Research Paper

Bone Density in Patients with Cervical Cancer or Endometrial Cancer in comparison with Healthy Control; According to the stages

Yubin Lee¹, Ari Kim², Heung Yeol Kim³, Wan Kyu Eo⁴, Eun Sil Lee⁵*, Sungwook Chun⁶*

¹. Department of Obstetrics and Gynecology, Cha Gangnam Medical center, Cha University, Seoul, Korea
². Department of Obstetrics and Gynecology, College of Medicine, Wonkwang University, Iksan, Korea
³. Department of Obstetrics and Gynecology, College of Medicine, Kosin University, Busan, Korea
⁴. Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea
⁵. Department of Obstetrics and Gynecology, College of Medicine, Soon Chun Hyang University, Seoul, Korea
⁶. Department of Obstetrics and Gynecology, College of Medicine, Inje University, Busan, Korea

* The last two authors equally contributed to this work for correspondence.

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Abstract

Objective: To evaluate the bone mineral density (BMD) in the lumbar spine and femur in postmenopausal women with cervical cancer and endometrial cancer without bone metastasis in comparison with that in healthy control postmenopausal women, and to assess the loss of BMD according to the cancer stage.

Materials and methods: We analyzed the BMD of the lumbar spine and femur using dual-energy X-ray absorptiometry (DXA) in 218 patients with cervical cancer, 85 patients with endometrial cancer, and 259 healthy controls. The serum levels of calcium (Ca), phosphorus (P), osteocalcin (OSC), and total alkaline phosphatase (ALP), and urine deoxypyridinoline(DPL) were measured in all participants.

Results: Age, body mass index, parity, and time since menopause were not significantly different between the three groups. Serum Ca level was higher in the cervical cancer group (p = 0.000), however, urine DPL was lower in endometrial cancer group (p = 0.000). The T-scores of basal BMD at the second and fourth lumbar vertebra (L2, L4) were significantly lower in patients with cervical cancer (p = 0.038, 0.000, respectively) compared to those in the healthy control groups. Additionally, the incidence of osteoporosis and osteopenia basal status of bone mass was significantly higher in patients with cervical cancer compared to that in controls (p = 0.016). No differences in basal BMD of the lumbar spine and femur were observed between patients with cervical cancer according to their stages.

Conclusion: Our results suggest that postmenopausal women with cervical cancer have a lower BMD and are at increased risk of osteoporosis in the lumbar spine before receiving anticancer treatment compared with postmenopausal women with endometrial cancer.

Key words: Bone density, Cervical cancer, Endometrial cancer, Osteoporosis, Osteopenia

Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fractures associated with chronic pain, disability, and mortality [1]. Osteoporosis is caused by a disturbance of the number or activity of osteoclasts, resulting in inappropriately

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high bone resorption, which exceeds the capacity of osteoblasts. Bone strength is an integration of bone density and bone quality, and bone mineral density (BMD) accounts for approximately 70% of bone strength [1,2]. Osteoporosis has become a significant public health problem throughout the world, and the identification of risk factors related to osteoporosis is important to predict and prevent this disease. Estrogen maintains a balance between osteoclastic and osteoblastic activity, and bone remodeling increases when estrogen levels decline [3]. Hormone levels are the main determinants of bone density; however, other factors such as smoking, excessive alcohol consumption, lean body mass, low levels of physical activity, and the presence of other medical conditions, including chronic renal disease, hyperparathyroidism, hyperthyroidism, and diseases requiring systemic corticosteroid use, also increase the risk of osteoporosis [4-6]. A variety of neoplasms without bone metastasis are also known to be related to osteoporosis by producing circulating bone resorption stimulatory factors, leading to bone destruction and hypercalcemia [7-12]. In patients with gynecologic cancers, reduced spinal BMD has been reported in patients with cervical cancer [13,14], but no significant differences were found in spinal or femoral BMD between patients with endometrial cancer and controls [15].

We hypothesized that hormone-dependent tumor, at least endometrial cancer, may preserve the BMD, contrary to cervical cancer. The aims of the present study were to compare the bone turnover markers, BMD, and frequency of osteoporosis or osteopenia at the lumbar spine and femur between patients with cervical or endometrial cancer and controls [15].

Methods

Subjects

In this cross-sectional study, patients aged 45 – 57 years who first visited 3 University Hospitals (Kosin University, Wonkwang University, and Inje University) and were diagnosed with cervical or endometrial cancer without bone metastasis between January 2008 and December 2013 were included in the study. This study was approved by the Institutional Review Board of Kosin University Gospel Hospital. All subjects provided their informed consent.

Cervical cancer was diagnosed by Papanicolaou smear and colposcopically directed biopsy, and endometrial cancer was initially diagnosed by dilatation and curettage of the uterus. Technetium-99m-labeled diphosphonate bone scans or 18F-fluorodeoxyglucose positron emission tomography/computed tomography were performed on all cancer patients for confirmation of bone metastasis. All participants received dual-energy X-ray absorptiometry (DXA) at the time of diagnosis before any cancer treatment. Study subjects who had not reached menopause or who received menopausal hormone therapy were excluded. Menopause was defined as no spontaneous menstruation for more than 12 months. Postmenopausal women aged 48 – 59 years who visited the University Hospitals as part of a group check-up for work and lacked specific health problems served as normal controls. All control women underwent a careful physical examination and a thorough review of medical history, and the subjects who had history of current treatment with drugs known to alter bone or calcium metabolism were excluded. Finally, 218 patients with cervical cancer, 85 patients with endometrial cancer, and 259 healthy controls were enrolled in this study. We retrospectively reviewed all medical records thoroughly. BMD data of the lumbar spine and femur and laboratory data of bone turnover markers were collected for all participants.

Measurements of BMD and body mass index

BMD was measured in grams per square centimeter at the first lumbar spine vertebrae (L1), L2, L3, L4 and the femur, using DXA (Lunar Radiation Corp, Madison, WI, USA). We used the T-score of total lumbar spine, total hip, or femoral neck as single measurement for the diagnosis of osteoporosis. BMD values were categorized into three groups according to the criteria of the World Health Organization [16] and Official Positions 2013 of International Society for Clinical Densitometry [17] as normal, osteopenic, or osteoporotic relative to the mean and standard deviation of young women. Osteoporosis group was classified as women whose T-score of the total lumbar spine, total hip, or femur neck was -2.5 or less. Normal group was composed with the women whose T-score of the total lumbar spine, proximal hip, and femur neck were over -1.5. The remained women were classified as the osteopenia group. Body mass index (BMI) was calculated by dividing bodyweight (kg) by the square of body height (m²).

Measurement of serum calcium (Ca), phosphorus (P), osteocalcin (OSC), and total alkaline phosphatase (ALP), and urine deoxypyridinoline (DPL)

Blood samples were collected from all participants in tubes without anticoagulants, and sera were obtained by centrifugation or determination of bone turn-over markers. 24 hours urine samples from all participants were also collected. Ca and P were measured by atomic extinction photometry. Serum
OSC was measured using a NovoCalcin kit (MetraBiosystems Inc., Mountain View, CA, USA). ALP was measured using the Kind and King method. Urine DPL was measured using a Pyrilink-D kit (Metra Biosystems Inc., Mountain View, CA, USA).

Statistical analyses

All data were expressed as mean ± standard error. All statistical analyses were performed using SPSS version 19.0 (SPSSInc., Chicago, IL, USA). For comparisons of demographic and anthropometric characteristics, serum and urine biochemical markers, and T-scores of basal BMD between patients with cervical cancer, those with endometrial cancer, and healthy controls, student’s t-test was performed. For comparison of these parameters in cancer patients categorized according to cancer stage, the student’s t-test was used. The frequencies of osteoporosis, osteopenia, and normal BMD according to basal bone mass were compared between the cancer groups and the healthy control group using the χ² test. The analysis between relatively normal BMD and decreased BMD according to the existence of cancer was carried out with logistic regression test. p-values < 0.05 were considered significant for all analyses.

Results

All patients who were diagnosed with cervical cancer underwent type I or II hysterectomy and pelvic lymphadenectomy. The distribution of the International Federation of Gynecology and Obstetrics (FIGO) stage in the cervical cancer patients was IB, 122 (55.96%) and IIA, 96 (44.04%). Of these 218 patients, 178 had squamous cell carcinoma, 27 had adenocarcinoma, 9 had adenosquamous carcinoma, and four had other types of cancer. Patients with endometrial cancer were initially diagnosed by dilatation and curettage of the uterus, and were pathologically proven after staging operations including pelvic and curettage of the uterus, and were pathologically

Comparison of these parameters in cancer patients categorized according to cancer stage, the student’s t-test was performed. The frequencies of osteoporosis, osteopenia, and normal BMD according to basal bone mass were compared between the cancer groups and the healthy control group using the χ² test. The analysis between relatively normal BMD and decreased BMD according to the existence of cancer was carried out with logistic regression test. p-values < 0.05 were considered significant for all analyses.

Table 1. Comparisons of demographic and anthropometric characteristics between patients with cervical cancer or endometrial cancer and healthy control

| Age (years) | Control (n = 259) | Cervical Cancer (n = 218) | p-value | Endometrial Cancer (n = 85) | p-value |
|------------|------------------|--------------------------|---------|----------------------------|---------|
|            | 51.66 ± 0.16     | 51.47 ± 0.23             | 0.478   | 51.51 ± 0.38               | 0.637   |
| BMI (kg/m²) | 24.43 ± 0.14     | 24.15 ± 0.25             | 0.308   | 24.19 ± 0.38               | 0.316   |
| Parity     | 2.35 ± 0.32      | 2.24 ± 0.42              | 0.591   | 2.49 ± 1.02                | 0.172   |
| YSM (years)| 1.72 ± 0.07      | 1.96 ± 0.12              | 0.074   | 1.88 ± 0.19                | 0.318   |

Values are mean ± standard error

p-value, compared with control group
Student’s t-test
BMI, body mass index; YSM, years since menopause

Age, BMI, parity, and time since menopause did not differ significantly between the three groups (Table 1). Serum Ca concentration was significantly high in the cervical cancer group compared to that of healthy control group (9.51 ± 0.01 vs 9.44 ± 0.01, p = 0.000). On the other hands, urine DPL concentration was significantly low in the endometrial cancer group in comparison with healthy control group (8.08 ± 0.76 vs 8.45 ± 0.05, p = 0.000) (Table 2).

For each T-scores of L1, L2, L3, L4, femur neck (FN), femur trochanter (FT), the T-scores of basal BMD at L2 and L4 were significantly lower in patients with cervical cancer (-0.62 ± 0.07 vs -0.44 ± 0.06, p = 0.038 in L2; -0.65 ± 0.08 vs -0.15 ± 0.06, p = 0.000 in L4) compared to those in the healthy control group. Endometrial cancer group did not showed significant difference in T-scores compared with the healthy control group (Table 3). Additionally, the incidence of osteoporosis according to the basal status of bone mass was significantly higher in patients with cervical cancer (18.81%) compared to that of healthy control (10.81%). The incidence of osteopenia was also significantly higher in cervical cancer group (38.99%) compared with the control group (36.29%) (p = 0.16). Endometrial cancer showed the higher incidence of osteoporosis (16.47%) and lower incidence of osteopenia (28.24%), but there was no statistical significance (p = 0.228). The dichotomization of the T-score according to the decreased (T-score < -1.5) or relatively normal (T-score ≥ -1.5) indicate more distinct results that cervical cancer group had higher risk of bone loss (p = 0.020) in comparison with the endometrial cancer group (p = 0.701) (Table 4).

No significant differences in clinical, laboratory, or BMD data were observed among patients with cervical cancer divided according to cancer stage (Table 5).
Table 2. Comparisons of serum and urine biochemical markers between patients with cervical cancer or endometrial cancer and healthy control

| Biochemical markers | Control n = 259 | Cervical Cancer n = 218 | p-value (95% CI) | Endometrial Cancer n = 85 | p-value (95% CI) |
|---------------------|----------------|------------------------|-----------------|--------------------------|-----------------|
| Ca (mg/dL)          | 9.44 ± 0.01    | 9.51 ± 0.01            | 0.000           | 9.49 ± 0.24             | 0.059           |
| P (mg/dL)           | 3.73 ± 0.01    | 3.70 ± 0.01            | 0.128           | 3.72 ± 0.02             | 0.667           |
| OSC (ng/ml)         | 17.19 ± 0.15   | 16.92 ± 0.12           | 0.173           | 17.04 ± 0.21            | 0.600           |
| ALP (IU/L)          | 122.54 ± 0.29  | 122.71 ± 0.26          | 0.670           | 123.08 ± 0.41           | 0.330           |
| DPL (pmol/umol creatinine) | 8.45 ± 0.05    | 8.58 ± 0.05                     | 0.074           | 8.08 ± 0.76             | 0.003           |

Values are mean ± standard error
p-value, compared with control group
Student’s t-test
ALP, total alkaline phosphatase; Ca, calcium; DPL, deoxypiridinoline; OSC, osteocalcin; P, phosphorus.

Table 3. Comparisons of T-scores of basal bone mineral density (BMD) between patients with cervical cancer or endometrial cancer and healthy control

| T-score of basal BMD value | Control n = 259 | Cervical Cancer n = 218 | p-value (95% CI) | Endometrial Cancer n = 85 | p-value (95% CI) |
|---------------------------|----------------|------------------------|-----------------|--------------------------|-----------------|
| L1                        | -0.62 ± 0.06   | -0.72 ± 0.06           | 0.277           | -0.71 ± 0.10             | 0.475           |
| L2                        | -0.44 ± 0.06   | -0.62 ± 0.07           | 0.038           | -0.40 ± 0.10             | 0.732           |
| L3                        | -0.40 ± 0.06   | -0.46 ± 0.06           | 0.468           | -0.44 ± 0.10             | 0.724           |
| L4                        | -0.15 ± 0.06   | -0.65 ± 0.08           | 0.000           | -0.52 ± 0.13             | 0.004           |
| FN                        | -0.19 ± 0.06   | -0.33 ± 0.07           | 0.124           | -0.23 ± 0.11             | 0.759           |
| FT                        | -0.20 ± 0.06   | -0.34 ± 0.07           | 0.106           | -0.27 ± 0.11             | 0.537           |

Values are mean ± standard error
p-value, compared with control group
Student’s t-test
BMD, bone mineral density; FN, femur neck, left; FT, femur trochanter, left

Table 4. Comparison of the frequencies of osteoporosis and osteopenia according to the World Health Organization and Official Positions 2013 of International Society for Clinical Densitometry using the T-score of total lumbar spine, total hip, or femoral neck.

| T-score | Control n = 259 | Cervical Cancer n = 218 | p-value (95% CI) | Endometrial cancer n = 85 | p-value (95% CI) |
|---------|----------------|------------------------|-----------------|--------------------------|-----------------|
| 3 classifications |                  |                        |                 |                          |                 |
| ≤ -2.5  | 28 (10.81%)    | 41 (18.81%)            | 0.016           | 14 (16.47%)              | 0.228           |
| -2.5 < -1.5 | 94 (36.29%) | 85 (38.99%)            |                 | 24 (28.24%)              |                 |
| -1.5 <  | 137 (52.90%)   | 92 (42.20%)            |                 | 47 (55.29%)              |                 |
| 2 classifications |                  |                        | 0.020           | 0.701                    |                 |
| ≤ -1.5  | 122 (47.10%)   | 126 (57.80%)           | (1.070 – 2.221) | 38 (44.71%)              | (0.745 – 1.219) |
| -1.5 <  | 137 (52.90%)   | 92 (42.20%)            |                 | 47 (55.29%)              |                 |

p-value, compared with control group
*Chi-square test
*Logistic regression test
FN, femur neck, left; FT, femur trochanter

Table 5. Comparisons of demographic and anthropometric characteristics, serum and urine biochemical markers, and T-scores of basal bone mineral density (BMD) in patients with cervical cancer categorized according to cancer stage

|                      | Stage Ib n = 122 | Stage IIA n = 96 | p-value |
|----------------------|-----------------|-----------------|---------|
| Age (years)          | 51.29 ± 0.40    | 52.25 ± 0.39    | 0.033   |
| BMI (kg/m2)          | 24.33 ± 0.44    | 23.92 ± 0.43    | 0.418   |
| Parity               | 1.95 ± 0.18     | 2.26 ± 0.19     | 0.227   |

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Discussion

As the long term survival has become longer and prognosis has been improved in gynecologic cancers, the quality of life in cancer survivors is important, these days. To support the quality of life, bone health is essential, especially in older women. Quality of life is increasingly important for long-term survivors of gynecologic cancers, and osteoporosis is one of the major quality-of-life issues among gynecologic cancer survivors. This study reveals that cervical cancer has higher risk of impaired bone health per se, and for the treatment of cervical cancer, osteoporotic aspect should be considered.

Cervical cancer ranks as the third most common cancer in women, and it is the second most frequent cause of cancer death among women [18]. There are numerous risk factors for cervical cancer including young age at first intercourse, multiple sexual partners, cigarette smoking, race, high parity, low socioeconomic status, and chronic immune suppression, whereas the association with oral contraceptive use is controversial. Many of these risk factors are linked to sexual activity, and not to hormone status.

In the present study, T-scores of basal BMD in L2 and L4 were significantly lower in patients with cervical cancer compared to those in controls, and the incidence of osteoporosis and osteopenia were significantly higher in patients with cervical cancer compared to that in controls. Our results were in agreement with those of previous studies [13,14]. The association between cervical cancer and BMD; however, it was limited by the fact that they used DPA, which was found to be less accurate than DXA for the measurement of BMD. Hung and colleagues [14] reported that premenopausal patients with cervical cancer without bone metastases had significantly lower BMD (0.95 ± 0.03 g/cm²) compared to that in controls (1.08 ± 0.02 g/cm²) in the lumbar spine (L2-4). By contrast, Lee and colleagues [19] reported that the spinal BMD inpatients was not statistically lower compared to that in controls, which is in disagreement with other studies including ours.

Human cancer cell lines can secrete a bone resorption stimulatory peptide. Several factors are related to the activation of osteoclasts by tumor cells including parathyroid hormone-like peptide [7-9], transforming growth factor [10], osteoclast activating factor [11], and prostaglandins [12,20], and these osteolytic factors may contribute to the development of cancer-induced bone loss (CIBL). In patients with cancer, greater osteoclastic activity, markedly reduced osteoblastic surface, osteoid surface, and osteoid volume have been noted by quantitative histochemical studies of the bone [11,21]. In rat model, tumor-bearing rats showed a reduction in the volume of trabecular bone and an increase in the number of osteoclasts, which was presumably mediated by a humoral factor that activates existing osteoclasts and induces monocytes to differentiate into osteoclasts [22]. Biochemical markers of bone metabolism are indicators of both the formation and resorption of bone [23]. Biochemical bone turnover markers provide clinically useful information about the normal and pathologic processes that reflect bone cell activity in the skeleton, and they can provide valuable insight into interactions between bone remodeling and tumors.

In the present study, Ca concentration in serum was higher in cervical cancer group. It can be explained by the possibility of higher bone resorption.

### Table: Biochemical markers

| YSM (years) | Ca (mg/dL) | P (mg/dL) | OSC (ng/ml) | ALP (IU/L) | DPL (pmol/umolcreatinine) |
|-------------|------------|-----------|-------------|------------|--------------------------|
| 2.00 ± 0.23 | 9.478 ± 0.025 | 3.725 ± 0.022 | 16.813 ± 0.205 | 123.206 ± 0.500 | 8.337 ± 0.095 |
| 2.28 ± 0.25 | 9.514 ± 0.026 | 3.712 ± 0.024 | 17.019 ± 0.230 | 122.263 ± 0.431 | 8.547 ± 0.086 |

Values are mean ± standard error.

Student’s t-test.

ALP: total alkaline phosphatase, BMD: bone mineral density, BMI: body mass index, Ca: calcium, DPL: deoxypiridinoline, FN: femur neck, left, FT: femur trochanter, left, OSC: osteocalcin, P: phosphorus, YSM: years since menopause.
process in cervical cancer in contrast with endometrial cancer of healthy women. Other significant biochemical marker, urine DPL, was lower in patients with endometrial cancer than in controls. DPL is one of two pyridinium cross-links that provide structural stiffness to type I collagen found in bones [24], and it is used as a bone turnover marker along with other bone markers. It can be assumed that endometrial cancer, as the hormone-dependent tumor, may have high bone resorption like other several cancers, however, osteoblastic action may also be increased in the response with hormone. There are many bone turnover markers such as carboxy-terminal collagen crosslinks (CTX), urine N-terminal collagen crosslinks (NTX), amino pro-peptide of type 1 collagen (PINP), and bone specific alkaline phosphatase (BSAP)[6]. Further study with these biomarkers in gynecologic cancer may give the clue for the diagnosis and management of cancer patients.

If the reduced bone mass in the lumbar spine observed in the present study was related to the bone-resorbing factors, we would expect to see hypercalcemia in patients with cervical cancer, but all the patients in our study were normocalcemic. Cho and colleagues [13] suggested two possible explanations for these results. First, calcium reflux from bone may have been too subtle to be detected by the technique used. Another explanation is that some cases of malignancy may have been associated with elevated levels of bone-resorbing material seven in the absence of hypercalcemia because of regulatory mechanisms that maintain normocalcemia, as proposed by Henderson and colleagues [25].

In the femur neck and trochanter, we found no differences of BMD between patients with cervical cancer and controls, which are inconsistent with the results reported by Lee and colleagues [19], who showed that total femoral BMD in patients with cervical cancer was significantly lower compared to that in controls.

Endometrial carcinoma is the most common malignancy of the female genital tract in the USA. Most of the risk factors for the development of endometrial cancer, such as nulliparity, late menopause, and unopposed estrogen therapy, are related to prolonged, unopposed estrogen stimulation of the endometrium, and several medical conditions leading to long-term estrogen exposure, such as polycystic ovary syndrome and functioning ovarian tumors, are associated with an increased risk for endometrial cancer [26].

To the best of our knowledge, only one regional study has examined BMD in patients with endometrial cancer. Lee and colleagues [15] retrospectively analyzed the BMD of the spine and femur using DXA in 31 patients with endometrial cancer without bone metastases and 61 controls who were treated with surgery for benign disease in Korea. These authors reported no differences in the BMD of the spine or femur between patients with endometrial cancer and controls. In the present study, there were no significant differences of basal BMD in the lumbar spine and femur between patients with endometrial cancer and controls, and the levels of biochemical bone markers did not differ significantly between the two groups. These results were similar to those of Lee and colleagues [15].

Osteoporosis is strongly related to the decline of endogenous estrogen level. On the other hand, endometrial cancer is associated with long-term exposure to unopposed estrogen. High levels of endogenous estrogen are related to endometrial cancer, which can lead to increased BMD. The persistent influence of estrogen can increase basal bone mass and reduce fracture risk. Previous studies have reported decreased risks of endometrial cancer among women with pre-existing bone pathologies such as low BMD, fracture, and osteoporosis [27-29]. In a Swedish cohort, a significantly reduced risk of hip fracture was observed in patients with endometrial cancer (standardized incidence ratio (SIR) 0.6; 95% confidence interval(CI) 0.5-0.8) [27]. McGlynn and colleagues conducted a cohort study of 20,880 women with osteoporosis in Denmark. They reported that women diagnosed with osteoporosis in all age groups were at decreased risk of endometrial cancer (SIR 0.61; 95% CI 0.46-0.79) [29].

In the present study, neither BMD nor bone turnover markers were different between patients with endometrial cancer and controls. We hypothesized that BMD values at the lumbar spine and femur were not different between these groups because bone mass in patients with endometrial cancer may have reached a balance between the negative effect of CIBL and the positive effect of high endogenous estrogen levels related to endometrial cancer.

Cancer-treatment-induced bone loss (CTIBL) may cause bone fragility and an increased susceptibility to fractures, and bone loss occurs more rapidly and tends to be more severe in patients with CTIBL than in those with normal age-related bone loss; therefore, prevention, early diagnosis, and treatment of CTIBL are essential to decrease the risk of fracture [30]. CTIBL is most common in patients with breast or prostate cancer who receive chemotherapy, hormone therapy, or surgical castration, as these can cause hypogonadism and induce bone loss. In women with gynecological malignancies, concurrent chemo-radiation therapy (CCRT), particularly in patients with cervical cancer, has been observed to reduce BMD [31,32]. Nishio and colleagues [31] re-

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ported that CCRT for cervical cancer significantly increases bone resorption marker levels and reduces BMD of the lumbar spine, particularly in patients with cervical cancer who have received CCRT. Hwang and colleagues [32] reported that the lowest T-scores for BMD were significantly lower in the women with cervical cancer treated with CCRT compared with the control women, and the serum total ALP level was also significantly higher in women with cervical cancer treated with CCRT.

In the present study, the T-scores of the basal BMDs of all lumbar vertebrae were not significantly different between patients with cervical cancer and controls in L2 and L4, not in femur. Lumbar spine is the vulnerable bone to CIBL or CTIIBL. Hwang and colleagues [32] reported that the BMDs of all vertebrae except L4 were not significantly different between patients with cervical cancer treated with CCRT and controls. Although this study shows the BMD status before the treatment such as surgery and CCRT, lumbar spine in patients diagnosed with cervical cancer should be evaluated because the risk of bone loss is high due to cancer itself and further treatment. In those patients, anti-osteoporotic treatment such as Ca supplementation or bisphosphonate can be considered before and during the anticancer treatment.

Although our study had a larger sample size compared to those in other studies that examined BMD in patients with gynecologic cancer, the limitations of this study mainly stem from its retrospective study design. We did not consider other confounding factors related to BMD and osteoporosis. The inclusion of confounding risk factors for BMD such as smoking, alcohol, dietary differences, vitamin D levels, and physical activity may have provided a clearer association between gynecologic cancer and osteoporosis. Especially, serum 25 hydroxy-cholecalciferol as vitamin D may be altered in patients in cancer. Further study considering those limitation can provide us the more distinct relationship between cancer and bone health.

In summary, women with invasive cervical cancer have a lower bone mass density and are at increased risk of osteoporosis in the lumbar spine before anticancer treatment. There were no differences in BMD at any site between patients with endometrial cancer and controls. Further prospective large scale trials are needed to clarify the association between the gynecologic cancers and bone mass density.

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Conflicts of interest
None of the authors have declared any conflicts of interest.

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