

# FACTORS THAT INFLUENCE CHANGES IN MAMMOGRAPHIC DENSITY WITH POSTMENOPAUSAL HORMONE THERAPY

Fang-Ping Chen<sup>1\*</sup>, Yun-Chung Cheung<sup>2</sup>, Yung-Kui Soong<sup>1</sup>

Departments of <sup>1</sup>Obstetrics and Gynecology and <sup>2</sup>Radiology, Chang Gung Memorial Hospital, Keelung, Chang Gung University, College of Medicine, Taiwan.

## SUMMARY

**Objective:** To evaluate the relationship between mammographic density and clinical factors in postmenopausal women using hormone therapy (HT).

**Materials and Methods:** Retrospective study of 467 postmenopausal women who received continuous estrogen or estrogen-progestin HT and had regular mammography between 1994 and 2001. A detailed clinical history was recorded, including age at start of HT, age at menopause, years from onset of menopause to start of HT, body mass index (BMI), and duration and regimens of HT.

**Results:** After adjustment for the effects of other variables, age at the start of HT and BMI were inversely associated with breast density ( $p=0.0025$  and  $<0.001$ , respectively). In contrast, duration of HT was positively related to mammographic density ( $p<0.001$ ). Although the mean density was significantly increased after 4 years of HT in women receiving combined HT compared with those using estrogen alone, after adjustment for the effects of other variables, the correlation between mammographic density and regimen of HT (combined HT vs. estrogen alone) did not reach the significance level of 0.05.

**Conclusion:** Higher mammographic density was associated with longer use of HT, especially in younger postmenopausal women and those with lower BMI. [*Taiwan J Obstet Gynecol* 2010;49(4):413–418]

**Key Words:** estrogen, estrogen-progestin, hormone therapy, mammographic density, postmenopausal women

## Introduction

Breast density has been shown to have a heritable component and may serve as a marker of genetic risk for breast cancer [1,2]. Other studies [3–8] have demonstrated that breast density is also associated with hormone exposure, reproductive factors, and dietary factors. In addition, it is also suggested that women with higher mammographic densities are at an increased risk for breast cancer [9,10]. Therefore, it is possible

that increased breast density may be related to genetic factors, environmental factors, or both.

Until reports from the Women's Health initiative addressed the adverse effect of using hormone therapy (HT) for more than 5 years on breast cancer [11], HT was increasingly prescribed to postmenopausal women for the relief of climacteric symptoms as well as for the prevention of osteoporosis. Several studies have demonstrated an association between the use of HT and breast density [8,12,13]. However, certain factors related to the effects of menopause, which affect breast density, have not been thoroughly investigated in postmenopausal women using HT.

If increased mammographic density is causally related to breast cancer, it is important to understand whether certain factors can have an effect on mammographic density. This will provide information for the development of individualized treatments with respect



ELSEVIER

\*Correspondence to: Dr Fang-Ping Chen, Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, 222 Mai-Chin Road, Keelung, Taiwan.

E-mail: fangping@cgmh.org.tw

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to breast receptivity to HT and may be useful in identifying postmenopausal women who suffer adverse effects resulting from HT.

As mentioned above, although the effects of HT on mammographic density have been well studied, the relationships between other factors and mammographic density have not been well examined. In this study, we investigated the association of menopause-related and hormonal factors with the mammographic density in postmenopausal women using HT.

## Materials and Methods

### Study sample

The study sample consisted of 1,415 postmenopausal women who attended the Keelung Chang Gung Memorial Hospital gynecologic clinic from 1994 to 2001. They had not received HT before and requested HT for climacteric symptoms. Before beginning HT, all of these patients received thorough examinations, including mammography, liver function, lipoprotein metabolism, and gynecologic evaluations. None of the participants had contraindications for estrogen or progesterone treatment. Women with the following conditions were excluded from HT: bleeding due to an undiagnosed cause, findings suggesting malignant disease of the breast, known or suspected estrogen-dependent tumors or fibroids, alcoholism, Rotor or Dubin-Johnson syndrome, severe liver or kidney disorders, endometrial hyperplasia, and severe hypertension. In addition, we only enrolled women who had regular follow-ups and maintained the same regimen and dosage of HT for at least 2 years following their first mammogram. In total, this study comprised 467 women. The remaining women were excluded for reasons such as discontinuous or irregular use of HT or follow-ups, changing regimens or dosage of HT, and evaluation through breast ultrasound.

Among the 467 postmenopausal women, 200 (42.8%) patients had hysterectomies for benign gynecological disorders and used only 0.625 mg/day conjugated estrogen (Premarin, Wyeth-Ayerst Canada Company, Montreal, Quebec, Canada). The other 267 women were treated with continuous combined 0.625 mg/day conjugated estrogen plus 2.5 mg/day medroxyprogesterone acetate (Provera, Pharmacia & Upjohn Company, Kalamazoo, Michigan, USA). Follow-up through mammographic screening was scheduled for every user with a time interval of 1–2 years following HT.

### Measures

From 1994 to 2001, 467 women completed a total of 1,438 mammograms using different screening

techniques including the mediolateral oblique and craniocaudal views of the bilateral breast. In addition to the first mammogram prior to the start of HT and the second screening mammogram after 1 to 2 years of HT, both of which were completed by all participants, 371 (79.4%) patients had a third mammogram, 281 (60.2%) had a fourth, 179 (38.3%) had a fifth, and 179 (38.3%) had a sixth.

Mammograms were reviewed, in a blinded manner, by a senior radiologist (Dr Y.C. Cheung) who specializes in breast examinations. Breast densities were coded on a 4-point scale according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) coding [14]. A score of 1 indicates almost entirely fat; 2 indicates scattered fibroglandular tissue; 3 indicates heterogeneously dense; and 4 indicates extreme density. Mammographic density was rated separately for each breast and the breast with the highest density was then used for analysis.

### Statistical analysis

Statistical analysis was evaluated by iSTAT Healthcare Consulting Co. Ltd. Student *t* tests were used to assess the differences in baseline characteristics between those using estrogen alone *versus* those using combined estrogen-progestin. The correlation between breast density and other variables was also evaluated by the generalized estimating equation.

## Results

From 1994 to 2001, there were 467 women who met the initial criteria for inclusion into our analysis. Data on age at start of HT, age at menopause, duration from onset of menopause to start of HT, body mass index (BMI), duration of HT use, and regimens (estrogen alone and combined estrogen-progestin) are summarized in Table 1.

At the time of starting HT, the mean age of women in our sample was  $50.4 \pm 5.8$  years (range, 43–69 years). As shown in Table 1, although women using estrogen alone ( $n=200$ ) tended to be younger than women receiving combined estrogen-progestin ( $n=267$ ), there was no significant difference. There were also no statistical differences in the duration of HT use and BMI between the women receiving estrogen alone and those receiving the combination of estrogen-progestin.

Table 2 shows the relationship between breast density and variables such as age at start of HT, age at menopause, years from menopause to start of HT, BMI, and duration and regimens of HT. After adjustment for the effects of other variables, age at start of HT and BMI were inversely associated with breast density

**Table 1.** Baseline characteristics by pattern of hormone therapy ( $n = 467$ )\*

	Estrogen alone	Combined HT <sup>†</sup>	<i>p</i>
No. of patients	200 (42.8)	267 (57.2)	
Age at start of HT (yr)	49.2 ± 5.6 (43–69)	51.3 ± 5.7 (43–67)	0.066
Age at menopause (yr)	46.2 ± 4.8 (42–56)	47.8 ± 5.1 (43–59)	0.691
Body mass index (kg/m <sup>2</sup> )	24.9 ± 3.6	24.5 ± 3.4	0.140
Duration from onset of menopause to start of HT (yr)	3.1 ± 4.7	3.6 ± 4.8	0.272
Duration of HT (yr)	3.2 ± 1.3	3.8 ± 1.8	0.464

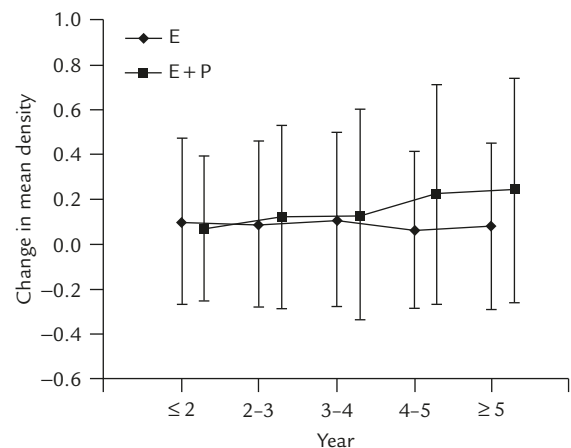
\*Data are presented as  $n$  (%), mean ± standard deviation (range) or mean ± standard deviation; <sup>†</sup>combined estrogen-progestin. HT = hormone therapy.

**Table 2.** Correlation between changes in breast density and other variables estimated by the method of generalized estimating equation ( $n = 467$ )\*

Variable	Value	Estimate	SE	<i>p</i>
Age at start of HT	50.4 ± 5.8 (43–69)	−0.0608	0.0201	0.003
Age at menopause	47.1 ± 5.0 (42–59)	0.0393	0.0216	0.069
Duration <sup>†</sup>	3.3 ± 4.7	0.0393	0.0222	0.076
Regimen	Estrogen alone vs. combined HT	−0.0308	0.0586	0.599
Year of use of HT	3.5 ± 1.6	0.0449	0.0096	<0.001
BMI	24.4 ± 3.3	−0.0287	0.0071	<0.001

\*Data are presented as mean ± standard deviation (range); <sup>†</sup>years from onset of menopause to start of HT. SE = standard error; BMI = body mass index; HT = hormone therapy.

( $p = 0.003$  and  $< 0.001$ , respectively). In contrast, the duration of HT was positively related to mammographic density ( $p < 0.001$ ). The Figure shows the association between different regimens of HT and breast density. Women using combined estrogen-progestin for more than 4 years had significant increases in their mean density scores, compared with those using only estrogen ( $p = 0.013$ ). After adjustment for the effects of other variables, the correlation between breast density and choice of HT regimens (combined HT vs. estrogen alone) did not reach the significance level of 0.05. In addition, age at menopause and years from onset of menopause to start of HT were not associated with changes in breast density.

**Figure.** Changes in breast density by pattern of hormone therapy. E = estrogen alone; E + P = combined estrogen-progestin.

## Discussion

Our study of mammographic density concentrated on postmenopausal women using HT because the effect of HT on the breast is complex and individualized. In addition to confirming other previous research, our study also explored changes in breast density while adjusting for possible affecting variables, such as BMI, age at menopause, age at start of HT, and duration from onset of menopause to the start of HT.

Most previous reports [3,15–19], though not all [20], found a positive association between the use of

HT and breast density, resembling the well-known association between HT use and the risk of breast cancer. However, the relationship between HT and mammographic density must be explored against the background of changes that normally occur during and after menopause. The time when involutionary changes normally occur may be an important factor with respect to breast receptivity to HT and may be useful in identifying women who suffer an adverse effect resulting from HT. In our study, the effect of HT on mammographic density was inversely associated with age at the initiation

of HT. This indicates that the breast may undergo involutionary change after cessation of the menses. Similar age-specific patterns were reported by two studies. These found that the relationship between HT and breast cancer risk was stronger in younger women [21,22], although this is not always seen [23]. In addition, the study of Titus-Ernstoff et al [24], as well as other reports [3,18], showed the impact of current HT use on breast density with an inverse association in younger women (> 50 years of age), and a positive association in older women. Since these reports did not adjust for the effect of HT duration as our study did, the age-related increase observed in these reports may reflect a longer HT duration.

In this study, we also found that women with increased BMI had reduced breast densities. This finding is supported by other studies [25,26] in which one might expect to find more fatty replacement and less dense patterns in obese women. In addition, several reports [21,27,28] found that the risk of breast cancer with use of either estrogen alone or combined estrogen-progestin was slightly greater among women with leaner body masses. The study of Schairer et al [29] observed that the use of estrogen alone was associated with an increased risk only among lean women and not among heavy women, whereas associations with combined use did not vary by weight. However, excluding the effects of HT, increased body weight and BMI have been consistently associated with elevated relative risk of breast cancer, especially in postmenopausal women [30,31].

In this study, we found that the duration of HT was related to increased mammographic density. Our study confirmed findings from previous studies demonstrating an association between using HT and increased breast density [8,12,18,19,25]. In contrast, two studies demonstrated no difference in the breast density associated with the duration of HT use, suggesting that density changes, if any, develop relatively soon after HT is started and then remain stable [3,4]. However, the positive influence of HT on breast cancer risk is usually observed in long-term use [21,23,27–29,32]. If the duration of HT is considered, it is possible that sustained breast density associated with long-term HT use mediates the relationship between HT and breast cancer risk. In our previous study [33], the long-term use of HT was associated with increased incidence of increased parenchymal breast density, from 8.6% to 18.4% during the 7-year follow-up, and the majority of the breast densities remained at pre-treatment levels. This means that long-term use of HT induced increased breast densities in some women. Therefore, in postmenopausal with increased breast densities after HT, the potential of exogenous hormones inducing epithelial or stromal

hyperplasia must be considered. If the effect is epithelial hyperplasia, the risk of breast cancer must be taken into account.

Effects of progesterone on the breast are suggested by reports that breast density is greater during the luteal phase of the menstrual cycle [34–36]. In an animal model for hormone replacement, continuous-combination estrogen-progestin treatment induced more proliferation than estrogen alone [37]. Our study showed that, in long-term HT use without adjustment for the effects of other variables, an increase in breast density was much more common and more pronounced among women receiving combined estrogen-progestin than among those using estrogen alone. Our data are in agreement with a number of previous studies [19,38–41]. In the present study, we found that in women using combined estrogen-progestin, the probability of increased mammographic density was progressively increased as the duration of administration was extended (from 7.5% to 22.4%, data not shown). In contrast, women using estrogen alone did not show an increased incidence of breast density over an increased duration of HT; the majority remained at the pre-treatment level. However, after adjustment for the effects of other variables, the duration of HT is the only significant factor in the mammographic density increase, and the effect of progesterone becomes non-significant. If increased breast density is associated with an increased risk of breast cancer, it is compatible with epidemiological studies [27] showing that the risk of breast cancer increases with long-term HT use.

The present results suggest that age at menopause and years from menopause to start of hormone therapy are not associated with the changes of breast density in postmenopausal HT, after adjustment for other variables. Similar results from other studies revealed that age at menopause was not significantly associated with percentage density [20,42], and women who started HT after the onset of menopause did not appear to be different from non-HT users with respect to high-risk patterns [25].

In conclusion, the effects of HT on the breast, as reflected by mammography, may be influenced by factors associated with menopause. A longer duration of HT, especially in younger postmenopausal women and those with lower BMI, results in a greater percentage of women who develop more glandular tissue, as seen in mammography. The implications of additional glandular tissue are unknown, but it might have an impact on the sensitivity of mammography or alter the risk for subsequent breast cancer. For patients needing long-term HT, we recommend close follow-up by mammography and even more detailed evaluations of the potential of exogenous

hormones inducing epithelial hyperplasia in those with increased breast densities.

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