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Different types of postmenopausal hormone therapy and mammographic density in Norwegian women

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Postmenopausal hormone therapy (HT) is associated with increased risk of breast cancer. The HTs used in Scandinavia is associated with higher risk estimates than those used in most other countries. Mammographic density is one of the strongest risk factors for breast cancer, and possibly an intermediate marker for breast cancer. We decided to examine the relationship between use of different types of HT and mammographic density in Norwegian women. Altogether, 1,007 postmenopausal participants in the governmental mammographic screening program were asked about current and previous HT use. Mammograms were classified according to percent and absolute mammographic density. Overall, current users of HT had on average 3.6% higher mean percent mammographic density when compared with never users ($p < 0.001$). After adjustment for age at screening, number of children and BMI in a multivariate model, women using the continuous estradiol (E_2) plus norethisterone acetate (NETA) combination had a mean percent mammographic density significantly higher than never users (6.1% absolute difference). Those using the continuous E_2 plus NETA combination had an 4.8% (absolute difference) higher mean percent mammographic density after <5 years of use when compared with never users, while the corresponding number for $\geq$5 years of use was 7% (p-trend < 0.001). We found similar associations when absolute mammographic density was used as the outcome variable. In summary, our study shows a statistical significant positive dose–response association between current use of the continuous E_2 plus NETA combination and both measures of mammographic density.
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Key words: postmenopausal hormone replacement therapy; mammography; breast density

Current and recent use of postmenopausal combined estrogen and progestin therapy (EPT) have been shown to increase the risk of breast cancer, both in Randomized Controlled Trials and in observational studies.[1–3] The dose and type of the progestin constituent of EPT seems to influence risk of postmenopausal breast cancer more than the estrogen constituent.[3] The risk estimates for breast cancer with current EPT use found in recent Scandinavian cohort studies were higher than those found in both the Women's Health Initiative (WHI) Study and the Million Women Study (MWS).[1,2,4,5] This may be attributed to the more potent testosterone-derived norethisterone acetate (NETA) progestin used in EPT's in Scandinavia compared to the less potent medroxyprogesterone acetate (MPA) progestin used in most other countries.[3]

Mammographic density is one of the strongest independent risk factors for breast cancer, and possibly an intermediate marker for breast cancer.[6] Percent mammographic density has consistently been shown to be strongly associated with breast cancer risk in different populations,[6] as well as associated with several breast cancer risk factors.[7–10]

There is substantial evidence that hormones are associated with mammographic density, both from cross-sectional and clinical trials.[11–14] However, most of these studies have been from the US, where the predominant preparation until recently has been EPT with conjugated equine estrogen (CEE) and MPA.

In a study from the Norwegian Breast Cancer Screening Program (NBCSP) cohort, mammographic density was assessed among 728 women using a coarse 3-point scale mammographic density classification. Wang *et al.* found a significant relationship between ever-use of postmenopausal hormone therapy (HT) and mammographic density, but no information on the type of HT was available.[15]

On the basis of the differences in HT formulas described, more knowledge about how different types of HT effect mammographic density could increase the understanding of the etiology of breast cancer.

The objective with this paper was to examine the relationship between use of different types of HT and quantitative measures of mammographic density among postmenopausal women attending the NBCSP in Tromsø, Norway.

We especially wanted to explore how the EPTs used in Norway are related to mammographic density, since this is not previously examined.

Material and methods

Study population

The Mammography and Breast Cancer Study is a cross-sectional study among postmenopausal women residing in the municipality of Tromsø, Norway, aged 55–71 years, and attending the NBCSP at the University Hospital of North Norway. The women were recruited in spring of 2001 and 2002. After the women had undergone their screening mammograms, they were interviewed by a trained research nurse about their current and previous HT use. The nurse showed a color photo-leaflet of the altogether 19 HT preparations ever available on the Norwegian market. The different estrogen therapy (ET), EPT and Tibolone formulas were also listed with the available strengths of the preparations. The women were asked about reproductive and menstrual factors, previous history of cancer, smoking status and use of other medications. The participants had their height measured to the nearest centimeter and weight measured to the nearest half kilogram. The women had a blood sample drawn, and were subsequently given a questionnaire to be completed at home, eliciting information on demographics, additional menstrual and reproductive factors, as

Abbreviations: BMI, body mass index; CEE, conjugated equine estrogen; CI, confidence interval; E_2, estradiol; EPT, estrogen and progestin therapy; ET, estrogen therapy; HT, postmenopausal hormone therapy; MPA, medroxyprogesterone acetate; MWS, Million Women Study; NBCSP, Norwegian Breast Cancer Screening Program; NETA, norethisterone acetate; ROI, region of interest; WHI, Women's Health Initiative.

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TABLE I – CHARACTERISTICS OF THE STUDY POPULATION (N = 1,007), OVERALL AND STRATIFIED BY POSTMENOPAUSAL HORMONE THERAPY USE, GIVEN AS MEAN (±SD) OR PERCENTAGE, MAMMOGRAPHY AND BREAST CANCER STUDY, TROMSØ (2001/2002)

	All (N = 1,007)	Postmenopausal hormone therapy use			p-value (past *vs.* never use)	p-value (current *vs.* never use)
		Never used (n = 573)	Past use (n = 175)	Current use (n = 259)		
Mean						
Age at screening (y)	61.4 (±4.6)	62.3 (±4.7)	60.6 (±4.0)	60.0 (±4.2)	<0.001	<0.001
Age at menarche (y)	13,3 (±1.4)	13.4 (±1.4)	13.3 (±1.3)	13.1 (±1.3)	0.98	0.07
Age at first birth (y)	22.9 (±3.7)	23.0 (±3.8)	22.5 (±3.1)	22.7 (±3.6)	0.11	0.36
Number of children[1]	2.7 (±1.4)	2.8 (±1.5)	2.6 (±1.3)	2.5 (±1.2)	0.14	0.01
Education (y)	9.8 (±3.4)	9.4 (±3.3)	10.0 (±3.0)	10.4 (±3.7)	0.05	<0.001
Age at menopause (y)	48.5 (±5.1)	48.5 (±4.9)	49.1 (±5.4)	48.3 (±5.1)	0.16	0.62
BMI (kg/m^2)	27.4 (±4.8)	27.6 (±5.1)	27.5 (±4.3)	26.7 (±4.4)	0.88	0.01
Alcohol consumption[2] (g/day)	3.7 (±3.9)	3.5 (±4.0)	3.7 (±3.7)	4.2 (±3.8)	0.66	0.07
Frequency (%)						
Ever oral contraceptive use	51.1	46.8	60.0	54.8	<0.01	0.03
Parous	92.8	92.7	92.0	93.4	0.77	0.69
Daily smokers	27.7	26.9	30.3	27.8	0.66	0.64
Family history of breast cancer	18.2	17.6	18.3	19.3	0.84	0.56

[1]Among parous women only.–[2]Among alcohol drinkers only.

well as lifestyle and dietary factors. All women signed an informed consent. The National Data Inspection Board and the Regional Committee for Medical Research Ethics approved the study. Altogether, 1,041 women were included in the study. This accounted for 70.1% of the women attending the breast cancer screening program during the recruitment period.

We excluded 22 women because of a previously (n = 16) or newly (n = 6) diagnosed breast cancer, and 1 woman because of ongoing chemotherapy treatment. Among the remaining 1,018 women, we were unable to retrieve 11 mammograms. Thus, 1,007 women had mammograms classified according to percent and absolute mammographic density. More details are described elsewhere.[7]

Mammographic classifications

The left cranio-caudal mammogram was digitized using a Cobrascan CX-812 scanner (Radiographic Digital Imaging, Torrance, CA) at a resolution of 150 pixels per inch. Percent and absolute mammographic density were determined using the University of Southern California Madena computer-based threshold method; this method has been described and validated elsewhere.[16] Briefly, the method works as follows: The digitized mammographic image is viewed on a computer screen, and a reader defines the total breast area using a special outlining tool. Next, the region of interest (ROI), excluding the pectoralis muscle, prominent veins and fibrous strands, is defined. The reader then uses a tinting tool to apply a yellow tint to dense pixels with grey levels at or above some threshold X and a pixel value of •255. The reader searches for the best threshold where all pixels •X within the ROI are considered to represent mammographic densities. The software estimates the total number of pixels and the number of tinted pixels within the ROI. Absolute density represents the count of the tinted pixels within the ROI. Percent density, or the fraction (%) of the breast with densities, is the ratio of absolute density to the total breast area multiplied by 100.

The reader of the mammograms was blinded to the characteristics of the study participants.

Menopausal status

Women were classified as postmenopausal if they were 56 years or older, or reported having no natural menses during the last 12 months, or if the serum follicle-stimulating-hormone level was above 20 IU/l. According to these criteria, 3 of the 1,007 women were equivocal for menopausal status. Excluding these, 3 women did not alter the results, and they were included as postmenopausal.

Classification of HT use

Women indicating use of HT (oral or transdermal administration) at the time of enrollment were classified as current users. Ever users not indicating current use were classified as past users. The EPT regimens in Norway have all contained 1 of the 3 available estrogens: estradiol (E_2), estriol or etinylestradiol. The progestins most commonly used are the testosterone-derived norethisterone/norethisterone acetate (NETA) and levonorgestrel. The most common HT regime used in Norway is the E_2 and NETA combination. The synthetic steroid tibolone, with a weak estrogenic, progestogenic and androgenic effect, was introduced in Norway in the late 1999. All the HT preparations reported used by the women could be categorized into the following 4 groups: (*i*) estrogen monotherapy, (*ii*) continuous estrogen plus progestin combination, (*iii*) sequential estrogen and progestin combination and (*iv*) tibolone.

Statistical analysis

We used analysis of variance for unbalanced design to study the association between use of HT and mammographic density (Proc GLM, SAS). Percent and absolute mammographic density were log transformed to obtain an approximate normal distribution. The unadjusted and adjusted mean mammographic density results were back-transformed and are presented with 95% confidence intervals (CI). Trend tests across the categories of HT use were performed by treating the categories as continuous variables in the analyses.

Analyses were performed for HT use overall, by type of HT, and also separately for transdermal and oral administration.

Each of the following factors was evaluated as a potential confounder of the relation between HT use and mammographic density: age at screening (continuous), age at menarche (continuous), age at menopause (continuous), number of children (continuous), age at first birth (continuous), years of education (continuous), family history of breast cancer in first degree relatives (yes, no), smoking (daily, sometimes, no), alcohol intake (grams/day) and body mass index (BMI: weight in kilogram divided by height in meters squared) (continuous).

We performed univariate and multivariate analyses with models that included the above listed variables as independent variables and mammographic density as the dependent variable. Since all the above factors were presumed to be associated with HT use, we used the following criteria to include them in the model as a confounder: the factor had to either have been associated with the outcome variable in this study population previously,[7] or it changed the estimate by 10% or more when included in the multivariate

TABLE II – ADJUSTED[1] MEAN[2] (95% CONFIDENCE INTERVAL) PERCENT MAMMOGRAPHIC DENSITY ACCORDING TO POSTMENOPAUSAL HORMONE THERAPY USER STATUS AND DURATION OF USE AMONG 1,007 NORWEGIAN WOMEN, MAMMOGRAPHY AND BREAST CANCER STUDY, TROMSØ

	Percent mammographic density	*p*-value trend
	Adjusted[1] mean[2]	
PHT use		
Never used ($n = 573$)	7.2 (6.6–7.8)	
Past use ≥5 years ago ($n = 45$)	6.8 (5.1–9.1)	
Past use <5 years ago ($n = 130$)	9.1 (7.4–11.3)	
Current use for <5 years ($n = 135$)	10.3 (8.7–12.2)	
Current use for ≥5 years ($n = 124$)	11.5 (9.7–13.7)	<0.001

[1]Analyses are adjusted for age at screening, number of children and BMI.–[2]Reported mean is back-transformed from log-transformed estimated mean.

TABLE III – ADJUSTED[1] MEAN[2] (95% CONFIDENCE INTERVAL) PERCENT MAMMOGRAPHIC DENSITY BY TYPE OF CURRENT POSTMENOPAUSAL HORMONE THERAPY USED AMONG 832 NORWEGIAN WOMEN, MAMMOGRAPHY AND BREAST CANCER STUDY, TROMSØ

Type of current postmenopausal hormone therapy used	Percent mammographic density	
	Adjusted[1] mean[2]	*p*-value[3]
Never used ($n = 573$)	7.2 (6.6–7.8)	
Tibolone ($n = 52$)	8.8 (6.7–11.5)	0.17
Estrogen monotherapy ($n = 70$)	9.0 (7.2–11.4)	0.07
Sequential estrogen and progestin combination ($n = 19$)	10.2 (6.5–15.9)	0.14
Continuous estrogen plus progestin combination ($n = 118$)	13.3 (11.1–15.8)	<0.001
All estrogen plus progestin combinations ($n = 137$)	12.8 (10.8–15.1)	<0.001

[1]Analyses are adjusted for age at screening, number of children and BMI.–[2]Reported mean is back-transformed from log-transformed estimated mean.–[3]Current versus never use.

TABLE IV – ADJUSTED[1] MEAN[2] (95% CONFIDENCE INTERVAL) PERCENT AND ABSOLUTE MAMMOGRAPHIC DENSITY BY DURATION OF CURRENT CONTINUOUS ESTROGEN PLUS PROGESTIN COMBINATION USE AMONG 691 NORWEGIAN WOMEN, MAMMOGRAPHY AND BREAST CANCER STUDY, TROMSØ

Duration of current continuous estrogen plus progestin combination use	Percent mammographic density	*p*-value trend	Absolute mammographic density (cm^2)	*p*-value trend
	Adjusted[1] mean[2]		Adjusted[1] mean[2]	
Never used ($n = 573$)	7.0 (6.5–7.6)		9.9 (9.0–10.8)	
<5 years ($n = 52$)	11.8 (9.0–15.5)		18.6 (13.4–23.4)	
≥5 years ($n = 66$)	14.0 (11.1–17.8)	<0.001	20.8 (15.8–27.2)	<0.001

[1]Analyses are adjusted for age at screening, number of children and BMI.–[2]Reported mean is back-transformed from log-transformed estimated mean.

model. This procedure left the following factors in the final model: age at screening, number of children and BMI.

Results were considered statistically significant if the two-sided *p*-value was <0.05. We performed data management and statistical analyses using the SAS statistical software package, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Study population characteristics

Among the women, 26% were current and 43% ever HT users. Table I shows selected characteristics of the study population overall, and according to HT use. Current users of HT were younger, had fewer children, were more educated, had lower BMI and were more likely to be ever oral contraceptive users, than never users. Altogether, 228 of the 259 current users used an orally administered HT. The remaining 31 (12%) women used an ET administered transdermally.

HT use and mammographic density

Overall, current users of HT had a significant higher mean percent mammographic density (10.8%; 95% CI 9.6–12.2) when compared with never users (7.2%; 95% CI 6.6–7.8) after adjustment for age at screening, number of children and BMI ($p < 0.001$). Trend tests across never-, past- and current use of HT were significant (*p*-trend < 0.001). We found similar associations when absolute mammographic density was used as the outcome variable (data not shown).

The median duration of HT use was 72 months among ever and 48 months among current users. Women who had used HT for 1 year or more had a significantly higher mean percent mammographic density (10.8%; 95% CI, 9.5–12.3) when compared with never users (7.2%; 95% CI 6.6–7.8, *p* for comparison <0.001). When we stratified according to status and duration of HT use, a positive trend was shown for percent mammographic density (Table II). Women with current use of HT for 5 years or more had the highest mean percent mammographic density. We also found a significant trend test for the different levels of HT use and absolute mammographic density (data not shown).

Type and duration of current HT use and mammographic density

The most commonly used HT among current users was a continuous EPT with E_2 plus NETA (46%), where 85% used 2 mg E_2 plus 1 mg NETA (Kliogest®) and the remaining 15% used the lower dose 1 mg E_2 plus 0.5 mg NETA (Activelle®).

Table III shows that when current HT use was stratified by type, users of the continuous EPT had a mean percent mammographic density that was 6.1% (absolute difference) higher when compared with never users ($p < 0.001$). This equals an 85% relative difference. Stratifying the women on ET according to the type of administration did not change the results (data not shown). Current use of tibolone gave an absolute difference in mean percent mammographic density of 1.6% when compared with never users ($p = 0.17$). Similar associations were found when we evaluated the relationship between the different types of current HT use with absolute mammographic density as the outcome variable (data not shown).

Table IV shows that mean percent mammographic density increased with longer duration of current continuous EPT use (*p*-trend < 0.001). Current users of continuous EPT had a 7.0% (absolute difference) higher mean percent mammographic density after ≥5 years of use when compared with never users ($p < 0.001$). The association was similar when we evaluated duration of continuous EPT with absolute mammographic density as the outcome variable (Table IV).

Discussion

Our study is, to our knowledge, the first to examine the relationship between use of different types of HT and quantitative mammographic density among Norwegian women. We find that cur-

rent users of systemic HT have a significant higher mean percent mammographic density when compared with never users. Furthermore, we find a dose–response relationship between HT user status and duration of use and mammographic density. When the association between the 4 types of HT and mammographic density was examined in detail, only the association with current use of continuous E_2 plus NETA EPT was statistically significantly different from that with never users. Also, our study finds a dose–response relationship between the duration of continuous E_2 plus NETA EPT and mammographic density. We found similar associations when absolute mammographic density was the outcome variable.

Strengths of our study are that it was a part of a population-based screening project with a high attendance rate, and that our study has a large sample size. The reader of the mammograms was experienced and blinded to the characteristics of the women. The limited number of HT preparations ever available in Norway, and the use of a photo-leaflet to aid in the recall of HT use, limits the misclassification of exposure. Even so, there will be some misclassification of HT use. However, this will most likely be nondifferential, and thus bias the results toward the null association.

One limitation with our study is that it is cross-sectional and we therefore do not have information on the temporal relationship between the HT use and mammographic density. Also, assessing mammographic density is partly based on a subjective component. We have previously shown that the reader of the mammograms had a good correlation (Pearson correlation coefficient 0.86) for a independent reread of percent mammographic density of 37 mammograms performed as long as 18 months after the first reading.[7]

In our study of postmenopausal women, the mean percent mammographic density is relatively low. However, it is similar to the baseline mean mammographic density found among non-Hispanic white in the WHI Study.[14]

Several studies, mostly from the US, have looked at the relationship between different types of postmenopausal HT and mammographic density.[11,13,14,17–19] The magnitudes of the differences in mammographic density in our study are comparable to those of other studies. In a subset of the Postmenopausal Estrogen/Progestin Interventions Trial, Greendale *et al.* found an increase in mean percent mammographic density of close to 5% in women treated with CEE plus MPA EPT for 12 months compared with baseline. This increase was significant, while the increase among ET users was not.[13] In the WHI Study, McTiernan *et al.* found that the 202 women in the continuous CEE plus MPA EPT group had a 6% higher mean percent mammographic density after 12 months when compared with what they had at baseline. This absolute difference decreased to 5% after 24 months.[14] In a Swedish Randomized Controlled Trial comprising 154 postmenopausal women, Lundström *et al.* found a significant increase in qualitative percentage mammographic density (5 class scale) among 48 women taking continuous E_2 plus NETA EPT for 6 months when compared with 55 women in the placebo group ($p < 0.001$). In contrast, the 51 women treated with tibolone did not differ from those in the placebo group according to percentage mammographic density.[17] Lundström has previously shown that current use of EPT was more likely to give an increase in qualitative mammographic density than the use of other HTs. Furthermore, they found that among EPT users, the use of a continuous E_2 plus NETA EPT was more likely to give an increase than the use of a continuous CEE plus MPA EPT.[18,19]

The dose–response associations between duration of HT use with mammographic density in our study are in agreement with a review on hormones and mammographic breast density that concluded that the effect is more likely to follow prolonged HT use.[11] This was based on the finding in a case-control study nested in the European Prospective Investigation on Cancer in Norfolk, where it was shown that the odds of having high-risk mammographic patterns increased significantly with increasing duration of current HT use.[20] Also, in a Observational Cohort Study of 5,212 postmenopausal women it was shown that women who were current users at first mammogram and continued to use HT were more likely to show an increase in mammographic density at the next mammographic screening when compared to nonusers.[21]

The higher mammographic density we find for current E_2 plus NETA EPT use compared to never users is in agreement with the more pronounced risk of breast cancer among HT users in the Norwegian when compared to the US population.[1,2,4,5,22] Although the differences in our study may seem small, the 7% absolute difference in mammographic density between never use and current EPT use for 5 or more years translate to a 100% relative difference.

Our results are also in support of the numerous studies having found that use of EPT is associated with a higher risk of breast cancer when compared with use of ET or tibolone.[2,23] In the MWS, those using the continuous CEE plus MPA EPT for 5 years or more had the highest risk estimates for breast cancer.[2] In the Norwegian Women and Cancer Study, comprising 31,451 postmenopausal women, Bakken *et al.* found that current use of E_2 plus NETA EPT conferred a higher relative risk for breast cancer than ET alone. However, this difference did not achieve statistical significance. Also, women who were current users of the continuous E_2 plus NETA EPT had a significantly higher risk of breast cancer than current users of the sequential E_2 plus NETA EPT. Women who had used the continuous E_2 plus NETA EPT for 5 years or more had the highest risk of breast cancer.[4] This increased risk of breast cancer with EPT use is supported by the findings from the Danish Nurse Cohort Study,[5] and from a Swedish Case-Control Study.[24] In an overview on EPT use and breast cancer risk, Lee *et al.* found a significantly higher risk of breast cancer with EPT use in European studies when compared to studies from the US, with Scandinavian studies finding the highest risk in Europe. The authors suggests that this might be due to the higher total dose of progestin used in sequential EPT regimens used in Europe, and also the use of the more potent NETA in Europe when compared with the progestins used in the US.[3]

Even though the estrogen constituent of the EPTs used in the US and in Europe also differs, CEE and E_2 are both considered to be of medium estrogen potency and have similar breast cancer risk estimates.[25] The hypothesis that the progestin EPT component confers most of the increased risk of breast cancer seen with EPT use is supported by studies on the proliferative effect of HT on postmenopausal breast tissue. HT use has been shown to increase proliferation and density of epithelial cells in the parenchyma of postmenopausal breast tissue,[26] and the use of EPT has a significantly greater proliferative effect when compared with the use of ET or tibolone.[26,27] In a study of benign breast biopsies from 86 postmenopausal women, the proliferative effect of progestins was localized to the terminal ductules and lobules in the breast, which is the site where most breast cancers origin.[28] An increase in the number and density of parenchymal epithelial cells in the human breast may be reflected in increased mammographic density.[29] Ursin *et al.* have shown that the change in percent mammographic density with EPT was primarily due to changes in the dense area of the breast, rather than a decrease in the nondense area.[30] This supports the hypothesis that epithelial cell proliferation related to EPT use is reflected in percent mammographic density changes.

The effects of the different HTs on mammographic density may give us more insight in the etiology of breast cancer.

In conclusion, our study shows a positive dose–response association between the use of the continuous E_2 plus NETA combination and percent mammographic density measured on a continuous scale. The associations are similar when absolute mammographic density is used as the outcome variable.

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