N. Ahmadi Nejad MD[1].
M. Guity MD[1].
M. Farahani MD[2].
S. Farzane MD[2].
M. Shakiba MD[3].
A. H. Jalali MD[3].

Evaluation of Mammographic Density Changes during Estrogen and Estrogen-Progesterone Therapy in Postmenopausal Women

Background/Objectives: To determine the effects of estrogen and estrogen plus progesterone on mammographic density in postmenopausal women.

Patients and Methods: In a descriptive cohort study, ba seline and 12-month mammograms were obtained from 97 healthy postmenopausal women, aged 45-55 years. Estrogen or combined estrogen and progesterone replacement ther apies were used for them. After one year, we classified breast density in the first and second mammograms according to Breast Imaging Reporting and Data System (BIRADS) as patterns 1 (mostly fatty) through 4 (mostly dense tissue).

Results: None of our cases had a decrease in density, while 35.1% showed an increased density. The results showed that an increase in mammographic density had no significant association with the type of prescribed hormone (P=0.77).

In cases with no change in density, the parity was 3.51.86; while in the group with one-level rise, it was 4.241.84; and 5.21. 92 in the two-level rise group.

Statistical analysis showed that changes in density had significant association with parity in our cases (P=0.015).

Conclusion: HRT was associated with increases in mammographic density, suggesting that increasing mammographic density may be a marker of elevated breast cancer risk in postmenopausal women who use postmenopausal ho rmone replacement therapies. However, the link between changes in breast density resulting from hormone use and the change in breast cancer risk remains uncertain.

Keywords: hormone replacement therapy, mammographic breast density, postmenopause

1. Assistant professor, Department of Radiology, Medical Imaging Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
3.Research Unit, Medical Imaging Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author:
Nasrin Ahmadi Nejad
Address: Medical Imaging Center, Imam Khomeini Hospital, Tehran, Iran.
PO Box: 1419733141
Tel: 009821-66438631-3
Fax: 009821-66945117
E mail:
n_ahmadinejad@yahoo.com

Received January 24, 2005;
Accepted after revision May 15, 2005.

June 2005; 2:103-106

Introduction

Hormone replacement therapy (HRT) is widely prescribed for women in postmenopausal age for relief of climacteric symptoms, as well as for prevention of osteoporosis.

Estrogens are responsible for the growth and development of mammary ducts, while progesterones stimulate the growth and development of lobules. During menopause, however, the levels of endogenous hormones decrease leading to regression of ductal and stromal elements, and their fatty replacement. The use of HRT may reverse this process resulting in an increase in mammographic density.[1] Mammographic breast density may be the most undervalued and underused risk factor in studies investigating breast cancer occurrence.[2] The risk for breast cancer is four to six times higher in women with dense breasts.[3-5] Breast density may also decrease the sensitivity and accuracy of mammography, besides increasing false negative and false positive results. The increase in mammographic density associated with HRT use varies according to the type of hormone therapy.[5-7] It is proposed that some factors such as age, parity and familial

history of breast cancer could affect the breast density from HRT.

Accordingly, in this study, we investigated the increase in breast density in a group of patients receiving HRT for one year according to some factors such as family history of breast cancer, age, age at first birth, parity, age of menopause, and type of prescribed HRT. Characterization of the mammographic response to hormone therapy is important because a woman's response to HRT may provide a visual tool to identify women for whom hormone use would be limited.

Patients and Methods

Between 2000 and 2001, we recruited 97 women aged between 45 and 55 years for our study. They were postmenopausal and had not taken estrogen or progestin for at least two months before screening. Our descriptive cohort study was done at the Medical Imaging Center, Imam Khomeini Hospital.

Each case had a baseline mammogram performed before the initiation of HRT and cases with suspicious features o n their mammograms were excluded. Mammography was performed using dedicated mammographic equipment (Senograph 600 T, General Electric Medical Systems, and USA). For each case, estrogen (0.625 per day) or combined estrogen and progesterone (estrogen 0.625 per day for the first 15 days, followed by medroxyprogesterone, 5 per day for 10 days) was prescribed. One year after HRT, mammography was done for them again. At this time, two expert radiologists reported mammograms, each classifying breast density on both the first and second mammograms according to the Breast Imaging Reporting and Data System (BIRADS), as patterns 1 (mostly fatty) through 4 (mostly dense tissue).[8] Formulation (estrogen alone, estrogen and progesterone combined) of HRT was not available to the radiologist at the time of reporting. The two radiologists evaluated these films together and a consensus was reached.

At each screening, the mammographic image of each breast was classified by the system proposed by ACR, [8] which divides images into four classes, in a roughly increasing risk of developing breast cancer.

Demographic and history information was collected at the time of the first mammography by using a data collection form, which was completed again one year later.

Sampling was done by convenient sampling and an informed consent was taken from all cases. The data analysis was performed by SPSS version 11.5. We used Wilcoxon, Mann-Whitney and Kruskal- Wallis tests for analysis. The confidence level was set equal to 95%.

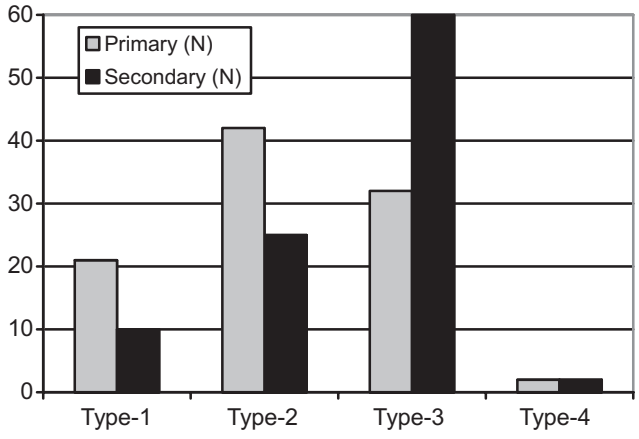

Fig-1. Mammographic characteristics based on BIRADS classification.

Results

Mammographic characteristics based on BIRADS classification are presented in Figure1.

None of our cases had a decrease in density and 35.1% showed increased density. In this group, six cases had progression from type 1 to 2; 5 cases from type 1 to 3; and 23 cases from type 2 to 3. We had no progression to type 4. Wilcoxon test showed that mammographic changes in primary and annual screening were significant ($P<0.0001$). Thirty–eight women (39.2%) were treated with estrogen alone and 59 (60.8%) with an estrogen and progesterone combination.

In the estrogen group, 31.6% had one-level and 5.3% two-level rise in density.

In the combined treatment group, 28.8% had one-level rise and 5.1% two-level rise in density. Results showed that the increase in mammographic density had no significant association with the type of prescribed hormone ($P=0.77$).

Table 1- The association between age and the increase in breast density.

Number (%) Age level	Without change (63 Cases)	One-level rise (29 Cases)	Two-level rise (5 Cases)
<50 y	47 (74.6%)	23 (79.3%)	3 (%60)
>50 y	16 (25.4%)	6 (20.7%)	2 (40%)

Our results also showed that the association between increased density and menopausal age was not significant (P=0.95). The mean menopausal age of women with no increase in density was 46.9±4.03; in one-level rise, 47.6±3.3; and in two-level rise, 49.4±2.4. The association between age and the increase in breast density is shown in Table 1.

The age at first birth in 61.1% of cases was under

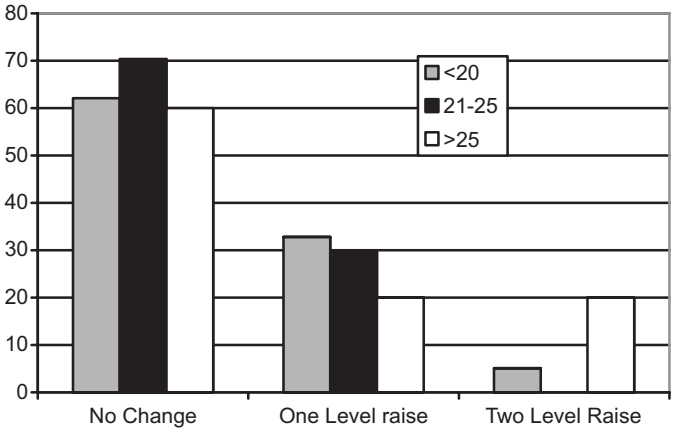

Fig-2. Changes in breast density based on age at first birth.

20, in 28.4 % between 21 and 25, and in 10.5% up to 25.

The association between age at first birth and the increase in density was not significant (P=0.528) (Figure 2).

At this study, 8.2% of cases mentioned a positive familial history for breast cancer and none of them had changes in mammographic density. In women with a negative familial history, 32.6% had one-level and 5.6% two-level rises in mammographic density. Statistical analysis showed a significant relationship between familial history and increasing breast density after HRT (P=0.033).

The parity was 3.5±1.86 in women with no change in density, 4.24±1.84 in the group with one-level rise, and 5.2±1.92 in the two-level rise group.

Statistical analysis showed that change in density had a significant association with parity in our cases (P=0.015) (Table 2).

The mean age in cases with no change was 51.12 ±3.34, 51.34±3.23 in the group with one-level rise, and 52±3.74 in the two-level rise group (P=0.66).

We categorized our cases in two age groups, i.e. equal to or higher and lower than 50 years. Those under 50 comprised 31.2% of cases, while 60.8% were higher than 50 years old. In individuals younger than 50, 26.3% showed one-level rise and 5.3%, two-level rises in density. In those 50 and over, 32.2% had one-level and 5.1% two-level rises. Statistical analysis showed a significant association between age of HRT initiation and increasing breast density (P=0.05).

Discussion

Mammogram density is an estimate of the proportion of fibroglandular tissue to fat in the breast. In the menopause period and with increasing age, the proportion of breast fat increases, rendering mammograms less radiodense.[9]

In addition to age and menopause, density is known to vary with other factors such as the age at first birth, parity, and HRT.[9, 10] Several studies have quantified mammogram density and have confirmed its associated risk as well as the risk factors. [9, 11, 12]

Women with extensively dense breasts on mammography have a risk of breast cancer that is up to 6.0 times greater than those with low density or no density do.[11, 12] About one-third of breast cancer cases can be attributed to the presence of dense tissue in more than 50% of the breast tissue.[3]

Our study confirms that HRT is significantly associated with an increase in breast density, and that most increase is seen from type 1 to 2. These results agree with several before-after studies that reported increases in density with hormone use. Some studies have reported increases in breast density in about 17-

Table 2- The association between changes in breast density and parity.

Parity	Number of cases	No change (%)	One-level rise (%)	Two-level rise (%)
≤2	26	84.6	15.4	0
3, 4	46	58.7	37	4.3
>4	25	56	32	12

27 percent of cases, but our results show a greater increase in comparison with them ($P<0.0001$).[13, 14]

Indeed, our findings showed that mammographic breast density changes related to postmenopausal HRT had no correlation with the selected hormone regimen (estrogen or combined). This is in contrast with many other reports. For example, two studies compared the effects of estrogens alone with the effects of combination treatments on changes in breast density and found that overall, starting estrogen-only treatment was not associated with breast density increases, whereas starting continuous combined estrogen-progestin therapy was related to increases in breast density.[6, 15]

This difference may be explained by the fact that our patients were not chosen randomly and were referred by physicians who had chosen the HRT regimen based on their conditions.

We confirm that changes in breast density have a significant association with parity, as several studies have already shown.[16-18]

Higher increases of breast density in women over 50 in our study is consistent with some other reports.[6]

Indeed, we found that there is no significant association between age at menopause and age at first birth with breast density in HRT users. To the best of our knowledge, there is no other study on the effects of these two variables on the relation between HRT use and BIRADS mammographic parenchymal pattern. It would be, therefore, very interesting to see if other studies have shown the same phenomenon.

A potential limitation of our study was that we focused on women at 45-55 years of age, which is perhaps one of the reasons for some differences between our results and others. In fact, choosing a control group matched with cases for age and menopause time could have helped us better understand the role of possible confounding factors, including age at menopause. In addition, it could have helped with further elucidating the effects of HRT on changes of breast density.

In conclusion, HRT was associated with increases in mammographic breast density, suggesting that increasing mammographic density may be a marker for elevated breast cancer risk in postmenopausal women who receive HRT. However, the possible relationship between changes in breast density resulting from hormone use and changes in breast cancer risk remains uncertain.

References

1. Sala E, Warren R, McCann J, Duffy S, Luben R, Day N. High-risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case-control study. International Journal of Epidemiology 2000; 29:629-636.
2. Byrne C. Studying mammographic density: implications for understanding breast cancer. J Natl Cancer Inst. 1997; 89:531-533.
3. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1998; 7:1133-1144.
4. Lam PB, Vacek PM, Geller BM, Muss HB. The association of increased weight, body mass index, and tissue density with the risk of breast carcinoma in Vermont. Cancer. 2000; 89:369-375.
5. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikoske K, Rosenberg R, Ruter CM et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med. 2003; 138:168-175.
6. Persson I, Thurfjell E, Holmberg L. Effect of estrogen and estrogen-progestin replacement regimens on mammographic breast density. J Clin Oncol. 1997; 15:3201-3207.
7. Litherland JC, Evans AJ, Wilson AR. The effect of hormone replacement therapy on recall rate in the National Health Service Breast Screening Programme. Clin Radiol. 1997; 52:276-279.
8. American College of Radiology. Breast imaging reporting and data system (BI-RADS). 2d ed. Reston, VA: American Coll Radiology.2002 ;Ch23 :377-393
9. Heine J J, Poonam M. Mammographic tissue, breast cancer risk, serial image analysis, and digital mammography. Part 1. Tissue and related risk factors. Acad. Radiol.2002; 9:298-316.
10. Vachon CM, Kuni CC, Anderson KVE, and Sellers T A. Association of mammographically defined percent breast with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control.2000; 11:653-662.
11. Boyd NF, Dite GS, Stone J, Gunasecara A. English DR, McCrdite MRE et al. Heritability of mammographic density, a risk factor for breast cancer. N. Engl. J. Med. 2002; 347:886-894.
12. Thurfjell E, Hsieh CC, Lipworth L, Ekbom A, Adami , Tricopoulos D. Breast size and mammographic pattern in relation to breast cancer risk. Eur. J. Cancer Prev. 1996; 5:37-541.
13. Berkowitz JE, Gatewood OM, Goldblum LE, Gayler BW. Hormonal replacement therapy. Mammographic Manifestations Radiology.1990; 174:199-201.
14. McNicholas MM, Heneghan JP, Milner MH, Tunney T, Hourihane JB, MacErlaine DP. Pain and increased mammographic density in women receiving hormone replacement therapy a prospective study. AJR. 1994; 163:311-315
15. Lundstorm E, Wilczek B, von Palffy Z, Soderqvist G, von Schoultz B. Mammographic breast density during hormone replacement therapy: differences according to treatment. Am J Obstet Gynecol 1999; 181: 348-352.
16. Saftlas AF, Szklo M. Mammographic parenchymal patterns and breast cancer risk. Epidemiol Rev. 1987; 9:146-174.
17. Berkvist L, Bergstorm R, Tabar L, Adami H. Epidemiologic determinants of mammographic parenchymal pattern: A population based study within a mammographic screening programme. Am J Epidemiol.1987; 126:1075-1081.
18. Gram IT, Funkhouser E, Tabar L. Reproductive and menstrual factors in relation to mammographic parenchymal patterns among perimenopausal women. Br J Cancer. 1995; 71:647-750.