Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Predictors of Breast Density Change After Hormone Therapy Cessation: Results from a Randomized Trial

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Abstract

Background: Postmenopausal hormone therapy cessation is associated with a decrease in mammographic density (MD), but it is unknown whether this effect is modified by woman-level characteristics. We investigated whether we could identify characteristics of women who were most likely to experience a decrease in MD due to hormone therapy cessation.

Methods: Postmenopausal hormone therapy users with a prior screening mammogram ($n = 1,168$) were randomized to continue hormone therapy or to suspend hormone therapy for 1 month or 2 months before their next screening mammogram. We estimated relative risks (RR) and attributable risks with 95% CIs of a $\geq$7.5% decrease in percentage MD (%MD) versus no change associated with hormone therapy cessation, stratified by age, body mass index (BMI), parity, and other factors.

Results: Hormone therapy cessation increased a woman's likelihood of experiencing a $\geq$7.5% decrease in %MD by 30% (95% CI = 1.03–1.7), but we found little evidence of effect modification by age, race, BMI, change in BMI, baseline %MD, parity, family history of breast cancer, hormone therapy type, or duration of hormone therapy use.

Conclusions: Woman-level factors do not appear to explain why some women experience a decrease in %MD following hormone therapy cessation and others do not.

Impact: We were unable to identify subgroups of women who are more likely to experience a decrease in MD due to hormone therapy cessation; other factors, such as genetic factors, may be important determinants of hormone therapy–related changes in MD. *Cancer Epidemiol Biomarkers Prev; 20(10); 2309–12. ©2011 AACR.*

Introduction

Mammographic density (MD) is a strong marker of breast cancer risk (1). Postmenopausal hormone therapy increases MD (2, 3), particularly combined hormone therapy (2), which also increases breast cancer risk (4). Postmenopausal hormone therapy cessation decreases MD in some women (5); reasons for this are not well understood. We examined whether the association between hormone therapy cessation and decrease in percentage MD (%MD) is modified by woman-level factors related to MD including age, race, body mass index (BMI), change in BMI between mammograms, baseline %MD, parity, and family history of breast cancer, as well as hormone therapy characteristics (type and duration of use; refs. 2, 3, 5). The purpose of this study was to gain insight into the relationship between hormone therapy and mammographic density change and to identify subgroups of women whose %MD might be more likely to decrease due to hormone therapy cessation.

Methods

Methods used in the Radiological Evaluation and Breast Density (READ) randomized trial have been described previously (5). Briefly, we identified women aged 45 to 80 years who reported hormone therapy use at a screening (index) mammogram conducted at Group Health Cooperative within the past 24 months. Women due for another screening (study) mammogram who had filled 2 or more hormone therapy prescriptions in the 6 months before recruitment were eligible. Of those who completed the study mammogram ($n = 1,471$), we excluded women with a baseline %MD of less than 10% ($n = 290$), as well as women missing information on BMI ($n = 13$). Study methods were approved by the Institutional Review Boards of Group Health and the U.S. Department of Defense.

Women randomized to 1 month or 2 months of hormone therapy cessation were considered "exposed" ($n = 738$) and those randomized to continue hormone therapy were "unexposed" ($n = 430$). We gathered data on potential effect modifiers (age, race, BMI, change in BMI

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Table 1. Change in %MD for continued use and hormone therapy cessation groups by demographic and reproductive factors

	Continued use group						Hormone therapy cessation group					
	Median change in %MD (95% CI)	N	Outcome: %MD change: row percent				Median change in %MD (95% CI)	N	Outcome: %MD change: row percent			
			Decrease		No change ±3%	Increase >3%			Decrease		No change ±3%	Increase >3%
			≥7.5%	>3% to <7.5%					≥7.5%	>3% to <7.5%		
Overall	−0.7 (−1.3 to −0.2)	430	15	20	36	29	−2.4 (−2.7 to −1.4)	738	21	24	32	23
Age, y												
45–55	−0.6 (−1.8 to 0.5)	116	17	17	35	30	−3.4 (−4.4 to −2.4)	199	26	25	28	20
56–65	−0.8 (−1.8 to 0.6)	214	15	21	35	29	−1.7 (−2.6 to −0.7)	381	18	24	32	25
66+	−0.6 (−1.9 to 0.9)	100	13	21	39	27	−1.4 (−3.1 to −0.3)	158	19	24	36	21
Caucasian												
No	−0.2 (−3.0 to 3.1)	31	16	16	32	35	0.7 (−2.2 to 3.0)	70	17	20	24	39
Yes	−0.8 (−1.4 to −0.2)	398	15	21	36	28	−2.4 (−3.0 to −1.7)	664	21	25	33	22
Baseline BMI, kg/m^2												
<25	−0.2 (−1.4 to 1.0)	191	17	15	34	34	−1.6 (−2.6 to −0.3)	311	20	22	31	27
25–30	−0.7 (−1.7 to −0.1)	147	12	23	39	26	−2.0 (−3.0 to −0.7)	244	20	24	32	24
>30	−1.4 (−3.5 to 0.05)	92	17	25	35	23	−3.4 (−4.4 to −2.0)	183	22	29	33	16
Baseline %MD												
10% to <20%	−0.3 (−1.4 to 0.6)	137	4	21	50	26	−0.8 (−1.8 to 0.3)	241	9	27	40	24
20% to <30%	0.2 (−1.0 to 2.0)	119	12	19	34	35	−1.7 (−2.5 to −0.6)	201	17	24	36	23
30% to <40%	−2.6 (−4.4 to −0.1)	87	25	23	26	25	−3.4 (−4.8 to −2.0)	152	28	25	26	20
40+%	−2.6 (−4.9 to −0.3)	87	29	16	26	29	−5.1 (−7.0 to −2.7)	144	38	20	18	24
Parity												
Parous	−0.9 (−1.5 to −0.2)	347	16	20	36	27	−2.3 (−2.9 to −1.5)	583	21	25	32	23
Nulliparous	−0.2 (−1.1 to 1.8)	82	12	18	35	34	−1.5 (-3.2 to −0.3)	153	20	24	33	24
Family history of breast cancer (first degree)												
No	−0.4 (−0.9 to 0.2)	330	16	18	36	30	−2.3 (−3.0 to −1.5)	589	21	24	31	23
Yes	−2.2 (−3.4 to −0.4)	89	12	30	31	26	−1.7 (−3.2 to −0.5)	130	19	24	35	22
Change in BMI, kg/m^2												
Decrease >1.5	1.1 (−3.4 to 4.3)	37	11	24	30	35	−0.9 (−3.6 to 0.2)	64	16	23	38	23
No change (≤1.5)	−0.4 (−1.4 to 0.4)	286	16	18	35	31	−2.0 (−2.6 to −1.1)	486	21	24	30	26
Increase >1.5	−1.8 (−3.5 to −0.7)	84	17	24	39	20	−2.9 (−4.1 to −1.7)	159	22	27	33	18
Hormone therapy type												
Estrogen therapy	−0.9 (−1.7 to −0.2)	264	16	22	35	27	−2.1 (−2.7 to −1.1)	450	19	25	33	23
Estrogen + progesterone	−0.2 (−1.4 to 0.8)	166	14	16	37	32	−2.4 (−3.4 to −1.2)	288	24	24	30	23
Duration of prior hormone therapy use at baseline, y												
<5	0.5 (−1.1 to −2.5)	57	16	14	37	33	−1.7 (−5.1 to 1.7)	86	31	13	24	31
5–9	−1.2 (−2.8 to 0.5)	93	18	18	35	28	−2.7 (−3.9 to −1.6)	159	23	25	35	17
10–14	−0.7 (−1.8 to 2.0)	83	14	20	29	36	−2.2 (−3.5 to −1.0)	167	17	28	32	23
15+	−0.9 (−1.6 to 0.2)	173	14	22	38	25	−2.0 (−3.1 to −0.6)	277	20	25	33	22

NOTE: Row percents may not add to 100 because of rounding to the nearest 1%. N's may not sum to totals due to missing values. The study had 88% power to detect a 7% change in density among exposed women, if there were no change among unexposed.

Table 2. Effect of hormone therapy cessation on likelihood of a decrease in %MD between mammograms: RRs and ARs of a decrease in %MD of ≥7.5% versus no change (3%), overall and by reproductive and demographic subgroups

	Continued hormone therapy use (referent group)		1- to 2-mo hormone therapy cessation		1- to 2-mo vs. no hormone therapy cessation	
	No change,[a] *n* (%)	Decrease ≥7.5%, *n* (%)	No change, *n* (%)	Decrease ≥7.5%, *n* (%)	RR[b] (95% CI)	AR[b,c] (%) (95% CI)
Overall effect	154 (100)	66 (100)	235 (100)	152 (100)	1.3 (1.03–1.7)	9 (2–17)
Age, y						
66+	39 (25)	20 (30)	57 (24)	30 (20)	1.5 (1.0–2.2)	9 (−6 to 25)
56–65	74 (48)	33 (50)	122 (52)	70 (46)	1.2 (0.8–1.7)	6 (−5 to 17)
45–55	41 (27)	20 (30)	56 (24)	52 (34)	1.4 (0.8–2.4)	15 (0–30)
BMI,[d] kg/m^2						
<25	65 (42)	32 (48)	96 (41)	54 (40)	1.2 (0.9–1.7)	7 (−5 to 19)
25–30	57 (37)	18 (27)	79 (34)	48 (32)	1.6 (1.0–2.5)	14 (1–27)
>30	32 (21)	16 (24)	60 (26)	41 (27)	1.2 (0.8–1.9)	7 (−9 to 24)
Baseline %MD[d]						
10% to <20%	68 (44)	5 (8)	97 (41)	21 (14)	2.6 (1.02–6.6)	11 (2–20)
20% to <30%	40 (26)	14 (21)	72 (31)	34 (22)	1.2 (0.7–2.1)	6 (−9 to 21)
30% to <40%	23 (15)	22 (33)	40 (17)	43 (28)	1.1 (0.7–1.5)	3 (−15 to 21)
40+%	23 (15)	25 (38)	26 (11)	54 (36)	1.3 (0.9–1.8)	15 (−2 to 33)
Parity						
Parous	125 (81)	56 (85)	185 (79)	121 (80)	1.3 (1.0–1.7)	9 (0–17)
Nulliparous	29 (19)	10 (15)	50 (21)	31 (20)	1.5 (0.8–2.7)	13 (−5 to 30)
Family history of breast cancer (first degree)						
Yes	28 (18)	11 (17)	45 (19)	25 (16)	1.3 (0.7–2.3)	10 (1–19)
No	120 (78)	52 (79)	185 (79)	125 (82)	1.3 (1.0–1.7)	8 (−11 to 26)
Change in BMI						
Decrease >1.5	11 (7)	4 (6)	24 (10)	10 (7)	1.1 (0.4–3.0)	3 (−24 to 30)
No change (≤1.5)	99 (64)	46 (70)	145 (62)	100 (66)	1.3 (1.0–1.7)	9 (0–19)
Increase >1.5	33 (21)	14 (21)	53 (23)	35 (23)	1.3 (0.8–2.2)	10 (−7 to 27)
Hormone therapy type						
Estrogen therapy	92 (60)	42 (64)	149 (63)	84 (55)	1.2 (0.8–1.6)	5 (−5 to 15)
Estrogen + progesterone	62 (40)	24 (36)	86 (37)	68 (45)	1.6 (1.1–2.3)	16 (4–29)
Hormone therapy duration,[e] y						
<5	21 (14)	9 (14)	21 (9)	27 (18)	1.9 (1.0–3.4)	26 (5–48)
5–9	33 (21)	17 (26)	55 (23)	37 (24)	1.2 (0.7–1.9)	6 (−10 to 23)
10–14	24 (16)	12 (18)	54 (23)	28 (18)	1.0 (0.6–1.8)	1 (−18 to 19)
15+	66 (43)	25 (38)	91 (39)	55 (36)	1.4 (0.9–2.0)	10 (2–22)

[a]Percentages may not add to 100 because of rounding to the nearest 1%.
[b]Unadjusted (assignment to the exposure was randomized and is not associated with other factors; ref. 5).
[c]AR: cumulative incidence (proportion) of women in the cessation group who experienced a decrease in MD of ≥7.5% due to hormone therapy cessation.
[d]At index mammogram.
[e]Duration of prior hormone therapy use at baseline.

between mammograms, baseline %MD, parity, and family history of breast cancer, hormone therapy type, duration of hormone therapy use) from automated databases and study questionnaires (5). We defined change in BMI between mammograms as a change of 1.5 units or more (kg/m^2), corresponding to a weight change of approximately 7 to 11 pounds for height 4′11″ to 6′0″. Buist and colleagues used Cumulus software to measure dense area and total breast area in digitized left breast craniocaudal projections; %MD was calculated as dense area divided by total area (5).

We report median change in %MD between mammograms with 95% CIs by woman-level characteristics, separately by exposure status. We used generalized

linear models (GLM) with a log link and a robust variance estimator to estimate relative risks (RR) of decreasing %MD versus no change associated with hormone therapy cessation (see definitions of change below). We used GLM with an identity link to estimate attributable risks (AR). We report RRs and ARs with 95% CIs by subgroup of each potential effect modifier to assess whether certain women were more likely to experience a decrease in %MD due to cessation. To estimate RRs and ARs, we compared women who decreased ≥7.5% MD versus women with no change (defined as an absolute change of ≤3% MD). A 7.5% decrease in %MD was approximately the median level of decrease among women whose %MD decreased (>3%) and may represent a clinically relevant level of decrease. Studies suggest that women with a given %MD have a 15% to 20% higher risk of breast cancer than women whose %MD is lower by 10% (6,7). All analyses were conducted using STATA version 11.1 (StataCorp).

Results

Women randomized to suspend hormone therapy had a greater median decrease in %MD between mammograms than continued users (−2.4% vs. −0.7%), and a greater proportion who decreased by ≥7.5% MD (21% vs. 15%; Table 1). Overall, hormone therapy cessation was associated with a 30% increased likelihood of a ≥7.5% MD decrease versus no change (RR = 1.3, 95% CI = 1.03–1.7) and an attributable risk of 9% (95% CI = 2–17). We found little evidence of effect modification by the factors studied on either a multiplicative or an additive scale (Table 2).

Discussion

We did not observe strong evidence that the effect of hormone therapy cessation on %MD varies by woman-level characteristics. Our findings suggest that hormone therapy cessation may have a similar biological effect on %MD regardless of age, BMI, baseline %MD, and the other factors we examined. Although we used continuous measures of %MD, which are more precise than commonly used categorical measures, and a single trained reader interpreted all mammograms, measurement error of %MD remains a concern. Quality control sampling indicated that less than 10% of mammography rereads differed by ≥7.5% MD. We were unable to measure %MD immediately before hormone therapy cessation. However, our comparison of 2 large, randomized groups allowed us to infer this change with reasonable confidence. Additional strengths include a large sample size, randomization of exposure, high compliance with the intervention (8), and high-quality administrative data.

Our findings suggest that hormone therapy cessation–associated decrease in %MD is not predicted by woman-level factors. Other explanations for why subsets of women experience %MD decreases due to hormone therapy cessation, such as genetic factors, should be considered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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