Correlation of Endogenous Hormonal Levels, Fibroglandular Tissue Volume and Breast Density Measured Using 3D MRI

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Background and Purposes:

Circulating sex hormones are implicated in the etiology of breast cancer. Women's endogenous hormone (EH), progesterone and estradiol, concentrations fluctuate over the course of the menstrual cycle (MC), which have been hypothesized to be responsible for variation in mammographic density [1]. Only a few studies examined premenopausal estrogen levels in relation to mammographic density and their findings were inconsistent [2, 3]. Mammographic density is limited by its 2D nature, with the problem of overlapping tissues. In this study we examined the correlation between levels of endogenous estrogen and progesterone and measures of fibroglandular tissue volume and percent breast density analyzed on 3D MRI.

Materials and Methods:

Twenty-four healthy premenopausal Asian women (age range 23-48, mean 29) were recruited for this correlative study. Each woman received weekly breast MRI, noted as Week-1 to Week-4. Week-1 was the MRI done after the starting of self-reported MC. Prior to the MRI, a blood sample was collected on the same day. Serum estradiol (E2) and progesterone levels were measured. The breast MRI was performed on a 1.5T MR. Only non-contrast 3D GE T1WI was acquired. The MR images were processed and analyzed by an experienced operator for breast volume (BV), fibroglandular tissue volume (FV), and percent breast density (PD) using our previously developed computer-based algorithm [4, 5]. Pearson's correlation coefficients were obtained between FV, PD and EH levels measured at each time points. To model mean FV and mean PD from predictor variables including timing, E2 and progesterone, statistical methods were applied that took into account the correlation between values for FV (or PD) measured weekly during a menstrual cycle for each woman and the fact that changes in EH levels may precede changes in FV and PD rather than coincide during the same week. The generalized estimation equation (GEE) method was applied with subjects as clusters, an autoregressive correlation structure, and a normal link function. Additionally, the GEE method was also performed wherein values of FV (or PD) measured during Week-2, Week-3, and Week-4 were modeled as a function of time and values for E2 and progesterone measured the week before (i.e. during Week-1, Week-2, and Week-3, respectively) to investigate the delayed effect on density, with subjects as clusters, an exchangeable correlation structure, and a normal link function. In this lag model, the exchangeable structure was utilized assuming the correlation between observations of FV (or PD) is constant.
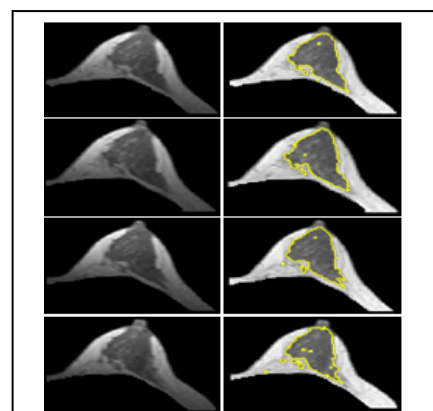
Results:

In Week-3 and Week-4, there was a significant correlation between E2 and progesterone (r=0.43; p=0.03; and r=0.70 p =0.0002). In Week-3, there was also a strong correlation between E2 and FV (r=0.42, p=0.04); between progesterone and FV (r=0.43, p=0.04); and between E2 and PD (r=0.43, p=0.04). GEE models showed no significant interaction between estradiol (or progesterone) and timing with regard to the outcome of mean PD or mean FV, thus simpler models without the interaction term are reported here. In separate autoregressive GEE models of mean PD, changes in mean PD were not significantly related to changes in E2 (p=0.21), adjusted for variation in mean PD across 4 weeks. Similarly, mean PD was not significantly related to progesterone level (p=0.15), adjusted for variation in mean PD across 4 weeks. Compared to Week-4, mean FV was significantly lower during Weeks-2 and -3 (p<.003), adjusted for variation in estradiol levels. Compared to Week-4, mean FV was significantly lower during Week-2 and -3 (p<.003), adjusted for variation in progesterone levels. In GEE models of the lag effect of changes in E2 and progesterone on PD and FV, it was found that neither changes in E2 nor progesterone affected mean PD or mean FV in the next (new) week (all p values > 0.05). For this model, predicted mean PD2 in Week-4, was significantly higher than those during Weeks-2 and -3 (p<0.05), adjusted for variation in estradiol levels of the previous week. For this model, predicted mean FV in Week-4, was significantly higher than those during Weeks-2 and -3 (p<0.02), adjusted for variation in estradiol levels of the previous week. **Figure 1** is an example of 4 breast MRI studies performed in a woman during her MC. The E2 were 100, 309, 96, and 125 pg/ml, and progesterone were 0.44, 0.85, 11.80, and 8.23 ng/ml, from Week-1 to Week-4 respectively. The corresponding FV were 27.2, 26.2, 26.9, and 28.5 ml respectively (**Figure 2**).
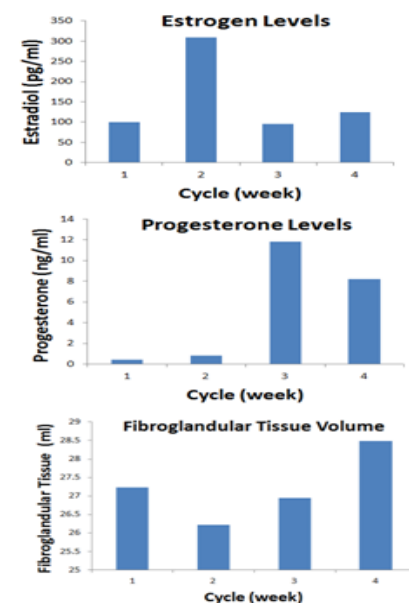
Discussion:

Our results quantify changes in PD and FV throughout the monthly cycle, adjusted for variation in endogenous estradiol and progesterone. Particularly in the third week after the starting of menstruation, there was significant correlation of FV and PD with endogenous estradiol, and FV with progesterone. The results were consistent with a study from mammographic density showing positive associations between percent breast density and sex hormone binding globulin, as well as estradiol during the menstrual cycle [6]. Our study did not find strong evidence of a weekly lag effect of endogenous hormone on the measured FV and PD. The positive correlation of FV and PD with endogenous hormonal levels at Week-3 observed in this study raised the possibility that the association between sex hormone and breast cancer may be mediated, in part, by increasing breast density.

Figure 1. Fibroglandular tissue from 4 weekly MRI studies of a healthy woman.

Figure 2. Estrogen, progesterone & FV measured in the woman shown in **Fig. 1.**

References: 1. Buist et al. Cancer Epidemiol Biomarkers Prev 2006;15:2303-6. **2.** Noh et al. Breast 2006;15:20-8. **3.** Boyd et al. Br J Cancer 2002; 87:876-82. **4.** Nie et al. Medical Physics 2008;35:5253-62. **5.** Lin et al. Med Phys 2011;38:5-14. **6.** Yong et al. Cancer Causes Control 2009;20:1039–53.