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Influence of different HRT regimens on mammographic density

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Abstract

Objectives: A prospective, randomized, open-label study was conducted to evaluate effects on mammographic density in postmenopausal and late perimenopausal women receiving continuous combined or sequential combined hormone replacement therapy (HRT). *Methods:* The subjects were randomized to treatment with low-dose continuous combined HRT containing 1 mg 17β-estradiol plus 0.5 mg norethisterone acetate (Activelle®) or a sequential combined HRT regimen consisting of 0.625 mg conjugated equine estrogens for 28 days plus 5 mg medrogestone for 14 days (Presomen®). Mammograms were obtained at baseline and after 9 cycles (each 28 days) of treatment. *Results:* The majority of women (approximately two-thirds in each treatment group) had no changes in mammographic breast density between baseline and the final study visit. There were no marked differences between treatment groups. Approximately 20% of women in both groups had a slight increase in mammographic density. Only 10–14% of women in both groups had a pronounced increase in mammographic density. The analyses of the degree of change showed no remarkable differences between treatments. *Conclusion:* These results indicate that the increase in mammographic density with a low-dose continuous combined HRT regimen is no greater than that with a sequential combined HRT regimen. The type of progestogen does not have an impact on the extent of mammographic density changes.

Keywords: Breast cancer; Estradiol; Hormone replacement therapy; Mammographic density; Mammography; Norethisterone acetate

1. Introduction

Screening mammography significantly reduces the rate of mortality from breast cancer in women 50 years of age and older [1,2]. HRT may increase the mammographic density of breast tissue and impair the ability to detect early signs of breast cancer [3–5]. The appearance of hormonally induced densities may also mimic that of breast disease, leading to diagnostic uncertainty and the need for additional mammographic assessments [5,6]. In women who are not taking hormones, radiographically dense breasts are associated with an increased risk of malignant breast tumors [7,8]. Conversely, no link has been established between hormonally related increases in breast density and an elevated risk of breast cancer [7,9–11]. Radiographic density related to HRT is nonetheless a matter of potential concern due to the risk of decreased sen-

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sitivity and specificity of mammography and the loss of a degree of diagnostic confidence [5,6,10,12–14].

Some analyses have suggested that mammographic density is influenced more by continuous combined HRT regimens than by sequential combined regimens, and less so by unopposed estrogen [4,15–18]. Observers have also suggested that mammographic changes vary with the type of progestogen [4,15,19,20]. To shed more light on these issues, effects on radiographic breast density were compared as part of a prospective, randomized, open-label, multicenter study in which late perimenopausal and postmenopausal women received either a low-dose continuous combined HRT regimen containing 1 mg 17β-estradiol (E_2) and 0.5 mg norethisterone acetate (NETA) (Activelle®, Novo Nordisk) or a sequential combined regimen containing 0.625 mg conjugated equine estrogens (CEE) and 5 mg medrogestone (MG) (Presomen® Comp, Solvay). The primary objective of the trial was to compare bleeding profiles with the two treatments. These results have been reported elsewhere [21]. Because the protocol called for all participants to undergo blinded mammographic assessments, the investigation also provided a valuable opportunity to examine changes in breast density with the two types of HRT regimens. Mammographic density was thereby designated as a secondary parameter.

2. Subjects and methods

2.1. Subjects

Women were considered eligible for the study if they were younger than 65 years old, had an intact uterus and a normal endometrium (endometrial thickness <5 mm (double layer) on transvaginal ultrasound), and experienced their last natural menstrual cycle at least 6 months before baseline screening. The women were also required to present with menopausal symptoms (e.g., hot flushes and sweating) that would benefit from HRT. Exclusion criteria included an abnormal mammogram, known or suspected breast cancer or a history of this disease, known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer), hepatic or renal impairment, type 1 or 2 diabetes mellitus; presence or history of deep venous thrombosis or thromboembolic disorders, known or suspected pregnancy or lactation, and known contraindications to estrogen treatment. Women were also excluded from the study if they had used any exogenous sex steroid hormones within the preceding 6 months.

2.2. Study protocol

Following baseline assessment, eligible women were randomized to 9 cycles of treatment (each 28 days) with either continuous combined HRT (1 mg E_2/0.5 mg NETA) or sequential combined HRT (0.625 mg CEE/5 mg MG). All subjects gave written informed consent of their willingness to participate in the trial. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and permission was secured from all local institutional review boards or independent ethics committees.

Mammography was performed at baseline (screening visit (1) unless the results of a bilateral mammogram obtained within the previous 6 months were available. Mammography was repeated at the final visit (after 9 treatment cycles) or at the time of patient withdrawal from the study in cases of premature discontinuation, provided at least 7 cycles of study treatment had been taken. Mediolateral or oblique and craniocaudal images of both breasts were obtained. The density of breast parenchyma in the baseline mammograms (taken at visit 1 or within 6 months before screenings) was compared with that in the mammograms taken at the final visit. The mammograms for each subject were visually compared in pairs by one radiologist who was blinded to the timing of the mammograms (i.e., which images were taken before or after study treatment) and to the type of HRT the patient received. Each pair of mammograms was judged according to whether there was no detectable change or a slight or marked change in breast density. The treatment effect was categorized as marked lower density, mild lower density, no difference, mild higher density, and marked higher density. Statistical analyses were performed using the Wilcoxon test and Fisher's exact test.

3. Results

A total of 513 postmenopausal or late perimenopausal women were enrolled in the study at 35