Correlation between bone mineral density and endometrial thickness over time in women with breast cancer history

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Abstract
As the efficacy of chemotherapy and adjuvant endocrine therapy for breast cancer increase, the quality-of-life to cancer survivors could be more important issue in strategies of breast cancer treatment. Bone health has become more compelling in care of breast cancer survivor than ever before. This retrospective study was aimed to evaluate factors relating to the change in BMD and to ascertain the correlation between changes in BMD and EMT of women with breast cancer in follow-up. Records of 164 women who underwent surgery for breast cancer were reviewed in this study. The basal characteristics included parity, menopausal state, medication with vitamin D, bisphosphonate, selective estrogen modulator (SERM), aromatase inhibitor (AI), gonadotrophin releasing hormone agonist (GnRHa), chemotherapy, radiotherapy, cancer type including positivity of estrogen receptor, progesterone receptor and HER2, combined the other gynecologic disease or the other origin cancer. At initial and follow-up visit, all subjective were checked with BMD, endometrial thickness (EMT). The mean age was 52.1 ± 8.5 years old and overall interval between initial and follow-up visits were 17.6 ± 7.5 month in this study. The BMDs of L1–4 (1.040 ± 0.166 g/

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cm² vs 1.070 ± 0.181 g/cm², p < 0.001), femur neck (0.850 ± 0.121 g/cm² vs 0.870 ± 0.136 g/cm², p < 0.001), and femur total (0.902 ± 0.132 g/cm² vs 0.915 ± 0.138 g/cm², p < 0.001) at follow-up visit were significantly lower than those at initial visit. The change in BMDs of L1–4 (ΔBMDL1–4, r=0.353, p<0.001, and r=0.228, p=0.003), femur neck (ΔBMDNeck, r=0.198, p=0.011, and r=0.282, p<0.001), femur total (ΔBMDTotal, r=0.294, p<0.001, and r=0.327, p<0.001) had positive correlation with age and the change in EMT (ΔEMT). After age correction, ΔEMT had positive correlation with ΔBMDNeck (r=0.245, p=0.002) and ΔBMDTotal (r=0.273, p<0.001). ΔBMDL1–4 and ΔBMDNeck differed according to menopausal state (p<0.001 and p=0.035), bisphosphonate (p<0.001 and p<0.001), and GnRHa (p<0.001 and p<0.001). In follow-up of women with history of breast cancer, ΔEMT could be an alternative screening marker for BMD decrease.

Keywords
Bone mineral density, endometrial thickness, breast cancer

Introduction
According to the Korean national cancer registration database, breast cancer is the leading cancer incidence in Korean women with 347.6 per 100,000 persons, and shows a relatively good prognosis with 92.7% of overall 5-year survival rate.¹ As the efficacy of chemotherapy and adjuvant endocrine therapy for breast cancer increase, the quality-of-life to cancer survivors could be more important issue in strategies of breast cancer treatment. So, follow-up of breast cancer survivors could be involved by multidisciplinary clinical care.²⁻⁴

Breast cancer survivors, women on selective estrogen receptor modulator (SERM) therapies in particular, should be recommended for an annual gynecologic assessment to surveilling the uterine endometrium and screening the other cancer, because long-term SERM therapy of postmenopausal women with breast cancer is associated with uterine pathology.⁴ For screening procedure, ultrasonography is useful in asymptomatic patients selecting cases with increased endometrial thickness for further investigation.⁵ The previous studies reported that increased endometrial thickness (EMT) as assessed by ultrasonography was associated with increased risk of endometrial pathologies including carcinomas, and identification of cancer at an early stage could be possible by the regular endometrial surveillance.⁶⁻⁷ However, a previous study suggested that frequent surveillance for EMT would not be necessary in the follow-up for this patients because most endometrial changes were not a serious problem even though adjuvant hormonal therapy after breast cancer surgery exhibited changes in the endometrium and ovary.⁸

Bone health has become more compelling in care of breast cancer survivor than ever before.⁹ The estrogen deprivation status after breast cancer treatment including chemotherapy and adjuvant hormone therapy disrupts the skeletal homeostasis, promoting loss of bone mineral density (BMD), and increasing the risk of osteoporosis.¹⁰⁻¹² Osteoporosis is a “silent disease” with rare symptoms in its early stages, and often goes undiagnosed until severe fractures occur.¹³,¹⁴ Therefore, the
multidisciplinary clinical care for breast cancer survivor should include surveillance of BMD change.\textsuperscript{15,16} Some previous studies found SERM could increase BMD without significant EMT change in breast cancer survivors.\textsuperscript{17,18} However, the correlation between changes in BMD and EMT has been rarely known up-to-date, even though both could be the alternative marker for estrogen status of breast cancer patients. This study was aimed to evaluate factors relating to the change in BMD and to ascertain the correlation between changes in BMD and EMT of women with breast cancer in follow-up.

**Materials and methods**

**Subjective**

The patients who had been undergone operative treatment due to breast cancer and visited gynecology clinic were recruited in this retrospective study. Records of a 164 women were reviewed from January 1, 2015 to December 31, 2018. The purpose of visit to gynecology clinic was routine gynecologic examination. All patients visited gynecology clinic twice a year. The first and the following visits were terms as “the initial visit” and “the follow-up visit.”

**Clinical variables**

The basal characteristics of all subject were checked at the initial visit. The basal clinical variables included age, parity, and menopausal state at breast cancer diagnosis. Cancer type including positivity of estrogen receptor, progesterone receptor and HER2 by pathologic report was checked. The information about receiving chemotherapy and/or radiotherapy after surgery, combined the other origin cancer and/or gynecologic disease was obtained. The current medication with vitamin D, bisphosphonate, selective estrogen modulator (SERM), aromatase inhibitor (AI), and gonadotrophin releasing hormone agonist (GnRHa) at visit were checked. All subjects were undertaken gynecologic ultrasonography for surveillance of EMT, and BMD at initial and follow-up visit.

**Statistical analysis**

Data were analyzed by Student $t$ test, paired $t$ test, and Pearson correlation test as appropriate. In all tests, significance was accepted for a $p$ value of $<0.05$. All data were analyzed using Statistical Package for the Social Sciences for Windows (version 25; SPSS, Chicago, IL).

**Ethics statement**

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University College of Medicine (approval No. H-1104-076-359) and Korea University Guro Hospital (approval No. 2018GR0355).
Results

Characteristics of the subject

The basal characteristics are summarized in Tables 1 and 2. The mean age of the subject was 52.1 ± 8.5 year-old and the mean BMI was 23.3 ± 3.2 kg/m² at initial visit in this study. The overall interval between initial and follow-up visits were 17.6 ± 7.5 month. In the subjective, the nulliparous, the primiparous and the multiparous were 20 (12.2%), 32 (19.5%), and 112 (68.5%). Sixty of women (36.6%) were premenopausal, and 104 of women (63.4%) were postmenopausal at the initial visit. One hundred and forty-one of women (86.0%) had no history of hormone therapy for menopausal symptom before breast cancer diagnosis. According to breast cancer tissue analysis, 159 of women (97.0%) had estrogen receptor, and 128 of women (78.0%) had progesterone receptor. By Her2/neu staining score according to the American Society of Clinical Oncology/College of American Pathologists guidelines,19 117 of women (71.3%) were negative (− to 1 +), 38 of women (23.2%) were equivocal (2 +), and 9 of women (5.5%) were positive (3 +). For adjuvant therapy, chemotherapy ($n=44$, 26.8%), tamoxifen ($n=122$, 74.4%), aromatase inhibitor ($n=43$, 26.2%), radiotherapy ($n=103$, 62.8%), and GnRHa ($n=36$, 22.0%) were conducted. Ninety-five of women (57.9%) took calcium combined with vitamin D, and 31 of women (18.9%) took bisphosphonate.

Table 1. The basal characteristics of the subject ($n=164$).

| Characteristics                  | Minimal value | Maximum value | Mean ± S.D.  |
|----------------------------------|---------------|---------------|--------------|
| Age (years)                      | 30.0          | 77.0          | 52.1 ± 8.5   |
| Height (cm)                      | 146.0         | 172.5         | 157.2 ± 5.3  |
| Weight (kg)                      | 41.2          | 84.1          | 57.6 ± 7.6   |
| BMI (kg/m²)                      | 17.3          | 36.4          | 23.3 ± 3.2   |
| Interval of measurements (month) | 6.0           | 46.0          | 17.6 ± 7.5   |

**BMD$_{L1-L4}$ (g/cm²)**
- Initial visit: 0.677, 1.592, 1.070 ± 0.181
- Follow-up visit: 0.680, 1.573, 1.040 ± 0.166
- The difference: −0.154, 0.101, −0.030 ± 0.052

**BMD$_{Neck}$ (g/cm²)**
- Initial visit: 0.590, 1.318, 0.870 ± 0.136
- Follow-up visit: 0.608, 1.259, 0.850 ± 0.121
- The difference: −0.324, 0.163, −0.020 ± 0.056

**BMD$_{Total}$ (g/cm²)**
- Initial visit: 0.620, 1.397, 0.915 ± 0.138
- Follow-up visit: 0.612, 1.376, 0.902 ± 0.132
- The difference: −0.108, 0.064, −0.013 ± 0.031

**EMT (mm)**
- Initial visit: 1.4, 15.3, 4.76 ± 2.57
- Follow-up visit: 1.5, 15.3, 4.21 ± 2.25
- The difference: −11.8, 9.0, −0.56 ± 3.18

BMD: bone mineral density; EMT: endometrial thickness; SD: standard deviation.
Eighty-five of women (51.8%) had other gynecologic disease, and 15 of women (9.1%) had other cancer.

### Change of BMD and EMT

Change of BMD and EMT were shown in Table 3. BMDL1–L4 (1.040 ± 0.166 g/cm² vs 1.070 ± 0.181 g/cm², \( p < 0.001 \)), BMD\textsubscript{Neck} (0.850 ± 0.121 g/cm² vs 0.870 ± 0.136 g/cm², \( p < 0.001 \)), and BMD\textsubscript{Total} (0.902 ± 0.132 g/cm² vs 0.915 ± 0.138 g/cm², \( p < 0.001 \)) decreased significantly at the follow-up visit compared to the initial visit. EMT at the follow-up visit (4.21 ± 2.25 mm) decreased significantly than EMT at the initial visit (4.76 ± 2.57 mm, \( p = 0.028 \)).

### Correlation between change of BMD and EMT

Analysis on correlation between ΔBMD and ΔEMT were summarized in Tables 4 and 5. ΔBMD\textsubscript{L1–L4} had significant positive correlation with age \( (r = 0.353, p < 0.001) \) and ΔEMT \( (r = 0.228, p = 0.003) \). ΔBMD\textsubscript{Neck} had significant positive correlation with age \( (r = 0.198, p = 0.011) \) and
Table 3. Change of BMD and EMT from initial to follow-up visit.

| Characteristics         | Minimal value | Maximum value | mean ± S.D.   | p Value |
|-------------------------|---------------|---------------|---------------|---------|
| **BMD_{L1–L4} (g/cm²)** |               |               |               |         |
| Initial visit           | 0.677         | 1.592         | 1.070 ± 0.181 | <0.001  |
| Follow-up visit         | 0.680         | 1.573         | 1.040 ± 0.166 |         |
| The difference          | -0.154        | 0.101         | -0.030 ± 0.052|         |
| **BMD_{Neck} (g/cm²)**  |               |               |               |         |
| Initial visit           | 0.590         | 1.318         | 0.870 ± 0.136 | <0.001  |
| Follow-up visit         | 0.608         | 1.259         | 0.850 ± 0.121 |         |
| The difference          | -0.324        | 0.163         | -0.020 ± 0.056|         |
| **BMD_{Total} (g/cm²)** |               |               |               |         |
| Initial visit           | 0.620         | 1.397         | 0.915 ± 0.138 | <0.001  |
| Follow-up visit         | 0.612         | 1.376         | 0.902 ± 0.132 |         |
| The difference          | -0.108        | 0.064         | -0.013 ± 0.031|         |
| **EMT (mm)**            |               |               |               |         |
| Initial visit           | 1.4           | 15.3          | 4.76 ± 2.57   | 0.028   |
| Follow-up visit         | 1.5           | 15.3          | 4.21 ± 2.25   |         |
| The difference          | -11.8         | 9.0           | -0.56 ± 3.18  |         |

BMD: bone mineral density; EMT: endometrial thickness; SD: standard deviation.

Table 4. Correlation coefficients of ∆BMD with the other continuous variables.

| ∆BMD | r with ∆BMD | p Value |
|------|-------------|---------|
| L1–L4| 0.353       | <0.001  |
| BMI  | 0.098       | 0.210   |
| EMT  | 0.228       | 0.003   |
| Neck | 0.198       | 0.011   |
| BMI  | -0.026      | 0.741   |
| EMT  | 0.282       | <0.001  |
| Total| 0.294       | <0.001  |
| BMI  | 0.144       | 0.066   |
| EMT  | 0.327       | <0.001  |

Table 5. Partial correlation coefficients of ∆BMD with ∆EMT adjusting for age.

| ∆BMD  | r with ∆BMD | p Value |
|-------|-------------|---------|
| L1–L4 | 0.151       | 0.054   |
| Neck  | 0.245       | 0.002   |
| Total | 0.273       | <0.001  |
Figure 1. The correlation scatter plots $\Delta$EMT compared to $\Delta$BMD by the linear model: (a) the correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD$_{L1-L4}$, (b) the correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD$_{Neck}$, and (c) The correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD$_{Total}$.

Figure 2. The correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD by the quadratic model: (a) the correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD$_{L1-L4}$, (b) the correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD$_{Neck}$, and (c) the correlation scatter plots of $\Delta$EMT compared to $\Delta$BMD$_{Total}$.
$\Delta \text{EMT} (r = 0.282, p < 0.001)$. $\Delta \text{BMD}_{\text{Total}}$ had significant positive correlation with age ($r = 0.294, p < 0.00111$) and $\Delta \text{EMT} (r = 0.327, p < 0.001)$. By partial correlation analysis with adjusting for age, $\Delta \text{BMD}_{\text{Neck}} (r = 0.245, p = 0.002)$ and $\Delta \text{BMD}_{\text{Total}} (r = 0.273, p < 0.001)$ had significant positive correlation with $\Delta \text{EMT}$. Figures 1(a) to (c) and 2(a) to (c) show the correlation scatter plots of $\Delta \text{EMT}$ correlated with $\Delta \text{BMD}_{\text{L1–L4}}$, $\Delta \text{BMD}_{\text{Neck}}$, and $\Delta \text{BMD}_{\text{Total}}$ by the linear and the quadratic model, respectively. The squared correlation coefficient ($R^2$) of $\Delta \text{EMT}$ correlated with $\Delta \text{BMD}_{\text{L1–L4}}$, $\Delta \text{BMD}_{\text{Neck}}$, and $\Delta \text{BMD}_{\text{Total}}$ were 0.052, 0.080, and 0.107 by the linear model, and 0.110, 0.108, and 0.155 by the quadratic model, respectively.

**Change in BMD and EMT according to the categorical variables**

Comparison of change in BMD and EMT according to the categorical variables were summarized in Table 6. $\Delta \text{BMD}_{\text{L1–L4}}$ showed significant differences according to menopausal status, Her2/neu and use of GnRH agonist and bisphosphonate. $\Delta \text{BMD}_{\text{Neck}}$ showed significant differences according to use of GnRH agonist and bisphosphonate. $\Delta \text{BMD}_{\text{Total}}$ showed significant differences according to menopausal status, use of GnRH agonist and bisphosphonate. $\Delta \text{EMT}$ showed significant differences according to menopausal status and use of GnRH agonist. There were no significant difference in BMD and EMT according to the other categorical variables.

**Discussion**

This study was aimed to evaluate factors relating to the change in BMD of women with history of breast cancer. We found change in EMT could be a screening marker of change in BMD in follow-up for breast cancer patients. Additionally, our results suggest some clinical factors including age, menopausal status, and use of GnRH agonist and bisphosphonate could have effects on the change in BMD.

Our results showed mean BMDs in all checked point decreased at the follow-up visit compared to the initial visit. These results suggest that breast cancer survivors could be at the risk of decrease in BMD during follow-up. Furthermore, $\Delta \text{BMD}$ had a positive correlation with age and $\Delta \text{EMT}$, even though it had no significant correlation with BMI. In the analysis of partial coefficients of $\Delta \text{BMD}$ with $\Delta \text{EMT}$ by adjusting for age, $\Delta \text{EMT}$ still showed positive correlation with $\Delta \text{BMD}$. Furthermore, the correlation scatter plots of $\Delta \text{EMT}$ correlated with $\Delta \text{BMD}$ by the linear and the quadratic model showed significant correlation. Ultrasonography is a popular screening tool for gynecologic surveillance of breast cancer follow-up, and measurement of EMT by ultrasonography could be an easily accessible screening marker. A few previous study reported that ultrasonographic EMT shows a positive correlation with BMD in postmenopausal women consistent with our results.\textsuperscript{20,21} Considering mean age and proportion of postmenopausal status of this present study (52.1 ± 8.5 and 63.4%), this result was consistent with the previous studies with subjects of similar age.\textsuperscript{22,23} Unlike these studies which showed this correlation with healthy postmenopausal women, this present study was conducted with breast cancer survivors.
Table 6. Comparison of $\Delta BMD_{L1-L4}$, $\Delta BMD_{\text{Neck}}$, $\Delta BMD_{\text{Total}}$, and $\Delta EMT$ according to the categorical variables.

|                      | $\Delta BMD_{L1-L4}$ | $\Delta BMD_{\text{Neck}}$ | $\Delta BMD_{\text{Total}}$ | $\Delta EMT$ |
|----------------------|-----------------------|-----------------------------|-----------------------------|--------------|
|                      | Mean ± SD             | p Value                     | Mean ± SD                   | p Value      | Mean ± SD             | p Value      |
| Parity               |                       |                             |                             |              |
| 0 (n = 20)           | -0.043 ± 0.045        | 0.460                       | -0.019 ± 0.028              | 0.662        | -0.019 ± 0.026        | 0.670        | -0.03 ± 0.31           | 0.948        |
| 1 (n = 32)           | -0.030 ± 0.052        |                             | -0.028 ± 0.027              | 0.111        | -0.011 ± 0.028        | 0.06 ± 0.33  | -0.06 ± 0.32           |              |
| $\geq$2 (n = 112)    | -0.028 ± 0.053        |                             | -0.018 ± 0.065              | 0.013        | -0.013 ± 0.033        | 0.06 ± 0.32  | -0.06 ± 0.32           |              |
| Menopausal status    |                       |                             |                             |              |
| Premenopausal (n = 60)| -0.050 ± 0.052        | < 0.001                     | -0.025 ± 0.041              | 0.382        | -0.020 ± 0.030        | 0.035        | -0.15 ± 0.41           | 0.004        |
| Postmenopausal (n = 104)| -0.018 ± 0.049    |                             | -0.017 ± 0.063              | 0.009        | -0.009 ± 0.032        | 0.01 ± 0.41  | -0.01 ± 0.41           |              |
| History of HRT       |                       |                             |                             |              |
| No (n = 141)         | -0.031 ± 0.052        | 0.372                       | -0.023 ± 0.058              | 0.151        | -0.015 ± 0.030        | 0.056        | -0.06 ± 0.33           | 0.797        |
| Yes (n = 23)         | -0.021 ± 0.052        |                             | -0.005 ± 0.034              | 0.002        | -0.002 ± 0.035        | 0.04 ± 0.21  | -0.04 ± 0.21           |              |
| Estrogen receptor    |                       |                             |                             |              |
| Negative (n = 5)     | -0.020 ± 0.051        | 0.675                       | -0.041 ± 0.015              | 0.398        | -0.025 ± 0.024        | 0.408        | -0.14 ± 0.18           | 0.527        |
| Positive (n = 159)   | -0.030 ± 0.052        |                             | -0.020 ± 0.056              | 0.013        | -0.013 ± 0.031        | 0.05 ± 0.32  | -0.05 ± 0.32           |              |
| Progesterone receptor|                       |                             |                             |              |
| Negative (n = 36)    | -0.030 ± 0.049        | 0.977                       | -0.026 ± 0.047              | 0.459        | -0.014 ± 0.029        | 0.972        | -0.01 ± 0.31           | 0.369        |
| Positive (n = 128)   | -0.030 ± 0.053        |                             | -0.019 ± 0.058              | 0.013        | -0.013 ± 0.032        | 0.06 ± 0.32  | -0.06 ± 0.32           |              |
| Her2/neu (IHC)       |                       |                             |                             |              |
| (-) or 1+ (n = 117)  | -0.037 ± 0.053        | 0.031                       | -0.015 ± 0.047              | 0.167        | -0.013 ± 0.031        | 0.736        | -0.07 ± 0.34           | 0.450        |
| 2+ (equivocal) (n = 38)| -0.014 ± 0.045    |                             | -0.035 ± 0.074              | 0.017        | -0.017 ± 0.027        | 0.02 ± 0.27  | -0.02 ± 0.27           |              |
| 3+ (n = 9)           | -0.010 ± 0.052        |                             | -0.021 ± 0.059              | 0.010        | -0.010 ± 0.050        | 0.04 ± 0.24  | -0.04 ± 0.24           |              |
| Chemotherapy         |                       |                             |                             |              |
| No (n = 120)         | -0.032 ± 0.055        | 0.381                       | -0.022 ± 0.059              | 0.534        | -0.014 ± 0.031        | 0.677        | -0.07 ± 0.34           | 0.318        |
| Yes (n = 44)         | -0.024 ± 0.043        |                             | -0.016 ± 0.046              | 0.012        | -0.012 ± 0.031        | 0.01 ± 0.24  | -0.01 ± 0.24           |              |
| Tamoxifen            |                       |                             |                             |              |
| No (n = 42)          | -0.033 ± 0.050        | 0.691                       | -0.029 ± 0.055              | 0.218        | -0.016 ± 0.031        | 0.481        | -0.06 ± 0.22           | 0.924        |
| Yes (n = 122)        | -0.029 ± 0.053        |                             | -0.017 ± 0.056              | 0.012        | -0.012 ± 0.032        | 0.05 ± 0.35  | -0.05 ± 0.35           |              |

(continued)
|                              | \( \Delta \text{BMD}_{L1-L4} \) Mean ± SD | \( \Delta \text{BMD}_{\text{Neck}} \) Mean ± SD | \( \Delta \text{BMD}_{\text{Total}} \) Mean ± SD | \( \Delta \text{EMT} \) Mean ± SD |
|------------------------------|------------------------------------------|---------------------------------------------|-----------------------------------------|----------------------------------|
|                              | \( p \) Value                             | \( p \) Value                              | \( p \) Value                           | \( p \) Value                     |
| No (\( n=121 \))             | -0.029 ± 0.053                            | -0.018 ± 0.056                             | -0.012 ± 0.031                          | -0.05 ± 0.35                     |
| Yes (\( n=43 \))             | -0.033 ± 0.050                            | -0.028 ± 0.055                             | -0.018 ± 0.031                          | -0.06 ± 0.22                     |
| Radiotherapy                 |                                          |                                            |                                        |                                  |
| No (\( n=61 \))              | -0.028 ± 0.046                            | -0.011 ± 0.048                             | -0.008 ± 0.033                          | -0.01 ± 0.27                     |
| Yes (\( n=103 \))            | -0.031 ± 0.056                            | -0.026 ± 0.059                             | -0.016 ± 0.030                          | -0.08 ± 0.34                     |
| GnRHa                        |                                          |                                            |                                        |                                  |
| No (\( n=128 \))             | -0.020 ± 0.050                            | -0.015 ± 0.051                             | -0.008 ± 0.030                          | -0.01 ± 0.24                     |
| Yes (\( n=36 \))             | -0.063 ± 0.046                            | -0.040 ± 0.068                             | -0.031 ± 0.028                          | -0.25 ± 0.16                     |
| Calcium + vitamin D          |                                          |                                            |                                        |                                  |
| No (\( n=69 \))              | -0.034 ± 0.045                            | -0.026 ± 0.054                             | -0.017 ± 0.028                          | -0.06 ± 0.24                     |
| Yes (\( n=95 \))             | -0.027 ± 0.056                            | -0.016 ± 0.056                             | -0.011 ± 0.034                          | -0.05 ± 0.37                     |
| Bisphosphonate               |                                          |                                            |                                        |                                  |
| No (\( n=133 \))             | -0.039 ± 0.050                            | -0.030 ± 0.055                             | -0.018 ± 0.032                          | -0.08 ± 0.32                     |
| Yes (\( n=31 \))             | 0.011 ± 0.039                             | 0.009 ± 0.047                              | 0.005 ± 0.021                           | 0.03 ± 0.29                      |
| Combined gynecology disease  |                                          |                                            |                                        |                                  |
| No (\( n=79 \))              | -0.022 ± 0.052                            | -0.013 ± 0.059                             | -0.009 ± 0.032                          | -0.01 ± 0.25                     |
| Yes (\( n=85 \))             | -0.037 ± 0.051                            | -0.027 ± 0.051                             | -0.017 ± 0.030                          | -0.01 ± 0.36                     |
| Combined other cancer        |                                          |                                            |                                        |                                  |
| No (\( n=135 \))             | -0.028 ± 0.052                            | -0.022 ± 0.059                             | -0.015 ± 0.032                          | -0.06 ± 0.32                     |
| Yes (\( n=29 \))             | -0.037 ± 0.054                            | -0.011 ± 0.038                             | -0.007 ± 0.026                          | -0.01 ± 0.32                     |
In the comparison of $\Delta$BMD according to the categorical variables, use of GnRH agonist and bisphosphonate showed a significance. Use of GnRH agonist showed more decreased BMD in all points. This finding suggests that the patients with long-term use of GnRH agonist may need more careful check for bone change. The previous studies reported that adjuvant treatment including GnRH agonist could enhance the rate of bone loss in breast cancer patients, consistent with our data. Use of bisphosphonate showed a protective effect against bone loss in this cohort study, and it was consistent with the previous studies. Menopausal status had a significance in only $\Delta$BMD$_{L1-L4}$ in this present study. Premenopausal women showed larger difference in $\Delta$BMD$_{L1-L4}$ than postmenopausal women. It implicates cessation of ovarian hormone production could affect homeosis of lumbar bone first rather than femoral bone. Interestingly, consistent with our results, a previous study reported that surgically induced menopause is associated with loss of the lumbar BMD and no significant change of BMD in the femoral neck in 2 years.

In the comparison of $\Delta$EMT according to the categorical variables, use of GnRH agonist and menopausal status showed a significance. Use of GnRH agonist enhanced change of EMT. A previous randomized controlled clinical trial also showed GnRH agonist had an effect of thinner EMT in breast cancer patients. It could be due to GnRH agonist-induced estradiol suppression. There was no significant effect on change of EMT according to use of calcium, vitamin D, and bisphosphonate. Postmenopausal women showed a smaller change of EMT than premenopausal women. We presumed that EMT of postmenopausal status already could have a low capacity to change.

Some questions to be answered remain from our results. First of all, no correlation between BMD and BMI were shown in our study. Many previous data suggested higher BMI could act as a protective factor for decreased BMD. However, in contrast with what has been reported above, some recent data suggested that lean body mass could have an impact on BMD rather than BMI in postmenopausal women, and BMI could not be a predictor of fracture risk in obese postmenopausal women. Our subjects included 23.7% (40/169) of obese women with BMI over 25.0 kg/m$^2$. We inferred that this characteristic could affect these results, due to small sample size of this study. Further study with large sample size should be necessary. The second one could be the low $R^2$ of $\Delta$EMT correlated with $\Delta$BMD. Concerning to this in our data, linear model $R^2$ showed 0.052 to 0.107, and quadratic model $R^2$ showed 0.108 to 0.155. It suggests that our functional correlation model could interpret exactly only 5% to 15% of all cases. However, our results suggested that $\Delta$EMT could be a useful screening marker for warning to a steep BMD decrease, rather than factor for calculating BMD decrease. Considering breast cancer survivors could be at the risk of BMD decrease, easy-accessible and cost-effective ultrasonographic screening could have an advantage.

Conclusions

In conclusion, $\Delta$EMT by ultrasonography between patient’s visits could be an alternative screening marker for BMD decrease in follow-up of women with history of
breast cancer. Easy accessibility and cost-effectiveness could be beneficial by using this ultrasonographic screening of gynecology clinics adding values to previously reported efficacy of gynecologic follow-up.\textsuperscript{35,36}

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by grant from the Ministry of Science and ICT (2020R1A2C1010293) and by the Medical Research Program at Seoul National University College of Medicine.

Ethics approval
Ethical approval for this study was obtained from the Institutional Review Board of Seoul National University College of Medicine (approval No. H-1104-076-359) and Korea University Guro Hospital (approval No. 2018GR0355).

Informed consent
Informed consent was not sought for the present study because of retrospective nature.

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