynia; conjugated equine estrogen; medroxyprogesterone acetate

Introduction

Breast tenderness is a common adverse effect of menopausal hormone therapy. Although estimates of its frequency vary due to differences in data collection and data reporting methods, the incidence of breast tenderness in double-blind randomized controlled trials is approximately 8% to 15% following initiation of oral conjugated equine estrogens (CEE) alone [1,2], and from 9%-26% after initiation of CEE combined with medroxyprogesterone acetate (MPA) [3,2,4-6].

In addition to causing breast tenderness, the use of menopausal estrogen plus progestin therapy is associated with increased breast density [7,8], an independent risk factor for breast cancer [9]. In a sub-study of the Women's Health Initiative (WHI), the WHI Mammogram Density Ancillary Study, the use of either CEE + MPA or CEE alone was associated with statistically significant increases in mammographic density, a strong risk factor for breast cancer [10,7,11]. Mammographic density is an indirect measure of breast parenchymal tissue proliferation [12,13].

The new-onset of breast tenderness during combination hormone therapy use has been linked to an increase in mammographic density in a few studies [2,14,15]. However, prior studies had some potential limitations, for example observational study design in which women were not blinded to hormone therapy regimen [14,15] and use of mammographic density assessment methods that were not described in detail [14]. Understanding factors associated with mammographic density changes during therapy with CEE+MPA may help give biological insights into hormone therapy-associated breast cancer risk.

To determine the association between the new-onset breast tenderness and increased mammographic density, we analyzed questionnaire and mammographic density data from the WHI Estrogen-Alone and WHI Estrogen + Progestin Trials.

Methods

Study Design

Eligibility criteria and recruitment methods for the WHI Estrogen-Alone and the WHI Estrogen + Progestin Trial were previously described [16-18]. For each of the trials, during the period between 1993 and 1998, 40 clinical centers recruited postmenopausal women aged 50-79 years. The WHI Estrogen + Progestin Trial recruited 16,608 women without prior hysterectomy [19]. The WHI Estrogen-Alone Trial recruited 10,739 women with prior hysterectomy [20]. Women were required to cease any menopausal hormone therapy for 3 months prior to randomization. Prior to enrollment, all women received a clinical breast exam and mammography; abnormal findings required clearance prior to study entry. All participants provided written informed consent. Human subjects committees approval was obtained at each participating institution.

In the Estrogen-Alone Trial, participants were randomly assigned to receive CEE 0.625 mg (N = 5310) or placebo (N = 5429) daily. In the Estrogen + Progestin Trial, participants were randomly assigned to receive CEE 0.625 mg + MPA 2.5 mg (N = 8506) or placebo (N = 8102) daily. Participants were required to undergo annual mammography (referral by the WHI clinic or the participant's health care provider) and clinical breast examination for continued administration of study medication. Participants were clinically monitored at 6-month intervals regardless of medication adherence.

Assessment of mammographic density

In a separately funded study, 17 of 40 WHI clinical centers agreed to participate in the Mammogram Density Ancillary Study [10,7]. Inclusion criteria included availability of a baseline pre-randomization mammogram and at least one follow-up mammogram after 1 or 2 years of trial participation. After participants provided written inform consent for inclusion in the Ancillary study, mammograms were retrieved from mammogram facilities and digitized for mammographic density assessment.

Films were digitized using a Lumisys 85 laser digitizer with a maximum resolution of 50 μm and 12-bit depth. Details of the mammographic density assessment method were previously described [10,7]. Mammographic percent density, i.e. the percent of the breast composed of dense tissue, was determined using a validated computer-assisted interaction thresholding method with software from the Imaging Research Program (Sunnybrook Health Science Centre, Toronto, Ontario, Canada) [9]. With the digitized mammogram displayed on a computer monitor, the observer selected threshold values of pixel brightness above which breast tissue was considered dense. The software calculated mammographic percent density ([dense area/total breast area] * 100). Two trained observers each assessed mammographic density on all films and were blinded to time sequence and treatment status. For each film, the mean percent density value of the two observers was considered to be the percent density value for that film. Intra-class correlation coefficients for mammographic density assessments were >0.92.

Assessment of breast tenderness

At baseline and year 1 follow-up, the presence of breast tenderness was ascertained using self-assessment questionnaires [21,22]. Participants rated the degree of bother from breast tenderness during the past 4 weeks using a four-point Likert-type scale. Response choices were: symptom did not occur, symptom was mild (did not interfere with usual activities), symptom was moderate (interfered somewhat with usual activities), and symptom was severe (so bothersome that usual activities could not be pursued). We classified participants as having *new-onset breast tenderness* if they reported absence of breast tenderness at

baseline and presence of breast tenderness (mild, moderate, or severe) at the first annual follow-up visit.

Other Questionnaire Measurements and Anthropometric Measures

At baseline, participants received questionnaires regarding medical and reproductive history, family medical history, race/ethnicity, education, income, and physical activity. Using standardized protocols, baseline height and weight were directly measured for calculation of body mass index (BMI, weight in kilograms divided by the square of the height in meters).

Analytic sample

Of 16,608 participants in the WHI Estrogen + Progestin trial, the mammograms of 473 participants (233 women assigned to CEE + MPA, 240 women assigned to placebo) were eligible for the Mammogram Density Ancillary study [7]. Of these 473 women, 437 women (214 women assigned to CEE + MPA, 223 women assigned to placebo) consented to participate in the Ancillary Study. We excluded data from 3 women with invasive breast cancer and 21 women for whom baseline and/or follow-up mammograms were incomplete. Thus, mammographic density data were complete for 413 participants (202 women assigned to CEE + MPA, 211 women assigned to placebo).

Of 10,739 participants in the WHI Estrogen-Alone Trial, the mammograms of 498 participants (234 women assigned to CEE, 264 women assigned to placebo) were eligible for the Mammogram Density Ancillary Study [10]. Of these 498 women, 458 women (220 women assigned to CEE, 238 women assigned to placebo) consented to participate in the Ancillary Study. We excluded data from 3 women with invasive breast cancer and 20 women for whom baseline and/or follow-up mammograms were incomplete. Thus, mammographic density data were complete for 435 participants (209 women assigned to CEE, 226 women assigned to placebo).

Of the total of 848 participants (from both trials combined) for whom we had complete mammographic density data, we excluded data from 14 participants for whom information regarding breast tenderness was missing, and from 139 participants who reported having breast tenderness at baseline. Thus, 695 participants comprise the analytic sample for the current study.

Statistical Methods

All primary analyses were based on the intention-to-treat principle. Baseline characteristics were compared among women by treatment assignment using chi-square tests of association. Using generalized linear models with a log-link function, we estimated the relative risk of new-onset breast tenderness of any severity (mild, moderate, or severe) at year 1 follow-up according to randomization assignment. We used chi-square tests to compare the magnitudes of associations between treatment assignment and risk of new-onset breast tenderness between the two trials.

We used linear mixed effects models to determine the association between new-onset breast tenderness at year 1 follow-up (exposure) and change in percent mammographic density from baseline, adjusting for age (continuous), race/ethnicity (Caucasian, Black, American Indian, Asian Pacific Islander, unknown), and BMI (kg/m^2, continuous and quartiles). Covariates were chosen based on previously documented associations with mammographic density [23-35].

In secondary analyses, we examined associations between new-onset breast tenderness and increases in mammographic density after stratifying by severity of breast tenderness (mild, moderate, severe).

All statistical tests were two-sided. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS/STAT software Version 9.2 (SAS Institute, Inc, Cary, NC) and R version 2.11 (R Foundation for Statistical Computing, http://www.r-project.org/).

Results

Key baseline characteristics of the 695 participants comprising the analytic sample were comparably distributed across the various treatment arms (**Table 1)**. Among women without baseline breast tenderness, the proportions of women reporting breast tenderness at year 1 follow-up were 31.8% among women assigned to CEE, 18.7% among women assigned to CEE placebo, 39.1% among women assigned to CEE + MPA, and 13.0% among women assigned to CEE + MPA placebo (**Table 2**). Compared to women assigned to placebo, the relative risk (RR) of breast tenderness was statistically significantly higher among women assigned to CEE alone (RR 1.70, 95% confidence interval [CI] 1.14-2.53) or to CEE + MPA (RR 3.01, 95% CI 1.96-4.62) (**Table 2**).

Increase from baseline in percent mammographic density was statistically significantly greater among women assigned to active therapy than among women assigned to placebo. Changes from baseline in percent mammographic density (year 1 minus baseline) according to treatment assignment were: 1.4% for CEE alone, -0.8% for CEE placebo, 6.3% for CEE + MPA, and -0.9% for CEE + MPA placebo (data not shown). Changes in percent mammographic density were statistically significantly greater among women assigned to active therapy than among women assigned to placebo ($P = 0.003$ for CEE alone vs. placebo, $P < 0.001$ for CEE + MPA vs. placebo), and were more marked among women assigned to CEE + MPA than among women assigned to CEE alone ($P_{Het} = 0.001$, data not shown). Changes in mammographic density were essentially unchanged after further adjustment for self-reported use (baseline and/or year 1) of non-steroidal anti-inflammatory medications (data not shown).

Among women assigned to CEE + MPA therapy, the mean increase in mammographic density from baseline was statistically significantly higher among women who reported new-onset breast tenderness compared to women who reported not having new-onset breast tenderness (11.3% vs. 3.9% at year 1, 9.4% vs. 3.2% at year 2, $P < 0.001$, **Table 3**). In contrast, among women assigned to CEE alone, mean increase in mammographic density was not statistically different among women who reported having new-onset breast tenderness compared to women who reported having no new-onset breast tenderness (2.4% vs. 0.6% at year 1, 2.2% vs. 1.0% at year 2, $P = 0.30$). Associations between new-onset breast tenderness and increases in mammogram density were statistically significantly stronger among assigned to CEE + MPA than among women assigned to CEE alone ($P_{Het} = 0.001$). Results were not notably altered by restricting the analyses to participants who were adherent to study medications (took at least 80% of medications at 6 month follow-up)(data not shown).

For each of the two trials, we fit a separate regression model with new-onset breast tenderness as the binary outcome and treatment assignment (active therapy vs. placebo) as the main predictor, adjusting for age, BMI, race/ethnicity, and Gail breast cancer risk score. Compared to placebo, CEE + MPA therapy was associated with a 3-fold elevation in the adjusted relative risk of new-onset breast tenderness (RR 3.07, 95% CI 2.01- 4.13). When

we added change in percent mammographic density to this model (linear and quadratic), the RR was decreased by a third to 1.98 (95% CI 1.14, 3.09). In contrast, the association between CEE vs. placebo and new-onset breast tenderness was barely altered by the addition of change in percent mammographic density to the model (RR 1.67, 95% CI 1.06-2.37 before vs. RR 1.62, 95% CI 1.02-2.30 after). Change in percent mammographic density was associated with increased odds of new-onset breast tenderness independent of treatment assignment among CEE + MPA trial participants ($P < 0.001$), but not among in CEE Trial participants ($P = 0.47$, data not shown).

We illustrate the associations between new-onset breast tenderness and change in mammographic density from baseline according to treatment group (**Figure 1**), and further subdivided according to severity of breast tenderness (**Figure 2**).

Figure 3 displays the bivariate mean (95% confidence region) between the effect of active therapy (vs. placebo) on change in mammographic density and incidence of new-onset breast tenderness. Compared to CEE, the effects of CEE + MPA are more pronounced when considered jointly. Moreover, change in percent mammographic density and new-onset breast tenderness associated with CEE + MPA are correlated, while these associations appear unrelated in the CEE trial.

Discussion

We found that increases in mammographic density were greater among women who developed new-onset breast tenderness, than among women who did not develop new-onset breast tenderness, after initiation of CEE + MPA. In contrast, increases in mammographic density after initiation of CEE alone were similar among women who reported developing new-onset breast tenderness and women who reported not developing breast tenderness. The difference in the magnitude of increase in mammographic density between women with, versus without, new-onset breast tenderness after CEE + MPA initiation was 7.4%. Associations between hormone therapy-induced increases in mammographic density and breast cancer risk are not yet delineated. However, in observational studies, each 10% higher breast density represents a 15% higher relative risk of breast cancer [9,36].

Three prior studies found that CEE + MPA-induced breast tenderness is associated with increased mammographic density [14,2,15]. Of these three, only one study used randomized treatment assignment and performed double-blind assessments [2]. The Postmenopausal Estrogen/Progestin Interventions (PEPI) randomized controlled trial included doses of CEE and CEE + MPA that were identical to those used in the current study. In the PEPI mammographic density ancillary study, among women assigned to CEE + MPA therapy, those who reported new-onset of breast tenderness at 12-month follow-up had greater increases in mammographic density (approximately 4.4% greater on average) than did women who reported the absence of breast tenderness [2]. Thus, the results of the current and previous study are similar. We suspect that the larger number of participants in the present study allowed us to detect a statistically significant difference in associations between new-onset breast tenderness and change in mammographic density among women assigned to CEE alone compared to women assigned to CEE + MPA.

Differential associations between new-onset breast tenderness and mammographic density changes among women assigned to CEE alone compared to CEE + MPA are consistent with previously reported differential effects of CEE and CEE + MPA on breast cancer risk, incidence of new-onset breast tenderness, rates of abnormal mammograms and breast biopsies, and increases in mammographic density [37,19,38,18,2,6,10,7,39,40].

Why estrogen + progestin therapy and estrogen therapy have different influences on the risk of breast cancer is not yet clear [41]. A partial explanation may lie in the pathway of receptor activator of nuclear factor-κβ (RANK) and its ligand, RANKL. Primary human breast tumors express RANK [42]. Estrogen is a key inhibitor of RANKL activity (reviewed in [42]). In contrast, MPA treatment in mice induces enormous increases in RANKL expression, increasing RANK signaling in the mammary epithelium and causing proliferation of mammary epithelial cells. Moreover, mammary-specific deletion of RANK decreases the progression of MPA-driven breast cancer. Conversely, RANKL blockade reduces progestin-driven tumorigenesis. The induction of RANKL in human breast cells may in part explain the differing magnitudes of effects of CEE alone and CEE + MPA on change in mammographic density and on breast tenderness [42].

Our 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. Our study was not designed to directly test whether CEE+MPA-induced breast tenderness is associated with increased breast cell proliferation. Finally, our results cannot be assumed to apply to other types, doses, routes of administration, or schedules of estrogen or progestogen therapy.

Strengths of our study include the large number of participants, the use of placebo controls, the blinding of participants and investigators to treatment assignment, a well-validated method of mammographic density assessment, and the serial prospective blinded assessment of breast tenderness in both placebo and active treatment groups.

In conclusion, women who reported new-onset breast tenderness after initiation of CEE + MPA, but not after initiation of CEE alone, experienced greater increases in mammographic density on average than did women without new-onset breast tenderness. These findings emphasize the complexity inherent in the use of surrogate risk markers to assess menopausal hormone therapy-associated breast cancer risk.

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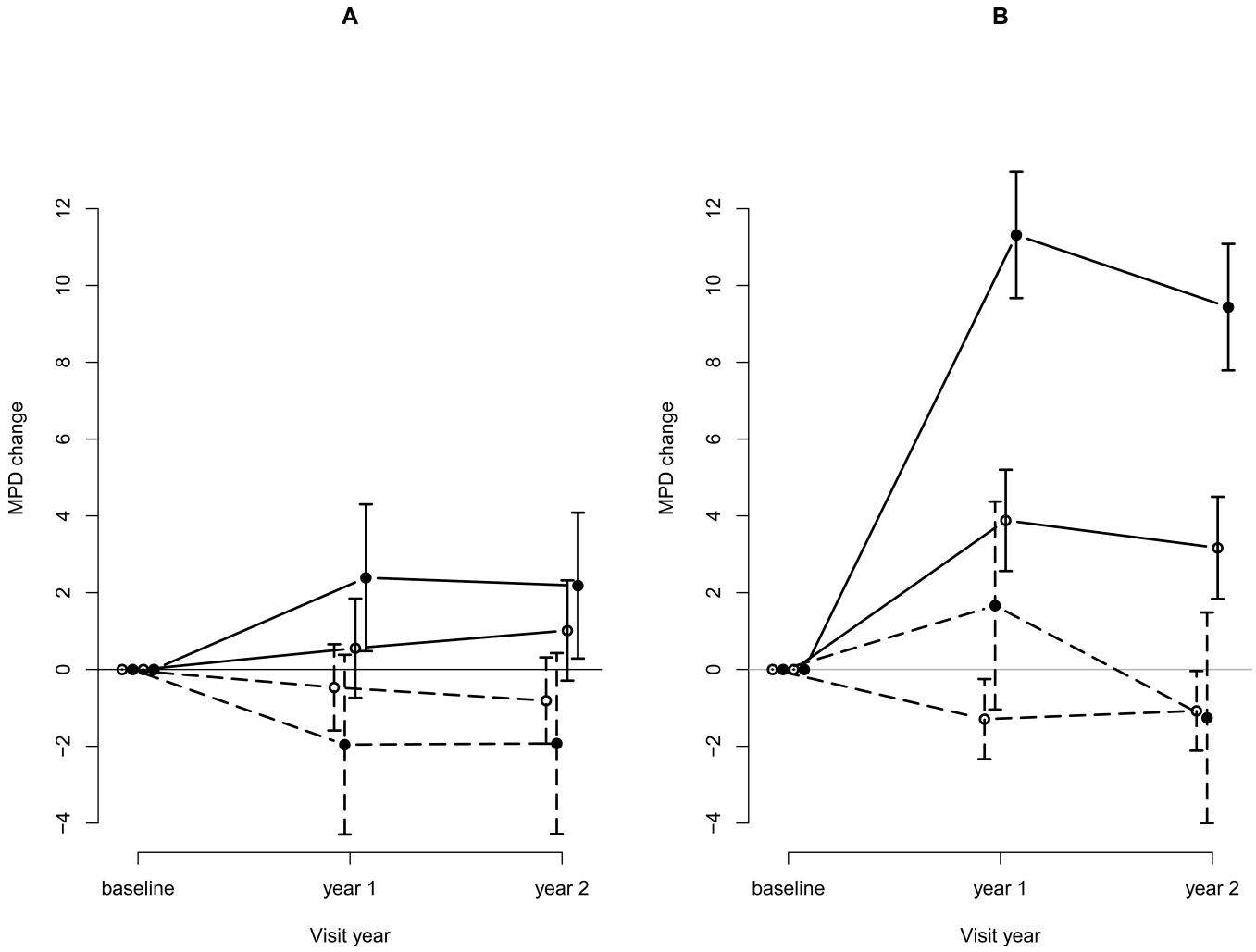

Figure 1. Associations between new-onset breast tenderness (NOBT) and change in mammographic density (MPD) from baseline according to treatment assignment, adjusted for age, ethnicity, BMI, and Gail risk score

Panel A compares the mean (95% CI) of the active arm of the CEE trial (solid line) to that of the placebo arm (dashed) by presence (solid dot) or absence (open dot) of NOBT. Panel B compares the mean (95% CI) of the active arm of the CEE + MPA trial (solid line) to that of the placebo arm (dashed) by presence (solid dot) or absence (open dot) of NOBT.

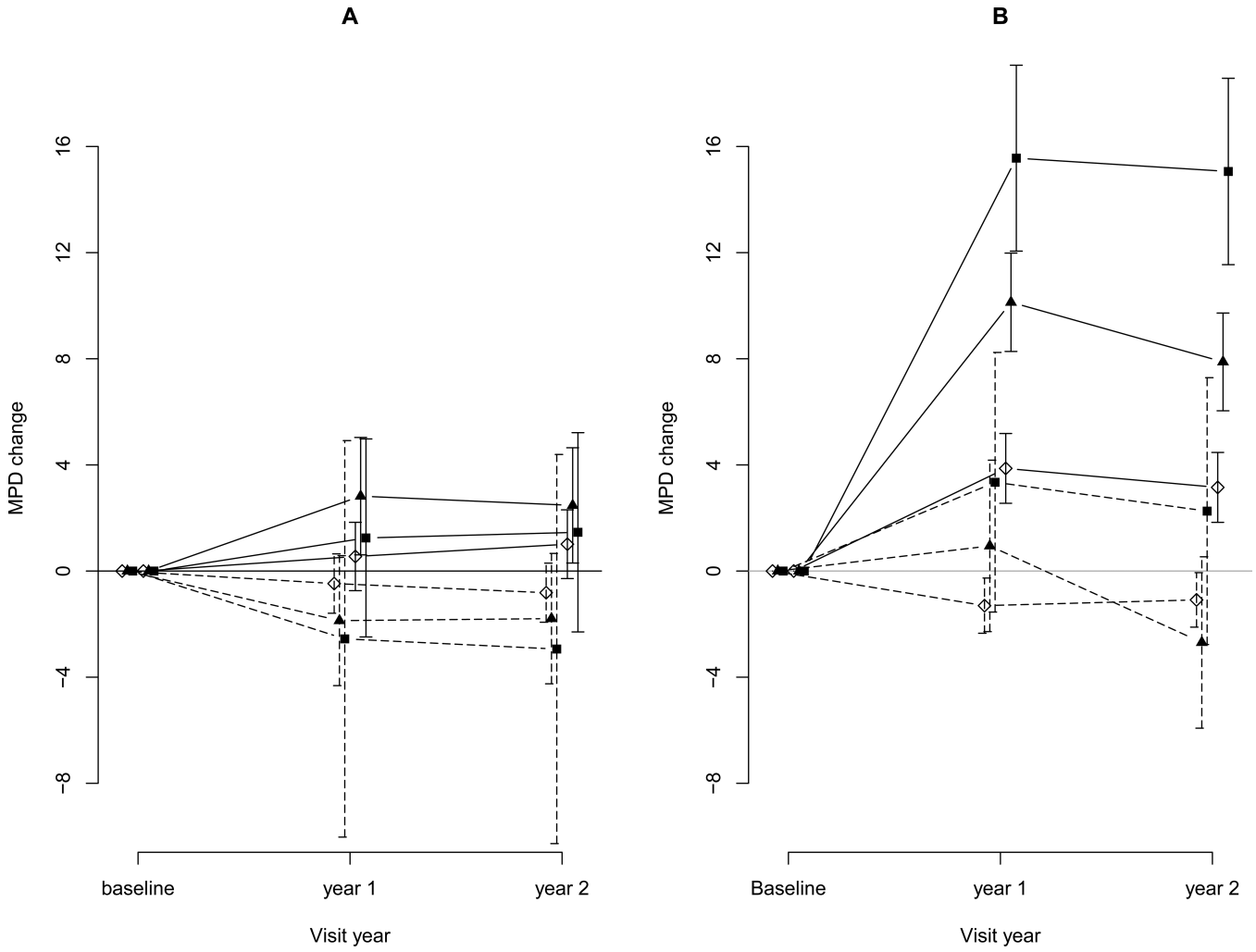

Figure 2. Associations between new-onset breast tenderness (NOBT) and change in mammographic density (MPD) from baseline, according to treatment assignment and severity of NOBT, and adjusted for age, ethnicity, BMD, and Gail risk score

Panel A compares the mean (95% CI) of the active arm of the CEE trial (solid line) to that of the placebo arm (dashed line) by moderate or severe NOBT (solid square), mild NOBT (solid triangle), or absence of NOBT (open square). Means (95% CI) for the CEE arm are based on samples of size N = 12, 35, and 101 for moderate/severe, mild, or absent NOBT, respectively. Means (95% CI) for the placebo arm are based on samples of size N = 3, 28, and 135 for moderate/severe, mild, or absent NOBT, respectively. Panel B compares the mean (95% CI) of the active arm of the CEE + MPA trial (solid line) to that of the placebo arm (dashed line) by moderate or severe NOBT (solid square), mild NOBT (solid triangle), or absence of NOBT (open square). Means (95% CI) for the CEE + MPA arm are based on samples of size N = 14, 49, and 98 for moderate/severe, mild, or absent NOBT, respectively. Means (95% CI) for the placebo arm are based on samples of size N = 7,16, and 154 for moderate/severe, mild, or absent NOBT, respectively.

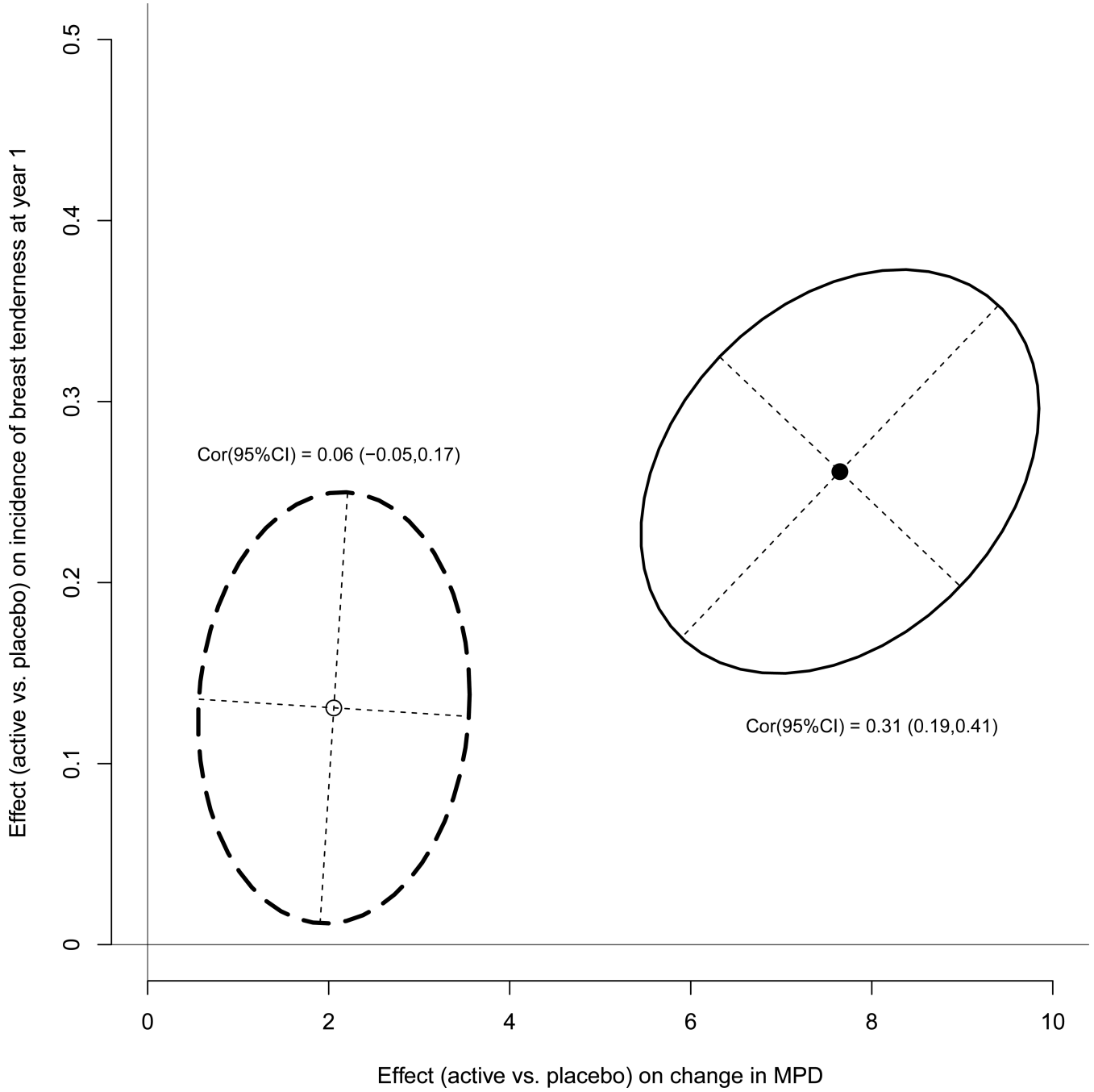

Figure 3. Bivariate effects of therapy on change in mammographic density (MPD; year 1-baseline) and incidence of new-onset breast tenderness (NOBT) at year 1 among WHI Mammogram Density Ancillary Study participants who reported having no breast tenderness at baseline, according to treatment assignment

The bivariate means (95% CI) are represented by open circle (dashed line) and filled circle (solid line) for the CEE and CEE + MPA trials, respectively, with ellipse axes indicated by dotten lines. Vertical and horizontal lines at zero represent the null hypothesis of no effect.

Table 1

Baseline Characteristics of the Mammogram Density Ancillary Study cohort without Breast Tenderness at Baseline (n=695)[1], according to Randomization Assignment

	CEE Active (N = 159)		CEE Placebo (N = 175)			CEE+MPA Active (N = 175)		CEE+MPA Placebo (N = 186)		
	N	%	N	%	P-Value[2]	N	%	N	%	P-Value
Age, mean years (sd)	62.9 (7.8)		62.2 (7.8)		0.38	62.1 (8.2)		62.1 (7.6)		0.98
Race/ethnicity					0.07					0.46
White	74	46.5	65	37.1		75	42.9	84	45.2	
Black	56	35.2	84	48.0		59	33.7	70	37.6	
Hispanic	28	17.6	23	13.1		28	16.0	24	12.9	
Asian/Pacific Islander	1	0.6	3	1.7		13	7.4	8	4.3	
BMI (kg/m^2)					0.46					0.29
<25	31	19.5	29	16.8		53	30.3	43	23.1	
25 - <30	58	36.5	56	32.4		55	31.4	67	36.0	
≥30	70	44.0	88	50.9		67	38.3	76	40.9	
Daily alcohol intake, No. (%)					0.16					0.47
Non-drinker	102	64.2	105	60.3		96	55.2	100	53.8	
≤ 1 drink/day	47	29.6	64	36.8		68	39.1	69	37.1	
> 1 drink/day	10	6.3	5	2.9		10	5.7	17	9.1	
Smoking status					0.05					0.81
Never	89	56.0	98	56.6		88	50.6	99	53.5	
Past	56	35.2	46	26.6		61	35.1	59	31.9	
Current	14	8.8	29	16.8		25	14.4	27	14.6	
Quartiles of Physical Activity					0.27					0.38
1	41	28.7	51	31.5		50	30.9	39	22.5	
2	46	32.2	50	30.9		36	22.2	41	23.7	
3	27	18.9	40	24.7		37	22.8	46	26.6	
4	29	20.3	21	13.0		39	24.1	47	27.2	

	CEE Active (N = 159)		CEE Placebo (N = 175)			CEE+MPA Active (N = 175)		CEE+MPA Placebo (N = 186)		
	N	%	N	%	P-Value[2]	N	%	N	%	P-Value
Parity, No. (%)					0.21					0.33
Never pregnant/Never had term pregnancy	14	9.0	20	11.5		17	9.8	26	14.1	
1	11	7.1	17	9.8		18	10.4	18	9.8	
2	26	16.8	40	23.0		36	20.8	27	14.7	
≥3	104	67.1	97	55.7		102	59.0	113	61.4	
Age at first birth, years					0.57					0.18
No term pregnancy	14	10.3	20	13.2		17	11.0	26	15.5	
<20	41	30.1	46	30.3		29	18.8	42	25.0	
20 - 29	71	52.2	80	52.6		90	58.4	88	52.4	
30+	10	7.4	6	3.9		18	11.7	12	7.1	
Age at menarche, years					0.92					0.72
<12	36	22.6	41	23.6		31	17.7	36	19.6	
12-13	84	52.8	88	50.6		94	53.7	91	49.5	
≥14	39	24.5	45	25.9		50	28.6	57	31.0	
Years since menopause					0.06					0.15
< 5 years	18	13.4	12	8.3		45	28.5	35	21.0	
≥ 5 - < 10 years	19	14.2	11	7.6		23	14.6	35	21.0	
≥ 10 - < 15 years	21	15.7	18	12.5		24	15.2	34	20.4	
≥ 15 years	76	56.7	103	71.5		66	41.8	63	37.7	
Benign breast disease					0.65					0.11
No	116	83.5	137	87.3		146	91.3	146	86.4	
Yes, 1 biopsy	16	11.5	14	8.9		10	6.3	21	12.4	
Yes, 2+ biopsies	7	5.0	6	3.8		4	2.5	2	1.2	
Family history of female relative with breast cancer	23	15.5	18	10.7	0.20	19	11.2	22	12.4	0.73
Bilateral oophorectomy, No. (%)	58	40.6	61	38.9	0.76	174	100.0	184	100.0	
Number of months breastfed										0.81
Never breastfed	62	39.2	75	43.6	0.18	68	39.3	73	39.9	

	CEE Active (N = 159)		CEE Placebo (N = 175)			CEE+MPA Active (N = 175)		CEE+MPA Placebo (N = 186)		
	N	%	N	%	P-Value[2]	N	%	N	%	P-Value
Breastfed ≤ 1 year	65	41.1	76	44.2		73	42.2	72	39.3	
Breastfed > 1 year	31	19.6	21	12.2		32	18.5	38	20.8	
Quartiles of Gail Risk score					0.19					0.86
1	78	49.1	106	60.6		86	49.1	94	50.5	
2	27	17.0	26	14.9		33	18.9	38	20.4	
3	29	18.2	24	13.7		28	16.0	24	12.9	
4	25	15.7	19	10.9		28	16.0	30	16.1	
Pre-WHI use of menopausal hormones					0.88					0.84
Never used	93	58.5	107	61.1		139	79.9	153	82.3	
Past user	51	32.1	53	30.3		28	16.1	26	14.0	
Current user	15	9.4	15	8.6		7	4.0	7	3.8	

[1]There are 848 participants in the WHI mammographic density cohort. 695 (82%) reported no breast tenderness at baseline, 139 (16%) reported having no tenderness at baseline, and information regarding breast tenderness was missing for 14 (2% of) participants.

[2]From a chi-square test of association between baseline characteristic and randomization assignment

Table 2

Prevalence and Relative Risk (RR) of Breast Tenderness at the First Annual Follow-up Visit among the WHI Mammogram Density Ancillary Study participants who reported having no Breast Tenderness at Baseline (n = 695), by Treatment Assignment

CEE-Alone							CEE+MPA							
Active		Placebo					Active		Placebo					
N	(%)[4]	N	(%)	RR[1]	(95% CI)	P-value[2] (%)	N	(%)	N	(%)	RR	(95% CI)	P-Value	P-Het[3]
47	(31.8)	31	(18.7)	1.70	(1.14, 2.53)	0.009	63	(39.1)	23	(13.0)	3.01	(1.96, 4.62)	<0.001	0.054

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

[2] P-values for main effect of treatment (active vs. placebo).

[3] P-het corresponds to whether estimated RR differs between the CEE-Alone and the CEE + MPA Trials.

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

Table 3

Change (Follow-up minus Baseline) in Mammographic Percent Density by prescence of New-onset Breast Tenderness (NOBT) in the WHI Mammogram Density Ancillary Study participants assigned to Active Hormone Therapy (n=334)[1]

Visit	CEE							CEE+MPA							
	N	NOBT		N	No NOBT		P-Value[2]	N	NOBT		N	No NOBT		P-Value	P-Het[3]
		Mean	(95% CI)		Mean	(95% CI)			Mean	(95% CI)		Mean	(95% CI)		
Year 1	47	2.4	(0.5, 4.3)	101	0.6	(-0.7, 1.8)	0.30	63	11.3	(9.7, 13.0)	98	3.9	(2.6, 5.2)	<0.001	0.001
Year 2	46	2.2	(0.3, 4.1)	93	1.0	(-0.3, 2.3)		60	9.4	(7.8, 11.1)	91	3.2	(1.8, 4.5)		

[1] There are 695 participants in the Mammographic Density Cohort that did not report breast tenderness at baseline. Of these, 334 are assigned to active hormone therapy (159 to active CEE and 175 to active CEE+MPA).

[2] From a multivariable repeated measures model that adjusts for age, race/ethnicity, BMI and Gail risk score. Test of whether effect of NOBT is significant within active arm.

[3] Test of whether effect of NOBT differs between active CEE and active CEE+MPA treatment groups.