Jpn J Clin Oncol 2002;32(10)422–424

Prospective Study of Decreased Bone Mineral Density in Patients with Cervical Cancer without Bone Metastases: a Preliminary Report

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Received March 25, 2002; accepted June 11, 2002

Background: In women, osteoporosis is a common chronic disease that induces spinal compression and femoral neck fractures, resulting in life-threatening complications. It is very important to identify risk factors in order to prevent this disorder. Bone destruction is a well-recognized complication in a variety of neoplasms without bone metastasis. Therefore, in the present study, we investigated the spinal bone mineral density (BMD) in patients with cervical cancer without bone metastases.

Methods: This was a prospective study. Before any treatment, the BMD in 50 patients with invasive cervical cancer without bone metastases was measured by dual-energy X-ray absorptiometry and compared with those in 50 control women with the same distribution of age, height, weight and body mass index. None of the patients and control women had reached menopause.

Results: The BMD in patients with cervical cancer was significantly lower ($P < 0.05$) than those of control women. However, serum levels of calcium and phosphate were not significantly different between the patients with cervical cancer and control women.

Conclusion: Our preliminary results suggest that patients with invasive cervical cancer have a lower BMD, resulting in an increased risk of osteoporosis.

Key words: bone mineral density – cervical cancer

INTRODUCTION

Osteoporosis has recently become recognized as a significant public health problem throughout the world. Osteoporosis is a common, chronic disease in aging women that induces spinal compression fracture and fracture of the femoral neck, causing life-threatening complications (1). As with other public health problems, it is important to identify risk factors in order to prevent the disorder. It has been reported that a variety of neoplasms without bone metastasis produce circulating osteolytic factors that lead to bone destruction. However, only hypercalcemia and osteolytic bone metastasis have been regarded as the principal clinical consequences of increased bone resorption in these patients (2). There has been only one densitometric study of bone mineral density (BMD) by dual-photon absorptiometry (DPA) in patients with cervical cancer (3). However, in recent decades, bone densitometry with dual-energy X-ray absorptiometry (DEXA) has been found to be more accurate than DPA, and it has been extensively developed to replace DPA and used to evaluate BMD (4). In the present study, we investigated the spinal BMD in patients with invasive cervical cancer without bone metastases and compared the results with those for control women.

PATIENTS AND METHODS

PATIENTS' CHARACTERISTICS

This prospective study was conducted between January 1998 and December 2000. Before any therapy, the BMD of 50 patients (mean age 40.1 ± 3.2 years) with invasive cervical cancers without bone metastases as diagnosed by negative results of technetium-99m-labeled diphosphonate (Tc-99m MDP) bone scans was measured. Cervical cancer was diagnosed by Papanicolaou smear and colposcopically directed biopsy. According to the International Federation of Gynecology and Obstetrics (FIGO) staging classification, the numbers of patients in stages I, II, III and IV were 12, 14, 11 and 13, respectively. The measurements of BMD in the lumbar spine were compared with those for 50 control women (mean age 41.0 ± 2.8 years). Control volunteer subjects were recruited from women undergoing Papanicolaou smear screening during

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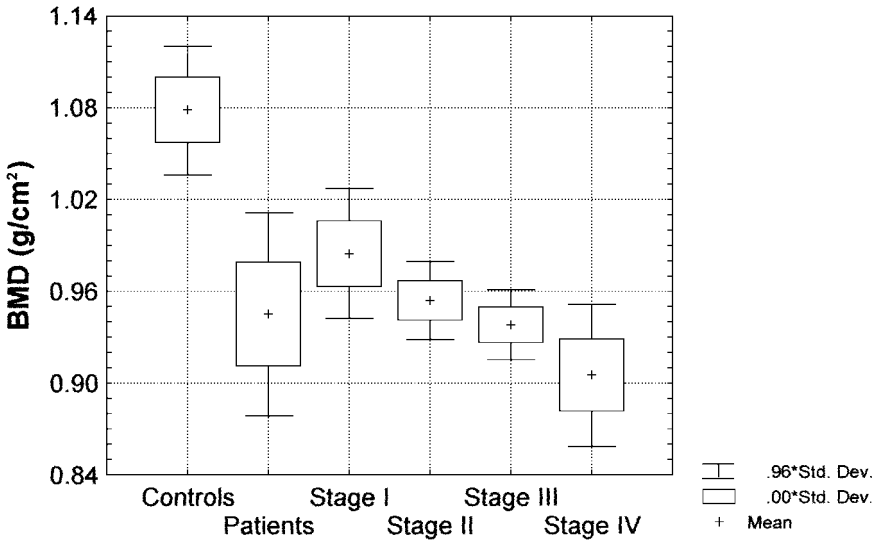

Figure 1. Graph showing significantly different BMD between patients and controls.

the same time period. Those with cervical intraepithelial neoplasia were excluded. Based on screening by medical history and physical examination, none of the study patients and control women used drugs known to influence bone and calcium metabolism. Study subjects who had reached menopause or were on estrogen replacement therapy were excluded. Height and weight were measured and the body mass index (BMI) (kg/m^2) was calculated on the scanning day. Because body weight is one of the most powerful determinants of BMD, subjects under 45 kg or over 75 kg were excluded (5). Serum levels of calcium and phosphate were measured in all study subjects on the day of BMD measurement.

Tc-99m MDP Whole-body Bone Scan and Bone Mineral Density

A Tc-99m MDP bone scan was performed on all study subjects. Routine bone scans were obtained with a large field-of-view, dual-head gamma camera fitted with a low-energy, medium-sensitivity and -resolution collimator. Anterior and posterior whole-body images (1–1.2 million counts) were acquired 2–3 h after the intravenous administration of 25 mCi (925 MBq) of Tc-99m MDP.

BMD was measured in all study subjects at the second to fourth lumbar vertebrae (L2–L4), using a commercial dual-energy X-ray absorptiometer (XR-26 Mark II, Norland, Fort Atkinson, WI, USA). The BMD was measured by one observer without knowledge of the patient's condition and reported as g/cm^2. This system in our laboratory has a relative standard deviation of <2% *in vivo* in the assessment of lumbar spine BMD. The mean values ± standard deviation of the BMD measurements in the two groups were compared using the independent two-tailed Student's *t*-test. Data were considered statistically significant at P values <0.05.

RESULTS

Age, height, weight, BMI, serum calcium and serum phosphate were not significantly different between cervical cancer patients and control women (Table l). The BMD in patients with cervical cancer (0.95 ± 0.03 g/cm^2) was significantly lower ($p = 0.0015$) than those of control women (1.08 ± 0.02 g/cm^2) (Table l and Fig. 1). The BMDs of patients in stage I, II, III and IV were 0.99 ± 0.02, 0.95 ± 0.01, 0.94 ± 0.01, 0.91 ± 0.02 g/cm^2, respectively (Fig. 1).

DISCUSSION

An association between cervical cancer and reduced BMD has been observed previously in only one study by DPA (3). Our preliminary results indicated that patients with cervical cancer without bone metastases showed significantly lower BMD than control women. It is possible that the initial menopausal loss was greater in patients with cervical cancer. Several studies (6–8) have shown that accelerated bone loss occurs in the first few years after menopause and cervical cancer may

Table 1. Characteristics and lumbar spine BMD in patients with cervical cancer and control women

Characteristic	Patients	Controls	*P* value
Age (years)	40.1 ± 3.2	41.0 ± 2.8	0.17
Height (m)	1.59 ± 1.3	1.57 ± 1.0	0.18
Weight (kg)	53.2 ± 4.2	52.6 ± 4.6	0.19
BMI (kg/m^2)	25.1 ± 0.5	25.1 ± 0.4	0.32
Calcium (mg/dl)	8.7 ± 0.7	8.8 ± 0.5	0.21
Phosphate (mg/dl)	4.4 ± 0.7	4.3 ± 0.6	0.24
BMD (g/cm^2)	0.95 ± 0.03	1.08 ± 0.02	0.0015

increase this loss. However, in our study, no patient with premature menopause was found in both groups.

Why should patients with cervical cancer have decreased BMD before menopause? Human cancer cell lines can secrete a bone resorption stimulatory peptide (9–11). Several factors, including prostaglandins, transforming growth factor, osteoclast activating factor and parathyroid hormone-like peptide (9–16), have been causally implicated in the activation of osteoclasts by tumor cells. In addition, quantitative histochemical studies of the bone revealed a reduction in the volume of trabecular bone, greater osteoclastic activity and markedly reduced osteoblastic surface in patients with malignancy (17,18). Therefore, most previous studies focused on bone resorption-associated hypercalcemia in malignancy combined with bone metastases (2). If the reduced BMD observed in our study had resulted from the production of bone resorption substances, then we would have expected patients to show hypercalcemia, but no hypercalcemia was seen in our patients with cervical cancer without bone metastases. It is possible that calcium reflux from bone is not abnormal, but the derangement may have been too subtle to be detected. Another possibility is that some cases of malignancy were associated with elevated bone resorption substances even in the absence of hypercalcemia, because of regulatory mechanisms that maintain normocalcemia (19). In agreement with our study, Lerner and Ljungberg (20) reported that fresh renal cell carcinoma tissue from normocalcemic patients also stimulates bone resorption *in vitro*. Therefore, the decreased BMD in our patients with cervical cancer without bone metastases is probably due to a variety of factors.

Cervical cancer appears to be the most common gynecological malignancy in Taiwan. Our preliminary findings of decreased BMD in patients with cervical cancer without bone metastases is very important, as it may imply that patients with cervical cancer have an increased risk of developing osteoporosis, resulting in severe complications. However, a further follow-up study with a large series of cases is needed to clarify the cause of increased lumbar spinal BMD in patients with invasive cervical cancer without bone metastases.

References

1. Lindsay R. Prevention of postmenopausal osteoporosis. *Obstet Gynecol* 1987;14:63–76.
2. Mundy GR, Ibbotson KJ, D'Souza SM, Simpson EL, Jacobs JW, Martin TJ. The hypercalcemia of cancer. Clinical implications and pathogenic mechanisms. *N Engl J Med* 1984;310:1718–26.
3. Cho SH, Cho SH, Lee JA, Moon H, Kim DS. Reduced spinal bone mass in patients with uterine cervical cancer. *Obstet Gynecol* 1991;78:689–92.
4. Sartoris DJ, Resnick D. Dual-energy radiographic absorptiometry for bone densitometry: current status and perspective. *Am J Roentgenol* 1989;152:241–6.
5. Heaney RP, Matkovic V. Inadequate peak bone mass. In: Riggs BL, Melton LJ III, editors. Osteoporosis: Etiology, Diagnosis and Management, 2nd edition. Philadelphia: Lippincott-Raven, 1995;115–31.
6. Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med* 1986;314:1676–86.
7. Elders PJM, Netelenbos JC, Lips P, van Cinkel FC, van der Stelt PF. Accelerated vertebral bone loss in relation to the menopause: a cross-sectional study on lumbar bone density in 286 women of 46–55 years of age. *Bone Miner* 1988;5:11–9.
8. Nilas L, Christiansen C. Rates of bone loss in normal women: evidence of accelerated trabecular bone loss after the menopause. *Eur J Clin Invest* 1988;18:529–34.
9. Strewler GJ, Stern PH, Jacobs JW, Eveloff J, Klein RF, Leung SC, et al. Parathyroid hormone like protein from human renal carcinoma cells. Structural and functional homology with parathyroid hormone. *J Clin Invest* 1987;80:1803–7.
10. Suva LJ, Winslow GA, Wettenhall RE, Hammonds RG, Moseley JM, Diefenbach-Jagger H, et al. A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. *Science* 1987;237:893–6.
11. Stewart AF, Wu T, Goumas D, Burtis WJ, Broadus AE. N-terminal amino acid sequence of two novel tumor-derived adenylate cyclase-stimulating proteins: identification of parathyroid hormone-like and parathyroid hormone unlike domains. *Biochem Biophys Res Commun* 1987;146:672–8.
12. Tashjian AH Jr, Voeikel EF, Levine L, Coldhaber P. Evidence that the bone resorption stimulating factor produced by mouse fibrosarcoma cells is prostaglandin E2. A new model for the hypercalcemia of cancer. *J Exp Med* 1972;136:1329–43.
13. Seyberth HW, Segre GV, Morgan JL, Sweetman BJ, Potts JT Jr, Gates JA. Prostaglandins as mediators of hypercalcemia associated with certain types of cancer. *N Engl J Med* 1975;293:127–83.
14. Tashjian AH Jr. Role of prostaglandins in the production of hypercalcemia by tumors. *Cancer Res* 1978;38:4138–41.
15. Martin TJ, Partridge NC. Prostaglandins, cancer and bone: pharmacological considerations. *Metab Bone Dis Relat Res* 1980;2:167–71.
16. Shewin SA, Twardzik DR, Bohn WH, Cockley KD, Todaro GJ. High-molecular-weight transforming growth factor activity in the urine of patients with disseminated cancer. *Cancer Res* 1983;43:403–7.
17. Mundy CR, Eilon C, Orr W, Spiro TP, Yoneda T. Osteoclast activating factor: its role in myeloma and other types of hypercalcemia of malignancy. *Metab Bone Dis Relat Res* 1980;2:173–7.
18. Troyer H, Sowers JR, Babich E. Leydig cell tumor induced hypercalcemia in the Fisher rat: morphometric and histochemical evidence for a humoral factor that activates osteoclasts. *Am J Pathol* 1982;108:284–90.
19. Henderson JE, Shustik C, Kremer R, Rabbani SA, Hendy GN, Goltzman D. Circulating concentrations of parathyroid hormone-like peptide in malignancy and in hyperparathyroidism. *J Bone Miner Res* 1990;5:105–13.
20. Lerner UH, Ljungberg B. Renal cell carcinoma in tissue culture secretes nondialyzable product that stimulates bone resorption in organ-cultured mouse calvaria. *J Bone Miner Res* 1989;4:365–7.