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EPIDEMIOLOGY

Hormone therapy use and mammographic density in postmenopausal Norwegian women

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Abstract While studies have shown that use of postmenopausal hormone therapy with estrogen and progestogen (EPT) increases mammographic density, aspects of this association remain unclear. We examined whether mammographic density differed by type of hormone therapy (HT) used, dose, duration of use, time since last use, and whether the effects are modified by age and body mass index (BMI). Using a cross-sectional design, we recruited 2,424 postmenopausal women aged 50–69 years participating in the Norwegian Breast Cancer Screening Program. Mammographic density was assessed with a computer-assisted method, and we estimated mean absolute and percent mammographic density through multiple linear regression, and adjusting for possible confounders. Mammographic density was higher among current HT users (percent density: 22.6%; 95% CI: 22.1–23.2%) than among former (17.7%; 17.2–18.2%) or never users (16.3%; 15.7–16.8%). The highest density was seen in current EPT users of high-dose norethisterone acetate (NETA) regimens who had a percent density of 26.2% (24.3–28.1%). Results differed when considering the combined effect of age and BMI. The effect of EPT on mammographic density was modified by age and BMI, with no apparent association among the youngest women (aged 50–55) with the highest BMI (BMI $\geq$ 26). A higher mammographic density was found in EPT users compared to never HT users, particularly in women using high-dose NETA regimens. Age and BMI modified the association between EPT use and mammographic density.

Keywords Hormone therapy · Mammographic density · Body mass index

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List of abbreviations

EPT	Estrogen and progestogen
HT	Hormone therapy
BMI	Body mass index
PD	Percent density
NETA	Norethisterone acetate
ET	Estrogen-alone regimens
NBCSP	Norwegian breast cancer screening program

Introduction

Mammographic density refers to the white (radiodense) areas on a mammogram and reflects the amount of stroma and epithelium in the breast, as opposed to fat that appears dark (radiolucent) [1]. High mammographic density is a strong risk factor for breast cancer and confers a four- to fivefold increase in risk [1, 2]. Mammographic density is highly related to screening sensitivity, with higher mammographic density inversely associated with poorer sensitivity [3, 4]. Hence, factors increasing mammographic density are expected to decrease mammographic sensitivity and, subsequently, the effectiveness of mammographic screening. It is therefore important to identify factors associated with mammographic density.

Mammographic density declines after menopause [5, 6], suggesting that hormonal factors are important determinants of mammographic density. It has been consistently shown that combined estrogen–progestogen therapy (EPT) increases mammographic density [7–18]. However, certain aspects of this association need to be further clarified. While mammographic density is clearly higher in users of EPT compared to never users [7–9, 11, 12, 15, 17, 18], the effect of estrogen-alone regimens (ET) remains unclear [8–10, 12, 15, 17, 18]. Furthermore, it is not clear whether different types of EPT have different effects on mammographic density. For example, norethisterone acetate (NETA) regimens have been shown to be associated with a higher risk of breast cancer than other types of EPT [19], but only a limited number of studies have examined whether this type of EPT affects mammographic density differently than other types [7, 15]. Furthermore, few studies have investigated mammographic density in relation to duration of hormone therapy (HT) use, or the time since stopping HT, and the results have been inconclusive [7, 14, 15].

Postmenopausal EPT is a recognized risk factor for breast cancer [20–23]. Several factors, important in the etiology of breast cancer, are also determinants of mammographic density. Studies have consistently shown that mammographic density declines with increasing age and body mass index (BMI) [9, 24]. Although there is evidence that age and BMI may separately modify the effect of HT on mammographic density [10–12, 16, 18], it is not clear how the two factors combined affect density.

In this article, we used a cross-sectional design and recruited women through the Norwegian Breast Cancer Screening Program (NBCSP), in order to examine the association between HT use and mammographic density.

Materials and methods

Participants and study design

All Norwegian women aged 50–69 years are biennially invited by the NBCSP to undergo a bilateral two-view mammogram. We recruited women to our cross-sectional study through the NBCSP. All women invited to participate in the screening program during specific weeks of 2004 in three selected counties (Oslo, Akershus, and Hordaland) were invited to our study. We sent a study invitation, a consent form, and a questionnaire with the invitation to attend the NBCSP. Women were asked to bring the completed informed consent and questionnaire with them on the day of their appointment. All women who returned a signed informed consent were eligible to participate. A total of 17,050 women were invited to participate in our study, among those 12,056 (70.7%) attended the screening. The project was approved by the regional ethics committee and the Norwegian Data Inspectorate.

The study questionnaire included questions on anthropometric measurements, age at menarche, reproductive history, history of oral contraceptive and postmenopausal HT use, family history of breast cancer, and demographic history. Among the 12,056 eligible women, 7,941 (66%) returned the questionnaire and a signed informed consent. A dietary questionnaire was sent to 7,174 women who had agreed to complete it. We requested mammograms of the women who had returned a completed dietary questionnaire and had undergone a mammogram in 2004 ($N = 3{,}180$), and we obtained mammograms for 2,876 of them.

Mammographic density assessment

Left breast cranio-caudal mammograms were digitized using a Kodak Lumisys 85 scanner (Kodak, Rochester, New York, USA). Mammographic density was assessed on the digital images using the University of Southern California Madena computer-based method, which has previously been described and validated [25]. In brief, the Madena program works as follows: A reader pulls up the mammogram on a computer screen and first defines the total breast area using a special outlining tool; the software then estimates the total number of pixels in the breast (total breast area). Next, the density is assessed as follows: The reader defines a region of interest in the breast that contains all the densities, but that excludes the pectoralis muscle, prominent veins, fibrous strands, and other light artifacts. The reader uses a tinting tool to apply a yellow tint to the area within the region of interest considered to represent densities. The software estimates the number of tinted

pixels within the region of interest (absolute density). The percent density is the absolute density area divided by the total breast area (multiplied by 100). The density assessments were performed by an experienced reader (GU), whereas the breast area measurements were taken by MH (after training by GU). The readers were blinded to all subject characteristics.

Exclusions

Women with previous history of breast ($N = 12$) or ovarian ($N = 5$) cancers were excluded. Fifteen women aged less than 50 or more than 69 years at recruitment were excluded. This report only considered postmenopausal women, and we therefore excluded 417 pre- or perimenopausal women. Women were considered postmenopausal if they had reported (a) complete cessation of menstruation for a period of at least 6 months, (b) previous bilateral oophorectomy, (c) hysterectomy without bilateral oophorectomy, or (d) used HT before menstruation had stopped. This report primarily investigates the effect of EPT and/or ET use on mammographic density; hence, 3 women exclusively using progestogen were excluded. In the present report, 2,424 women were included.

Statistical analyses

We used multiple linear regression models to calculate least square means of percent and absolute density according to HT use. The mammographic density variables were treated in a continuous manner, without any transformations, as the models' residuals satisfied the normality and homoscedasticity assumptions [26]. We assessed mean mammographic density in never, former, and current HT users and examined the effect of duration of use, as well as time since cessation of HT use, and type of HT (EPT vs. ET regimens, low and high EPT doses, and NETA users or not). Women were considered as current users if they had been using the specified HT for more than 3 months. Users of low-dose NETA regimens were women using 1 mg of estradiol and 0.5 mg of NETA (Activelle®), and high-dose NETA preparations were 2 mg of estradiol and 1 mg of NETA (Kliogest®). Ascertainment of HT use was done with two questions asking about (1) ever use of HT—with a proposed list of HT preparations—and (2) current use of HT. Therefore, a woman could have used more than one type of HT, and, in particular, she could have used both ET and EPT, or NETA and non-NETA regimens in her lifetime. Previous and current use of HT was entered in the model simultaneously to account for the fact that women could have used different HT preparations in their lifetime. HT use was also examined constructing variables that measured the combined use of different HT types considering all possible combinations of use. Models were adjusted for confounders selected a priori: age at screening (continuous), BMI (in kg/m^2, continuous), number of children (continuous), age at first childbirth (continuous), first-degree family history of breast cancer (categorical: yes/no), and number of years spent in school (continuous). The categorical variables for HT use and breast cancer family history were entered in the model constructed as dummy variables, with never HT use representing the reference category for HT use, and no breast cancer in a first-degree relative as a reference category for breast cancer family history. We also considered a number of other potential confounders, such as age at menarche, age and type of menopause, oral contraceptive use, consumption of alcohol, and physical activity. However, as adjusting for these variables influenced the estimates by less than 5%, they were not included in the final model. We investigated possible effect modification by age and BMI on the association between EPT use and mammographic density by stratifying analyses by age and BMI. We used χ^2 tests for heterogeneity and trend to evaluate differences in estimates of mammographic density by EPT use. Interaction by age and BMI, respectively, was evaluated by entering interaction terms in the model, and, in each case, using a likelihood ratio test to compare the model with an interaction term with the model without the interaction term.

Results

Ever users of HT had a lower BMI, were more likely to have used oral contraceptives, had fewer children, and no first-degree relative diagnosed with breast cancer compared to women who never used HT (Table 1).

Overall, the average percent mammographic density was 18.2% (95% CI: 17.9–18.5%), and the average absolute density was 23.5 cm^2 (95% CI: 23.3–23.7 cm^2) (Table 2). Both percent and absolute density were higher in women who reported to have ever used HT compared to never users. When comparing current, former, and never HT users, we found the highest mammographic density in current HT users, followed by former users, and the lowest densities in never HT users, with percent densities of 22.6% (22.1–23.2%), 17.7% (17.2–18.2%), and 16.3% (15.7–16.8%), respectively. Similar results were obtained for absolute density. Women who reported having ever used EPT had higher percent density, with the highest density seen in current EPT users. Women who were currently using EPT had percent density of 25.4% (24.6–26.1%) compared to 16.3% (15.7–16.8%) in never HT users, with similar results seen for absolute density. Current ET users had percent density of 18.9% (17.6–20.2%). However, mammographic density in ET

Table 1 Characteristics of never and ever users of hormone therapy

	Hormone therapy use	
	Never users	Ever users
Hormone therapy use (N)	1,053	1,371
Age at screening (mean, ±SD)	58.2 (±5.8)	58.6 (±5.0)
Body mass index (N, %)		
≤23	320 (31.1)	424 (31.7)
>23, ≤26	322 (31.3)	486 (36.3)
>26	386 (37.5)	427 (31.9)
Years of school (N, %)		
≤9	181 (17.4)	209 (15.4)
10–12	373 (36.0)	463 (34.2)
13–16	307 (29.6)	443 (32.7)
17+	176 (17.0)	240 (17.7)
Age at menarche (in years, N, %)		
<12	115 (11.0)	137 (10.1)
12–14	788 (75.3)	986 (72.6)
15+	143 (13.7)	235 (17.3)
Oral contraceptive use (N, %)		
No	590 (58.0)	588 (45.6)
Yes	427 (42.0)	701 (54.4)
Age at first child (in years, mean, ±SD)	22.1(± 8.2)	22.4 (± 7.5)
Number of children (N, %)		
0	100 (9.5)	115 (8.4)
1	108 (10.3)	161 (11.7)
2–3	702 (66.7)	999 (72.9)
4+	143 (13.6)	96 (7.0)
Age at menopause (in years, mean, ±SD)	49.5 (±5.1)	49.2 (±5.5)
Type of menopause (N, %)		
Natural	872 (89.2)	748 (62.4)
Use of hormone therapy	0 (0)	230 (19.2)
Surgical menopause	101 (10.3)	217 (18.1)
Radiotherapy or chemotherapy	4 (0.4)	3 (0.2)
First-degree family history of breast cancer (N, %)		
None	923 (87.6)	1251 (91.2)
At least one fist-degree relative	130 (12.3)	120 (8.7)

Due to missing values, numbers in subcategories do not add up

users was higher than never HT users' only in women who had formerly used EPT with percent density of 22.3% (20.3–24.3%), compared to 15.0% (13.8–16.2%) in former users of ET. Current tibolone users had a mammographic density similar to never HT users: 17.7% (16.5–19.0%) compared to 16.6 (16.0–17.1%) in never users. All former tibolone users had also used another HT type (ET or EPT); specifically, 21 out of the 89 former users of tibolone were also current users of another HT type, and 68 had also formerly used another HT type. When examining the association between duration of EPT use and mammographic density in current users, percent and absolute densities remained the same across different strata of duration (Table 2). When considering total duration in ever EPT users, higher percent and absolute densities were seen with higher total duration of EPT use. Women who had used HT for 8 or more years had percent densities of 21.6% (20.7–22.6%), compared to 19.6% (18.5–20.6%) in women who had used HT for 4 years or less (p for trend = 0.01). We also examined the association between time since last EPT use and mammographic density and found different results for percent and absolute densities (Table 2). While we found significantly lower percent density with higher numbers of years since stopping EPT (p for trend = 0.03), no statistically significant association was found between absolute density and years since stopping EPT (p for trend = 0.17).

Overall, lower percent mammographic density was seen with lower age and BMI (Table 3). In statistical analyses stratified by BMI or age, we found higher densities with EPT use in all categories of BMI or age. However, when stratifying the analyses by both age and BMI, no association between EPT use and percent density was found in younger women (aged ≤ 55) with a higher BMI (BMI ≥ 26). Among these women, the percent density was 12.3% (11.2–13.4%) in never HT users and 12.0% (10.5–13.2%) in ever EPT users. In all other categories of age and BMI considered, percent density was statistically higher in ever EPT users compared to never HT users. We found an interaction between age and EPT use for absolute density ($P = 0.01$). However, there was no statistically significant interaction between age and never/ever EPT use with respect to percent density ($P = 0.10$). For BMI, there was a statistically significant interaction for percent density ($P = 0.03$) and no statistically significant interaction for absolute density ($P = 0.56$).

Percent density differed according to the type of EPT regimens used (Table 4). Higher densities were seen in ever NETA regimen users compared to ever users of other EPT types. Estimates of percent density were 20.7% (20.2–21.1%) in ever NETA regimen users and 19.6% (18.3–20.8%) in ever users of other types of regimens. Most current users of non-NETA regimens (7 out of 12) were former users of NETA preparations. Lower percent densities were seen in users of low doses of NETA EPT regimens (1 mg of estradiol, 0.5 mg of NETA, Activelle®) compared to high-dose (2 mg of estradiol, 1 mg of NETA, Kliogest®) users. Among current NETA users, the estimates of percent density were 24.6 (23.7–25.5%) and 26.2% (24.3–28.1%) in low- and high-dose NETA regimen users, respectively. However, differences in mammographic density between high- and low-dose NETA regimen users did not reach statistical significance.

Table 2 Percent and absolute mammographic density according to hormone therapy use, duration of use, and time since last use

		Percent density		Absolute density	
		% (95% CI)		cm^2 (95% CI)	
	N[a]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Overall	2424	18.3 (17.6–18.9)	18.2 (17.9–18.5)	23.4 (22.6–24.2)	23.5 (23.3–23.7)
Hormone therapy use					
Never	1053	16.4 (15.4–17.3)	16.3 (15.7–16.8)	21.1 (19.9–22.3)	21.0 (20.6–21.3)
Ever	1371	19.8 (18.9–20.6)	19.6 (19.3–20.0)	25.2 (24.0–26.3)	25.4 (25.1–25.7)
Former	842	18.1 (17.0–19.1)	17.7 (17.2–18.2)	23.4 (22.0–24.8)	23.6 (23.3–23.9)
Current	529	22.5 (21.0–23.9)	22.6 (22.1–23.2)	28.1 (26.2–30.0)	28.2 (27.8–28.6)
Never	1053	16.4 (15.4–17.3)	16.3 (15.7–16.8)	21.1 (19.9–22.3)	21.0 (20.6–21.3)
Former ET/No EPT	118	15.4 (12.6–18.1)	15.0 (13.8–16.2)	22.4 (18.6–26.3)	22.7 (21.9–23.6)
Former EPT[d]/No ET	609	18.8 (17.5–20.0)	18.4 (17.9–19.0)	23.9 (22.3–25.5)	24.1 (23.7—24.4)
Former EPT/Former ET	80	16.3 (13.2–19.5)	16.3 (14.8–17.8)	21.1 (17.3–24.8)	22.1 (21.1–23.1)
Current ET/No EPT	94	17.7 (14.6–20.8)	17.4 (15.8–19.0)	22.4 (18.6–26.2)	22.6 (21.6–23.7)
Current ET/Former EPT	42	21.9 (17.7–26.0)	22.3 (20.3–24.3)	27.7 (21.1–34.3)	27.1 (25.7–28.5)
Current EPT/No ET	274	25.1 (23.0–27.1)	25.4 (24.7–26.2)	30.2 (27.6–32.8)	30.5 (30.0–31.0)
Current EPT/Former ET	22	25.1 (16.8–33.5)	23.7 (20.7–26.8)	34.2 (23.9–44.4)	31.9 (29.8–34.0)
Never		16.4 (15.4–17.3)	16.6 (16.0–17.1)	21.1 (19.9–22.3)	21.4 (21.1–21.8)
Former ET	220	16.7 (14.6–18.8)	16.4 (15.4–17.4)	23.4 (20.4–24.8)	23.5 (22.3–24.2)
Former tibolone	89	24.9 (20.4–29.4)	25.6 (24.2–27.1)	28.5 (24.1–33.0)	29.4 (28.4–30.4)
Former EPT	731	18.7 (17.6–19.8)	18.4 (17.9–18.9)	23.8 (22.3–25.3)	24.0 (23.7–24.4)
Current ET	136	19.0 (16.5–21.5)	18.9 (17.6–20.2)	24.1 (20.7–27.4)	24.0 (23.1–24.9)
Current tibolone	83	17.2 (13.8–20.5)	17.7 (16.5–19.0)	23.3 (18.3–28.4)	24.5 (23.7–25.4)
Current EPT	296	25.1 (23.1–27.1)	25.4 (24.6–26.1)	30.5 (28.0–33.0)	30.6 (30.3–31.1)
Duration of hormone therapy use (in years, in EPT users)[f]					
In current users					
<2	86	25.7 (22.3–29.0)	25.6 (23.7–27.4)	29.7 (25.8–33.6)	29.7 (28.6–30.3)
2–3	82	22.5 (18.9–26.2)	22.7 (21.0–24.5)	29.0 (24.1–34.0)	29.0 (28.4–29.5)
4+	110	25.9 (22.4–29.3)	26.4 (24.9–28.0)	31.7 (27.1–36.2)	32.0 (31.6–32.5)
			$p_{(trend)} = 0.43$		$p_{(trend)} = 0.56$
Total duration of hormone therapy use (in years, in ever EPT users)					
<4	231	19.0 (17.0–20.7)	19.6 (18.5–20.6)	23.7 (21.4–26.0)	24.2 (23.6–24.8)
4–7	289	21.8 (19.8–23.7)	21.7 (20.7–22.6)	26.9 (24.4–29.5)	27.0 (26.5–27.5)
8+	260	21.7 (19.6–23.7)	21.6 (20.7–22.6)	27.6 (24.7–30.4)	28.0 (27.5–28.5)
			$p_{(trend)} = 0.01$		$p_{(trend)} = 0.01$
Time since last hormone therapy use (in years, in former EPT users)					
≤1.5	158	20.0 (17.4–22.5)	19.5 (18.5–20.5)	24.6 (21.3–27.8)	24.5 (24.0–25.1)
>1.5–3	166	18.4 (16.2–20.7)	18.8 (17.5–19.8)	23.4 (20.6–26.2)	24.5 (23.9–25.1)
>3	149	15.2 (13.1–17.3)	14.3 (13.2–15.4)	21.2 (18.1–24.3)	20.5 (19.8–21.1)
			$p_{(trend)} = 0.03$		$p_{(trend)} = 0.17$

[a] Due to missing values, numbers in subcategories do not add up

[b] Adjusted for age at screening (continuous), body mass index (continuous), number of children (continuous), age at first childbirth (continuous), first-degree family history of breast cancer (yes/no), and number of years spent at school (<6, 7–9, 10–11, 12, 13–14, 15–16, 17+)

[c] *ET* estrogen-only hormone therapy

[d] *EPT* estrogen and progestogen therapy

[f] The analyses were adjusted for use of ET further to the above mentioned variables (no ET use, former ET user, and current ET user)

Discussion

Ever users of postmenopausal HT had higher percent and absolute mammographic densities compared to never users, with higher densities found in EPT users. The difference observed between users and nonusers of EPT was modified by age and BMI, with no statistical association between EPT use and mammographic density seen in younger women (aged 50–55), with a higher BMI (BMI $\geq$ 26).

Our results are consistent with the published literature [8–12, 17]. Previous studies have also reported higher mammographic density among EPT users compared to ET users [9–12, 17, 18]. Mammographic density is a strong risk factor for breast cancer [1, 2], and the use of EPT is a recognized risk factor for breast cancer. Studies investigating the relationship between HT use and breast cancer risk reported similar results with higher breast cancer risk associated with the use of EPT than with ET [21, 23, 27]. However, while studies have consistently showed that EPT use is associated with higher densities than ET, results on whether ET users have a higher mammographic density than never HT users are more contradictory [8–10, 12, 15, 17, 18]. Several studies have examined the effect of HT type on mammographic density (or breast cancer risk) without accounting for the possible use of different preparations in a woman's life. This may explain the differences in results seen in the published literature. In our study, we have only observed higher densities in ET users compared to never HT users in women who have also used EPT preparations at one point in their life.

Age and BMI are strong determinants of mammographic density; mammographic density declines with increasing age and BMI [9, 24]. When stratifying the analyses by age and BMI, no statistical association between EPT use and mammographic density was found in women aged 50–55 years with a BMI of 26 and greater. To our knowledge, no previous study has examined the combined effect of both age and BMI on the association between mammographic density and HT use. Studies examining the possible modifying effect by age have reported no association between HT use and mammographic density in women aged 55 or less [10–12, 16, 18]. Two studies examining HT use and mammographic density reported no interaction by BMI [8, 16]. Our results suggest that epidemiological studies investigating the association between mammographic density and EPT should consider both age and BMI as possible effect modificators. These results may indicate that a woman's age and BMI should be considered when deciding whether to prescribe HT. We cannot rule out that the differing results seen when stratifying by both age and BMI are due to chance. More studies are needed to investigate the possible modifying effect of age and BMI on the association between EPT use and mammographic density.

Studies investigating HT use and breast cancer risk have shown that the increase in breast cancer risk observed in current HT users is not seen in the past HT users [20, 21]. Consistent with these studies, we found the highest mammography density in current users, followed by former and never users. Furthermore, our results suggest that percent mammographic density declines with years since last EPT use, with women who stopped using EPT more than 3 years ago having percent density similar to never users. Epidemiological studies have also investigated the effect of short-term HT cessation on mammographic density [28–30]: One observational study mentioned no effect [29] and another one [30] and a clinical trial [28] reported reduced mammographic density after stopping use of postmenopausal HT. The reduction in density was reported following cessations for 2 weeks [30] and 1 or 2 months [28]. Our data showed that while percent mammographic density was lower with higher time since last EPT use, no association was found for absolute density. It is possible that it is the breast area, rather than the dense area, that changed. We examined breast area according to time since last use and found average breast areas of 141.4 cm^2 (135.5–147.3), 1,492 cm^2 (142.6–155.8), and 163.8 cm^2 (157.0–170.5) for women stopping within the past 2 years, for more than 2 years and up to 4 years, and for more than 4 years, respectively (p for trend = 0.08).

A strength of this study is that women completed the study questionnaire ascertaining covariates of interest before coming to mammographic screening. Further, women are usually not aware what their mammographic density is as this is not a variable that is typically reported by radiologists in Norway. Thus, chances of recall bias are minimal. Furthermore, previous and current use of HT was ascertained allowing to adjust analyses for the use of different HT type in a woman's lifetime.

One weakness of this study is that mammographic density was measured only once and relied on cross-sectional mean differences between the study groups, rather than changes in density following start of HT use. However, our results are consistent with both observational studies [6, 9, 12, 13, 17, 31] and clinical trials [8, 10, 11] that have examined changes in mammographic density with postmenopausal HT use and that have consistently reported higher mammographic density in EPT users than in never users.

The evidence published to date indicates that it is possible that use of postmenopausal EPT counteracts the beneficial effect of menopause on mammographic density [6]. During menopause, levels of estrogen decrease leading to a decline in epithelial cell proliferation rates, a reduction in stromal elements, and fatty replacement [32]. Exogenous hormone use, such as HT, may reverse this effect by increasing hormone level. McCormack et al. [6] have

Table 3 Percent mammographic density according to the use of combined estrogen–progestogen therapy (EPT) by tertiles of body mass index and age at screening

	Percent density (number of women[a] and % (95% CI)[b]					
	Stratification by body mass index (BMI)					
	≤23		>23–<26		≥26	
Overall	648	26.4 (25.9–26.8)	711	18.8 (18.4–19.2)	674	10.3 (10.0–10.5)
Never used HT[c]	320	24.6 (24.0–25.2)	322	16.8 (16.2–17.3)	386	8.9 (8.6–9.3)
Ever EPT[d] users	328	28.1 (27.5–28.7)	389	20.4 (20.0–20.8)	288	12.0 (11.7–12.3)
Never used HT	320	24.6 (24.0–25.2)	322	16.8 (16.3–17.3)	386	8.9 (8.6–9.3)
Former EPT users	212	25.8 (25.1–26.5)	282	18.8 (18.3–19.3)	219	11.4 (11.1–11.8)
Current EPT users	116	32.0 (31.0–33.0)	107	24.6 (23.8–25.3)	69	14.1 (13.5–14.6)
		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$
	Stratification by age at screening (in years)					
	≤55		56–60		61+	
Overall	685	21.3 (20.7–21.9)	671	18.9 (18.3–19.5)	714	15.1 (14.5–15.6)
Never used HT	410	20.5 (19.7–21.3)	281	16.1 (15.1–17.1)	355	11.6 (10.9–12.3)
Ever EPT users	275	22.4 (21.5–23.4)	390	20.8 (20.2–21.5)	359	18.6 (18.0–19.1)
Never used HT	410	20.5 (19.7–21.3)	281	16.1 (15.2–17.1)	355	11.6 (10.9–12.3)
Former EPT users	169	21.3 (20.1–22.5)	275	18.6 (17.8–19.4)	284	16.7 (16.0–17.3)
Current EPT users	106	24.3 (22.8–25.8)	115	25.9 (24.7–27.1)	75	25.6 (24.6–26.6)
		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$
Total duration of EPT use (in years, in tertiles specific to each age strata[e])						
Short duration	92	21.7 (19.9–23.5)	116	21.3 (20.0–22.5)	80	14.9 (13.3–16.5)
Middle duration	70	24.7 (22.4–26.9)	90	20.0 (18.3–21.7)	87	22.7 (21.2–24.2)
Long duration	65	22.1 (19.9–24.4)	92	22.5 (20.9–24.0)	73	20.9 (19.3–22.5)
		$p_{(\text{trend})} = 0.49$		$p_{(\text{trend})} = 0.44$		$p_{(\text{trend})} = 0.13$
	Stratification by age at screening and BMI					
	≤55 years old		56–61 years old		62+ years old	
BMI of ≤23						
Never used HT	141	27.4 (26.5–28.4)	73	25.9 (24.8–26.9)	103	19.5 (18.5–20.5)
Ever EPT users	94	29.2 (27.9–30.4)	115	29.5 (28.5–30.4)	118	26.0 (25.0–27.0)
		$p_{(\text{heterogeneity})} = 0.02$		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$
BMI of >23–<26						
Never used HT	140	20.0 (19.4–20.5)	88	16.4 (15.4–17.4)	92	12.3 (11.5–13.2)
Ever EPT users	108	22.9 (22.3–23.6)	143	20.6 (19.8–21.3)	137	18.1 (17.4–18.8)
		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$
BMI of 26+						
Never used HT	119	12.3 (11.2–13.4)	112	9.4 (8.8–9.9)	153	6.3 (5.9–6.6)
Ever EPT users	66	12.0 (10.5–13.2)	128	13.6 (13.2–14.0)	93	10.0 (9.5–10.6)
		$p_{(\text{heterogeneity})} = 0.74$		$p_{(\text{heterogeneity})} < 0.01$		$p_{(\text{heterogeneity})} < 0.01$

Women exclusively using estrogen-alone regimens (ET) were excluded

[a] Due to missing values, numbers in subcategories do not add up

[b] Analyses were adjusted for age at screening (continuous), body mass index (continuous), number of children (continuous), age at first childbirth (continuous), first-degree family history of breast cancer (yes/no), number of years spent at school (<6, 7–9, 10–11, 12, 13–14, 15–16, 17+), and use of ET and tibolone (nonuser, former user, and current user)

[c] *HT* hormone therapy

[d] *EPT* estrogen and progestogen therapy

[e] *Tertiles* ≤55 = ≤2, 3–5, >5; 57–60 = ≤4, 5–8 > 8; 61+ = ≤6, 7–11, 12+

Table 4 Percent and absolute mammographic density according to the type of combined estrogen–progestogen therapy (EPT) used

Type of hormone therapy used	N^a	Percent density % (95% CI)[b]	Absolute density cm^2 (95% CI)[b]
Never HT users	1053	16.2 (15.7–16.7)	21.0 (20.6–21.3)
Ever No NETA[c]	124	19.6 (18.3–20.8)	25.1 (24.2–25.9)
Ever NETA	983	20.7 (20.2–21.1)	26.1 (25.8–26.4)
Never HT users	1053	16.2 (15.7–16.7)	20.9 (20.6–21.3)
Former no NETA	112	18.3 (17.1–19.7)	24.1 (23.2–25.1)
Former NETA	699	18.8 (18.3–19.3)	24.3 (24.0–24.7)
Current no NETA	12	33.4 (29.4–37.4)	35.5 (32.3–38.6)
Current NETA	284	25.1 (24.4–25.8)	30.5 (30.0–31.0)
Never HT users	1053	16.6 (16.1–17.1)	21.6 (21.3–22.0)
Former no NETA	112	18.3 (17.1–19.6)	24.1 (23.3–25.0)
Former NETA low dose[d]	208	19.4 (18.4–20.4)	24.2 (23.4–24.9)
Former NETA high dose[e]	377	20.1 (19.4–20.9)	26.0 (25.5–26.5)
Current no NETA	12	33.4 (29.1–37.8)	35.5 (31.9–39.0)
Current NETA low dose[d]	182	24.6 (23.7–25.5)	29.3 (28.6–29.9)
Current NETA high dose[e]	48	26.2 (24.3–28.1)	32.8 (31.4–34.1)

Women exclusively using estrogen-alone regimens (ET) were excluded

[a] Due to missing values, numbers in subcategories do not add up and women can be in more than one category (e.g., both former NETA and no NETA)

[b] Analyses were adjusted for age at screening (continuous), body mass index (continuous), number of children (continuous), age at first childbirth (continuous), first-degree family history of breast cancer (yes/no), number of years spent at school (<6, 7–9, 10–11, 12, 13–14, 15–16, 17+), and use of ET and tibolone (nonuser, former user, and current user)

[c] *NETA* norethisterone acetate

[d] *Low-dose* Activelle®, 0.5 mg of NETA, 1 mg of estradiol

[e] *High-dose* Kliogest®, 1 mg of NETA, 2 mg of estradiol

estimated that mammographic density decreases by 2.4% (95% CI: 1.4–3.4%) during the menopausal transition and increases by 2.4% (1.4–3.5) with the use of HT in postmenopausal women. Thus, the total effect would be a slightly lower density in postmenopausal HT users as compared to premenopausal women. The association of EPT use with percent density has been shown to be greater among those who later developed breast cancer [33], suggesting that the response of breast tissue to exogenous hormones is to some degree predictive of the future development of breast cancer. Furthermore, the Women's Health Initiative trial reported that the relationship between EPT use and breast cancer risk appears to be mediated through mammographic density [34]. Likewise, in data from an international randomized clinical trial of tamoxifen versus placebo, the risk of breast cancer was reduced only among women who obtained a 10% or greater reduction in mammographic density while on tamoxifen [35].

In this study, we found a higher mammographic density in EPT users, with the highest densities seen in current users of high-dose NETA regimens. We also showed that the association between EPT use and mammographic density is modified by age and BMI, where the association is apparent in all but the youngest EPT users with a higher BMI. Our results suggest that women's age and BMI should be taken into account when deciding on whether to use EPT.

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Conflict of interests The authors declare that they have no conflict of interests.

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