

# Continuous Combined Postmenopausal Hormone Replacement Therapy Regimens and Mammographic Density Changes

## KESİNTİSİZ KOMBİNE HORMON REPLASMAN TEDAVİ REJİMLERİ VE MAMMOGRAFİK DANSİTE DEĞİŞİKLİKLERİ

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### Summary

**Objective:** To determine the degree of changes in mammographic breast densities in postmenopausal women receiving continuous combined hormone replacement therapy regimens.

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**Material and Methods:** The mammographies of 74 postmenopausal women receiving 2 mg estradiol (E<sub>2</sub>) combination with 1 mg norethisterone acetate (NETA) (n=47) or 0.625 mg conjugated estrogen combination with 2.5 mg medroxyprogesterone acetate (n=27) were evaluated retrospectively. Mammographic density was quantified according to the Wolfe classification.

**Results:** The mean age of the patients was 57.8±3.7 years. The mean time interval from baseline to the first visit was 16.3±4.7 months and to the second visit was 30.2±7.8 months. The mean duration of mammographic follow-up was 22.5±5.8 months (range 12-60 months). In continuous combined postmenopausal hormone replacement therapy with E<sub>2</sub> + norethisterone acetate, the increase in mammographic density was 36% (17 of 47), followed by CEE + medroxyprogesterone acetate 25.9% (7 of 27) (p=0.36,  $\chi^2=0.82$ ).

**Conclusion:** Our findings showed that both continuous combined hormone replacement regimens increase mammographic density; however, there was no statistically significant difference between the treatments.

**Key Words:** Hormone replacement therapy, Mammographic density

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### Özet

**Amaç:** Kesintisiz kombine hormon replasman tedavi rejimleri alan postmenopozal kadınlarda mammoğrafik dansite değişikliklerini belirlemek.

**Çalışmanın yapıldığı yer:** Ege Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Bornova, İzmir.

**Materyal ve Metod:** Kesintisiz kombine hormon replasman tedavisi olarak 2 mg östradiol (E<sub>2</sub>) + 1 mg noretisteron asetat (NETA) (n=47) veya 0.625 mg konjuge östrojen (CEE) + 2.5 mg medroksiprogesteron asetat (MPA) (n=27) kullanan 74 postmenopozal kadının mammoğrafileri retrospektif olarak değerlendirildi. Mammoğrafik dansite Wolfe sınıflamasına uygun olarak değerlendirildi.

**Bulgular:** Hastaların ortalama yaşı 57.8±3.7 yıl idi. Tedavi öncesi ile ilk ziyaret arasında geçen ortalama süre 16.3±4.7 ay, ikinci ziyaret için ise 30.2±7.8 ay idi. Ortalama mammoğrafik takip süresi 22.5±5.8 ay (12 ile 60 ay arasında) idi. E<sub>2</sub> + NETA tedavisi alan grupta mammoğrafik dansite artışı %36 (17/47), konjuge östrojen + MPA alan grupta ise %25.9 (7/27) olarak bulundu (p=0.36,  $\chi^2=0.82$ ).

**Sonuç:** Her iki kesintisiz kombine hormon replasman tedavi rejimi mammoğrafik dansiteyi arttırmaktadır. Bu iki tedavi rejimi ile meydana gelen mammoğrafik dansite artışları arasında istatistiksel anlamlı bir fark tespit edilmedi.

**Anahtar Kelimeler:** Hormon replasman tedavisi, Mammoğrafik dansite

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Mammography is a valuable tool for the early detection of breast cancer. Mammographic mass screening programs have been shown to reduce breast cancer mortality rates in women over 50 years of age (1). Hormone replacement therapy is associated with an increase in mammographic breast density in a significant proportion of postmenopausal women (2-6). Current use of hormone replacement therapy may also be associated with a lower sensitivity of screening mammography (7,8).

Mammographic breast density may be a surrogate marker for the development of breast cancer. Epidemiologic studies have found increased mammographic breast density to be a strong and independent risk factor for breast cancer (9).

Many different therapeutic regimens are used for postmenopausal hormonal replacement including estrogen alone, estrogen in cyclic combination with a progestin, and estrogen in continuous combination with a progestin.

Recently, we reported that an increase in mammographic density was much more common among women receiving continuous combined hormone replacement therapy than among those receiving other treatments (10).

The present study is designed to determine the degree of changes in mammographic breast densities in postmenopausal women receiving two different continuous combined hormone replacement therapy regimens.

### Materials and Methods

According to the postmenopausal follow-up program, the postmenopausal patients using hormone replacement therapy are invited for mammography every year. From this material, consecutive women who were nonusers of hormone replacement therapy and other hormone-containing drugs and who started continuous combined hormone replacement therapies after their first mammogram and having at least one control mammogram were included in the study. At one or more succeeding mammographic visits, all the women reported continuous use of these hormone replacement therapies. The total material comprised 74 women. All patients were in natural menopause.

Forty-seven women were using 2 mg estradiol and 1 mg norethisterone acetate in 1 tablet daily (Kliogest<sup>®</sup>, Novo Nordisk) (group 1), and 27 women were using 0.625 mg conjugated estrogen and 2.5 mg medroxyprogesterone acetate in 1 tablet daily (Premelle<sup>®</sup>, Wyeth) (group 2). From these women between 1995 and 2000 a total of 322 mammograms of the mediolateral oblique and craniocaudal view of both the right and left breast were available. The mean duration of mammographic follow-up was 22.5±5.8 months (range 12-60 months). The number of patients obtained one control mammogram was 62 (83.8%); two control mammograms was 11 (14.9%), and one patient (1.3%) had three control mammograms at the end of the study. The films were analyzed by an independent radiologist with specialization in mammography and blinded to treatments, without any information about which mammograms were taken first.

All mammograms were obtained by Sonographe 500 (General Electric, USA) and Mammomat 3000 (Siemens, Germany). Quantification of density changes which occurred during the follow-up was done subjectively and with reference to the densities in initial mammograms. The mammographic parenchymal pattern in bilateral craniocaudal and mediolateral oblique projections of each women was classified according to Wolfe (11,12) in four categories: N1, essentially normal breast with parenchyma composed primarily of fat and with, at most, a few fibrous connective tissue strands; P1, prominent ductal pattern in up to one fourth of breast volume; P2, prominent ductal

pattern in more than one fourth of breast volume; and DY, extremely dense parenchyma, which usually denotes connective tissue hyperplasia.

We also subjectively classified the degree of increase in mammographic density as follows: approximately 10-25% change in initial mammographic densities, which was barely visible, was considered slight; 26-50% change was considered moderate; and >50% change was considered as marked change in density. Two example of mammographic density increases were shown in Figure 1 and 2.

Mann-Whitney U test and t-test were used to compare differences between the groups using SPSS for windows.  $P < 0.05$  was considered statistically significant. Chi-square test was used to compare the degree of density increase in the two therapy groups. Data were expressed as the mean ± standard deviation.

### Results

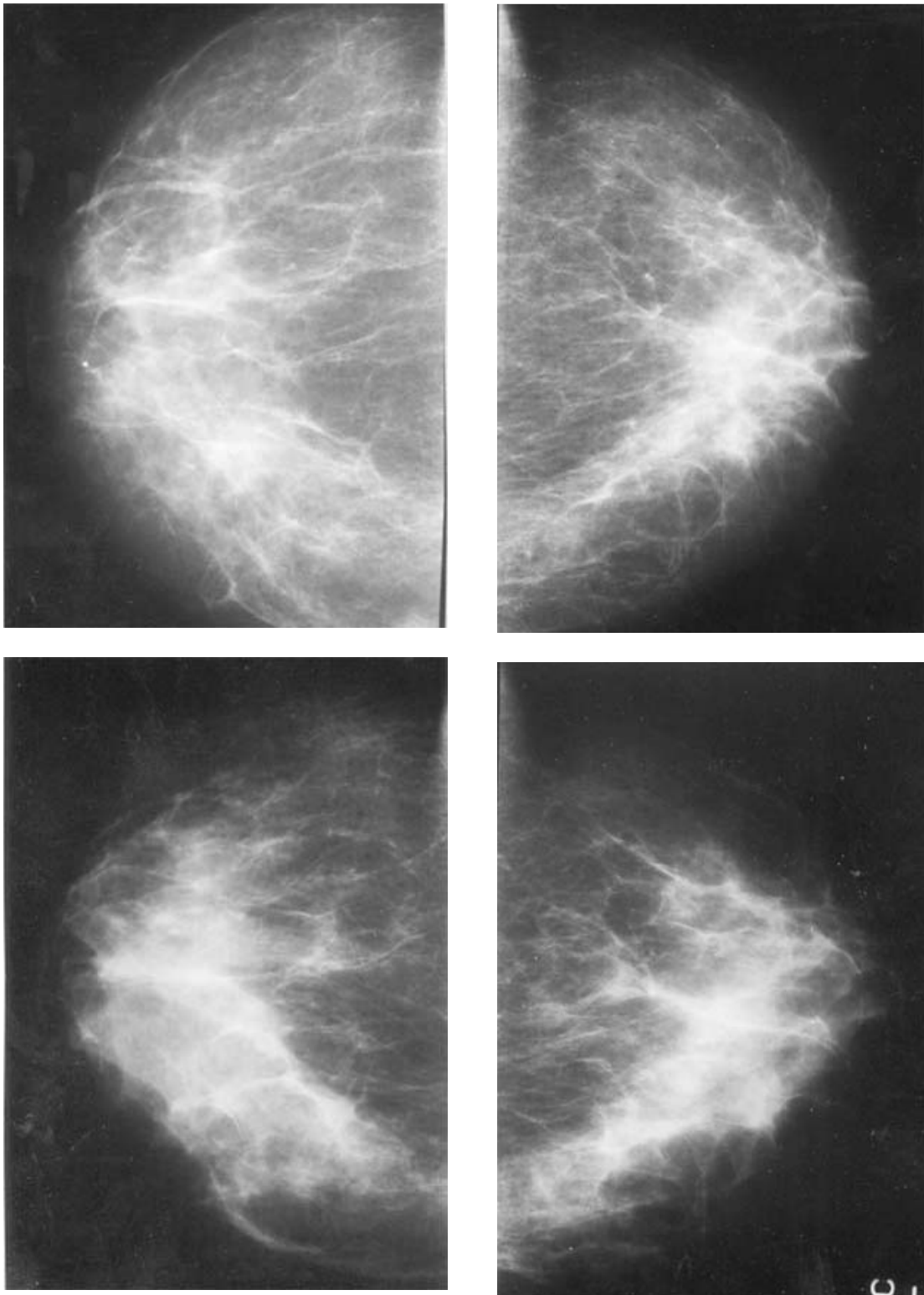
The mean age of the patients was 57.8±3.7 years. The mean time interval from baseline to the first visit was 16.3±4.7 months and to the second visit was 30.2±7.8 months. The mean duration of mammographic follow-up was 22.5±5.8 months (range 12-60 months). There were no differences between the demographic parameters of the two groups (Table 1). Data on findings of mammographic density changes at baseline and at first visit for the two groups are given in Table 2. The increase recorded at the first visit after the start of postmenopausal hormone replacement therapy remained stable in all the women at subsequent examinations.

In continuous combined postmenopausal hormone replacement therapy with norethisterone acetate the increase in mammographic density was 36.2% (17/47) and with medroxyprogesterone acetate 25.9% (7/27). The difference of mammographic density increase between the two groups was not statistically significant ( $p=0.36$ ,  $\chi^2=0.82$ ). There was no increase in breast density after first visit and the changes of density were summarized in Table 3.

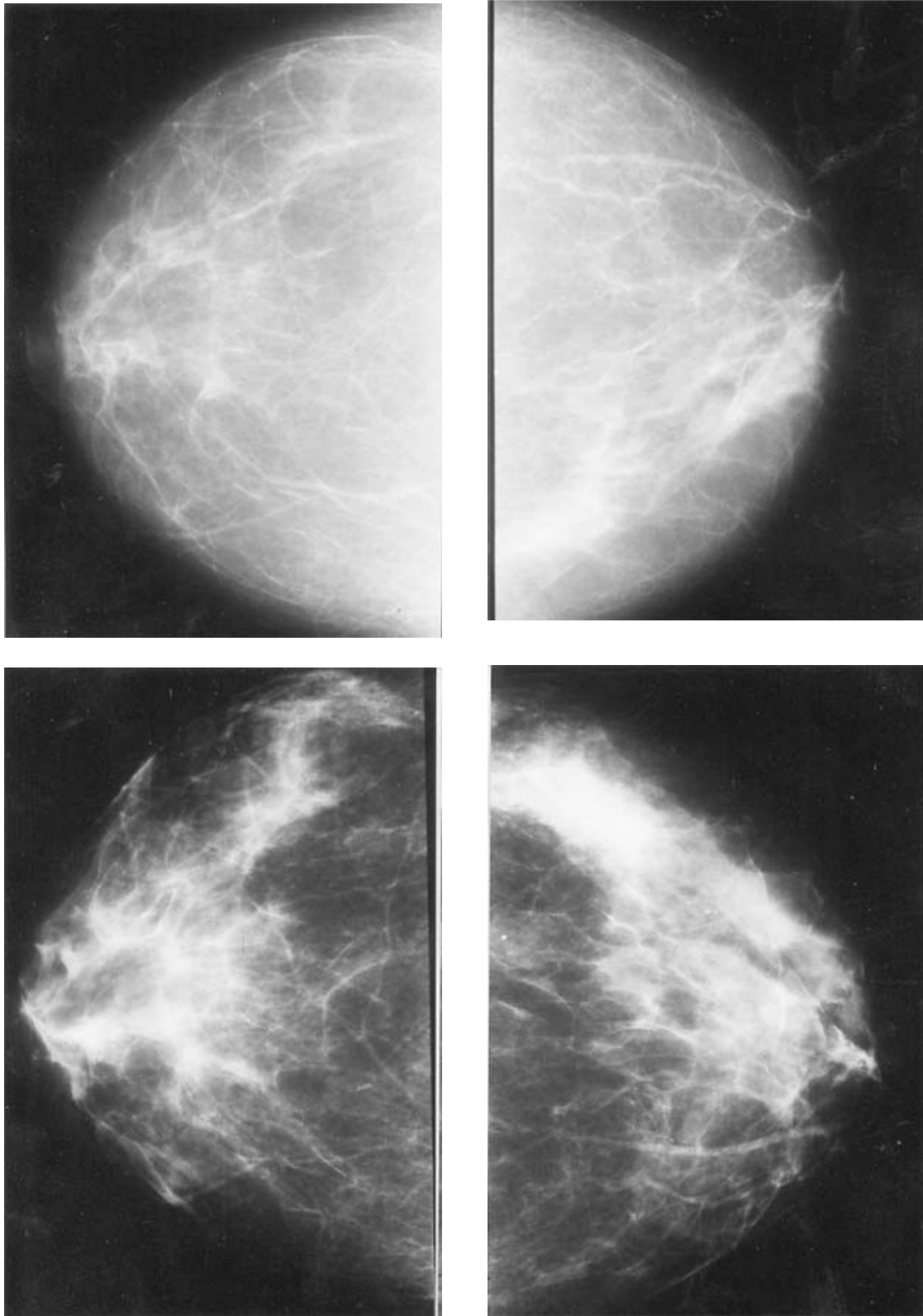
In all cases, the pattern of mammographic density change was the same in both breasts. Also, in all subjects, mammographic density increase was bilateral. No breast cancers were diagnosed in follow-up mammographies. New cyst formation occurred in four patients. All of them in the group of continuous combined hormone replacement therapy with E<sub>2</sub> + NETA.

### Discussion

Mammographic density is affected by hormone replacement therapy and adversely affects diagnostic accuracy and may be a risk factor for breast cancer. The mammographic density decreases significantly after age 55 with the greatest change occurring between age 55 and 64. This



**Figure 1.** Changes in mammographic density in a 56-year-old woman after CEE/MPA therapy. Mammograms were obtained at craniocaudal position before (A and B show right and left breasts, respectively) and after (C and D show right and left breasts, respectively) 14 months of therapy. The woman receiving CEE/MPA therapy had an increase, from P1-P1 Wolfe classification to a P2-P2 classification at first visit after the beginning of the therapy.



**Figure 2.** Changes in mammographic density in a 51-year-old woman after E<sub>2</sub>/NETA therapy. Mammograms were obtained at craniocaudal position before (A and B show right and left breasts, respectively) and after (C and D show right and left breasts, respectively) 16 months of therapy. The woman receiving E<sub>2</sub>/NETA therapy had a marked increase, from N1-N1 Wolfe classification to a P2-P2 classification at first visit after the beginning of the therapy.

**Table 1.** Demographic characteristics of the groups

	E <sub>2</sub> + NETA (n=47)	CEE + MPA (n=27)	P
Age (years)	58.2 ± 3.3	57 ± 4.2	0.2
BMI (kg/m <sup>2</sup> )	27.7 ± 1.9	27.4 ± 2.5	0.64
Time since menopause (months)	76.6 ± 33.6	82.6 ± 44.1	0.51
Duration of HRT (months)	26.5 ± 7	27.3 ± 14.2	0.72

BMI: Body Mass Index, HRT: Hormone Replacement Therapy

**Table 2.** Mammographic status at baseline and at first visit in the two groups according to Wolfe classification

Treatment	Baseline density								Density at first visit							
	N1		P1		P2		DY		N1		P1		P2		DY	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
E <sub>2</sub> + NETA (n=47)	18	38	27	57	2	5	0	0	5	11	31	66	10	21	1	2
CEE + MPA (n=27)	9	33	18	67	0	0	0	0	4	15	20	74	2	7	1	4

**Table 3.** Number of women with change in mammographic density between baseline and after first visit in the two groups

Treatment	No change at first visit				Increase at first visit				Total			
	No		%		slight		moderate		marked		No	%
	No	%	No	%	No	%	No	%	No	%	No	%
E <sub>2</sub> + NETA (n=47)	30	63.8	7	14.8	7	14.8	3	6.4	17	36.2		
CEE + MPA (n=27)	20	74.1	3	11.1	3	11.1	1	3.7	7	25.9		

decrease does not occur in the majority of postmenopausal hormone replacement therapy users. Usually hormone replacement therapy maintains the density present at the time it is started.

The histologic correlates to the increase in mammographic density are not fully clear and may involve edema, vasodilation, fibrosis, and epithelial proliferation. In menstruating women, breast epithelial proliferation is increased during the luteal phase, when levels of endogenous progesterone are high (13). In an animal model for hormone replacement, continuous combination estrogen-progestin treatment induced more proliferation than did estrogen alone (14). The total amount of progestin given could be one important factor, but it has also been suggested that the cyclic withdrawal of progesterone may stimulate spontaneous apoptosis (15). Recent evidence suggests that progesterone is mitogenic in the breast (16), but the effects of progestin may differ according to dosage, duration of exposure, and the estrogenic environment (17).

One of the aim of our study was to investigate the possible variations in the reaction of breast tissue in two

different continuous combined hormone replacement regimens. Observed differences according to the selected type of progestin were meaningful in this aspect. The increase in mammographic density was found much more in continuous combined postmenopausal hormone replacement therapy with E<sub>2</sub> + norethisterone acetate (36%) than with CEE + medroxyprogesterone acetate (25.9%). But, there was no statistically significant difference between the treatments.

These results are in agreement with previous data extracted from a population-based screening program where E<sub>2</sub>/NETA (18) and also conjugated estrogens 0.625 mg/medroxyprogesterone acetate 5 mg (19) caused an overall increase in mammographic density in 40% to 50% of investigated women.

From a clinical perspective an increase in mammographic density should be regarded as an unwanted and potentially hazardous side effect of HRT. An increase in mammographic density may also be associated with breast discomfort and pain. During the last years independent epidemiologic studies have suggested that treatment with

estrogen in combination with progestogen may cause an increase in breast cancer risk beyond that associated with estrogen alone (10,20-24).

In conclusion, our findings showed that both continuous combined hormone replacement regimens increase mammographic density. Although an increase in mammographic density was much more in continuous combined hormone replacement therapy with E<sub>2</sub> + NETA than with CEE + MPA, there was no significant difference between the treatments.

Efforts should be made to define treatment regimens for postmenopausal women that have a minimum of effects on the breast but still maintain the many advantages of conventional HRT.

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