



# Estradiol plus drospirenone therapy increases mammographic breast density in perimenopausal women

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## ABSTRACT

**Objective:** To investigate the effects of 17 $\beta$ -estradiol 1 mg plus drospirenone 2 mg (E2/DRSP) treatment on mammographic breast density in perimenopausal women.

**Study design:** In this prospective study, 80 healthy perimenopausal women aged 41–49 years were enrolled and assigned to either E2/DRSP ( $n = 40$ ) or a control group ( $n = 40$ ). Mammograms were performed at baseline and after 12 months of treatment. Mammographic breast density was quantified according to the Wolfe classification.

**Results:** We demonstrated an increase in mammographic breast density in 37% (95% CI (confidence interval): 18.8–55.3%) of women treated with E2/DRSP after 12 months. The percentage of women with increased density was 0% (95% CI: 0.0–0.0%) in the control group. The difference in breast density between the E2/DRSP group and the control group was statistically very significant ( $p < 0.001$ ).

**Conclusions:** E2/DRSP therapy for 12 months in perimenopausal women significantly increased mammographic breast density in comparison to a control group. Further long-term and large scale prospective studies are needed to evaluate this issue.

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## 1. Introduction

Breast cancer is the second most frequent cause of mortality in women for cancer diseases, next to lung cancer. Mammography is widely used to screen for breast cancer. It estimates the proportion of fibroglandular tissue relative to the amount of fat [1]. Wolfe first described an association between a qualitative classification of dense mammographic patterns and an increased risk of breast cancer [2]. High mammographic density has been associated with a three- to six-fold increase in breast cancer risk [3,4].

Hormone therapy (HT) is used to relieve climacteric symptoms and to prevent osteoporosis [5] and urogenital atrophy [6] in menopausal women. Although estrogen therapy (ET) is effective for vasomotor symptom control, in women with an intact uterus, a progestin must be added to prevent the risk of endometrial hyperplasia or cancer [7]. Observational and clinical trials have shown that ET either has no effect or slightly increases breast density, while the addition of a progestin enhances breast cell

proliferation, leading to a marked density increase [8,9]. In the Postmenopausal Estrogen/Progestin Intervention (PEPI) study, the progestin-containing treatment groups were associated with the greatest number of breast density increases (five to seven times more) compared with the estrogen-only group [8]. Increased density may affect the sensitivity and predictive value of mammography in detecting breast pathology [10,11].

Progestins differing in pharmacological properties may have a variable impact on breast density [12]. Drospirenone (DRSP) is a novel progestin with antialdosterone effects that, in combination with 17 $\beta$ -estradiol (E2), has been developed for use in postmenopausal women as a HT [13,14]. Progestational activity is four times greater than that of progesterone [15]. There are few studies demonstrating an increase in mammographic breast density in postmenopausal women treated with 17 $\beta$ -estradiol 1 mg plus drospirenone 2 mg (E2/DRSP) [12,16]. In the present study, we investigated the effects of an E2/DRSP regimen on breast density in healthy perimenopausal women for 12 months.

## 2. Materials and methods

A total of 80 healthy perimenopausal women with climacteric symptoms (hot flushes and/or outbreaks of sweating, generally oligomenorrhoeic), aged 41–49 years, were enrolled as eligible for

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our study between June 2008 and December 2009. The majority of perimenopausal women have serum FSH concentrations of  $>20$  IU/L. They were randomly assigned by a computer-generated randomisation program either to E2/DRSP (Angeliq, Bayer-Schering, Germany) ( $n = 40$ ) or to the control group ( $n = 40$ ). Inclusion criteria were as follows: no contraindication for the use of HT, previous nonuse of HT for at least 12 months, lack of benign mastopathies and of familiarity for breast cancer. Treatment was continuous and lasted 12 months. Research ethics approval was obtained from the Ethics Committee of Kahramanmaraş Sutcuimam University before the commencement of the study and signed-informed consent was obtained from all patients and volunteers.

Mammograms were interpreted by an independent radiologist with extensive experience in mammography. No information about the treatment was given, nor any information about which mammograms was taken first. All mammograms were obtained by Senographe DMR (General Electric). The quantification of density changes that 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 woman were classified according to Wolfe [2] 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.

### 2.1. Statistical analysis

Continuous variables were analysed by an independent samples *t*-test. In cases of skewed distribution of the data, the Mann–Whitney *U* test was used. Fisher's exact test was used for nominal data. A *p* value of less than 0.05 was accepted as significant. The analyses were conducted using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

## 3. Results

The follow-up at 12 months was completed with 55 women; 25 women were absent for the execution of the second mammography, specifically 13 women in the HT group and 12 women in the control group. No statistically significant differences were found for clinical characteristics such as age, age at menarche, body mass index (BMI), age at first pregnancy, parity and smoking of the groups ( $p > 0.05$ ) (Table 1).

We found an increase in mammographic breast density in 37% (95% CI: 18.8–55.3%) of women treated with E2/DRSP after 12 months. Following treatment with E2/DRSP, we found an upgrading in breast density, according to Wolfe's classification,

**Table 1**  
Clinical characteristics of the groups of women in this study.

| Variables                                  | E2/DRSP group<br>( $n = 40$ ) | Control group<br>( $n = 40$ ) | <i>p</i> value |
|--------------------------------------------|-------------------------------|-------------------------------|----------------|
| Age (years)                                | $44.8 \pm 1.9$                | $44.5 \pm 1.7$                | 0.314          |
| Age at menarche (years)                    | $12.8 \pm 0.9$                | $13.0 \pm 1.1$                | 0.586          |
| Body mass index ( $\text{kg}/\text{m}^2$ ) | $29.3 \pm 1.0$                | $29.2 \pm 1.6$                | 0.441          |
| Age at first pregnancy (years)             | $18.6 \pm 2.9$                | $19.7 \pm 3.5$                | 0.228          |
| Parity                                     | $3.8 \pm 1.9$                 | $3.4 \pm 1.7$                 | 0.374          |
| Current smoking                            | 5.0%                          | 7.5%                          | 1.00           |

Data are shown as mean  $\pm$  standard deviation or as a percentage.

No parameter was statistically significant between the two groups at baseline ( $p > 0.05$ ).

**Table 2**

Mammographic state in accordance with Wolfe's classification in women treated with E2/DRSP and controls at the beginning and after 12 months.

|    | E2/DRSP group (%) ( $n = 27$ ) |           | Control group (%) ( $n = 28$ ) |           |
|----|--------------------------------|-----------|--------------------------------|-----------|
|    | Basal                          | 12 months | Basal                          | 12 months |
| N1 | 11.1                           | 0         | 7.1                            | 10.7      |
| P1 | 44.4                           | 40.7      | 35.7                           | 39.2      |
| P2 | 44.4                           | 51.8      | 42.8                           | 35.7      |
| DY | 0                              | 7.4       | 14.3                           | 14.3      |

in 10 of the 27 patients. Between the first and second mammography, mammographic pattern has changed from N1 to P1 in 3 patients, from P1 to P2 in 5 patients, and from P2 to DY in 2 patients (Table 2). Mammographic density increase in a 45-year-old woman after E2/DRSP treatment is shown in Fig. 1. There was no involution of breast parenchyma in any of the women in the E2/DRSP group. In the control group, breast density was unchanged in 25 women (89.3%) and reduced in 3 women (10.7%). The percentage of women with density grade increases was 0% (95% CI: 0.0–0.0%) in the control group. The difference in breast density between the E2/DRSP group and the control group was statistically significant ( $p < 0.001$ ) (Fig. 2).

## 4. Comments

Mammographic density is clearly indicated as one of the strongest risk factors for breast cancer in a systematic outline and meta-analysis [17]. Breast density, representing the relative presence of fatty and fibroglandular elements, varies among women and is influenced by age, parity, BMI and ovarian steroids [1]. Nevertheless, in premenopausal women, variations in mammographic density are associated with blood and tissue levels of insulin-like growth factor I, and in postmenopausal women with blood levels of prolactin [18]. High mammographic density is usually seen in young women, whereas density decreases with age and shows a larger decline around menopause [19].

The two most frequently used classifications of breast densities are Wolfe's parenchymal pattern and the percentage of the breast with densities [20]. We used the Wolfe classification system in this study. This classification system, when compared with the percentage density method, may not offer more precision for assessing change in mammographic density (which could indicate a limitation to our study), but most of the combined data presented in the literature confirm that breast density measured using either Wolfe's system or percentage density is strongly associated with a breast cancer risk, as determined by general population studies of either incident or prevalent cancer risk [17]. Furthermore, Wolfe's classification was the earliest method of evaluating mammographic parenchymal patterns and is still widely used in most countries as it allows analysis of large study populations. In addition, breast cancer risk seems to be determined not only by the absolute amount of radiologically dense tissue but also by the degree of heterogeneity of the parenchymal pattern and, by other mammographic features additionally captured by the Wolfe classification [21].

Different kinds of HT and routes of administration seem to have different influences on breast density. Hormone therapy use may be associated with subtle breast tissue changes, such as edema or vascular dilation [22]. Thus, HT is associated with a reduction in the sensitivity of mammography [23]. Breast density changes occur rapidly with HT, with the greatest changes occurring in the first year [8]. After HT withdrawal, this density drops to the baseline level within 14 days [24].

Progestins are required in HT regimens for women with an intact uterus to prevent the development of an inappropriate estrogen-dependent endometrial proliferation. A variety of pro-

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