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Report

Bone mineral density in women with breast cancer treated with adjuvant tamoxifen for at least two years

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Summary

While in limited animal studies tamoxifen is reported to protect against loss of bone mineral, data in humans are lacking. We measured bone mineral density (BMD) using single photon absorptiometry at the radius and dual photon absorptiometry at the lumbar spine in breast cancer patients treated with chemotherapy at our institution. In this group, 37 women were not treated with tamoxifen (NT) and 48 women were treated with tamoxifen (T) for at least two years. Younger age, greater weight and height, premenopausal status, and shorter time since menopause were found to be significant predictors of greater BMD. Tamoxifen-treated women had been postmenopausal for more years ($p = 0.012$). Regression analyses used to adjust for differences in risk of bone loss did not reveal significant differences in BMD between the two groups of women. For the postmenopausal women (27 NT and 34 T subjects), the adjusted mean BMD (g/cm^2) at the spine was 1.11 (NT), 1.11 (T) ($p = 0.93$); and at the radius 0.63 (NT), 0.62 (T) ($p = 0.30$). This limited retrospective study suggests that tamoxifen does not have 'anti-estrogenic' effects on BMD.

Introduction

Tamoxifen is a nonsteroidal antiestrogen used widely in the treatment of breast cancer [1]. Therapy with tamoxifen in advanced disease is accompanied by favorable effects in approximately half of unselected subjects and in greater fractions of women selected on the basis of tumors with increased levels of estrogen and/or progesterone receptor protein. Because it has only limited and non-life threatening toxicity, tamoxifen has been increasingly used as a single agent in adjuvant therapy programs [2, 3] where it is now considered to be standard therapy for postmenopausal women with estrogen receptor positive and node positive cancers [4]. Long term therapy has been considered to be necessary because of the predominantly cytostatic effect of the drug [5, 6] and current data have supported this concept [7]. Recently, the possibility of using tamoxifen as a chemosuppressive agent in women at high risk of breast cancer has been raised [8]. The suggested need for long term tamoxifen therapy in the adjuvant setting and the possible use in healthy women have focused attention on the systemic effects of this drug.

Estrogen supplementation prevents loss of compact bone at the menopause [9, 10] and stabilizes bone loss in older women [11]. The effects of anti-

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estrogens on bone mineral density (BMD) have not been studied extensively. One metabolic study of short term tamoxifen use among premenopausal women showed equivalent changes in recipients of tamoxifen with breast cancer and in a control group receiving other forms of therapy [12]. In the mature ovariectomized rat, clomiphene citrate, a mixed estrogen agonist-antagonist, was found to protect against changes in total body calcium and deterioration of femur structure [13]. In intact and ovariectomized female rats, a recent paper reported no evidence of decrease in bone density associated with tamoxifen [14]. These limited data suggest the possibility of a beneficial effect of tamoxifen on bone tissue, despite its antiestrogenic effects in other tissues.

The goal of this study was to determine whether tamoxifen therapy of two years or more duration in women with early stage breast cancer who were clinically disease-free was associated with significant adverse bone changes.

Methods

All study subjects were being followed during 1986 in the oncology clinic at the University of Wisconsin Hospital and Clinics, Madison. We identified all female patients of any age who had a diagnosis of pathologically confirmed Stage I, II, or III breast cancer greater than two years prior to entry on study. To be eligible for this study, women must have been treated on various local or national chemotherapy adjuvant therapy protocols and remained disease-free following initial treatment. Disease-free status was confirmed by: (1) a negative review of systems, a physical examination demonstrating no evidence of recurrent breast cancer, and normal liver chemistries and calcium all within one month of entry on study; and (2) a normal chest x-ray within three months and a normal bone scan within six months of entry on study. Women potentially eligible by these criteria were then divided into two treatment groups: (1) tamoxifen-treated women, who had been continuously on this drug (20 mg per day) for greater than two years; and (2) women never treated with tamoxifen.

One hundred forty-eight eligible patients were identified and approached regarding study participation. Of the 73 patients treated with tamoxifen for at least two years, 49 (67.1%) agreed to participate. Of the 75 patients without a history of tamoxifen therapy, 37 (49.3%) consented. Between October, 1986, and June, 1987, the BMD of each patient was evaluated at one study visit. The BMD of the left radius was measured by ^{125}I single photon absorptiometry (SPA) at the standard 33% site on the shaft (compact bone). Spine BMD (L2-L4) was measured by ^{153}Gd dual photon absorptiometry (DPA) from L2-L4. One patient with BMD values three standard deviations below the group mean was excluded from all analyses.

Following the bone densitometry, patients were interviewed about their reproductive and medical histories. Information from patients' medical records was also used to supplement, when necessary, interview data on menopausal status. Date of menopause was calculated using the reported date of the last menstrual period (LMP) for patients with natural menopause, or date of surgery for patients with bilateral oophorectomies. For women 40 years or older who became postmenopausal as a result of chemotherapy, date of menopause was considered to be 6 months after LMP. Women aged 40–52 years old at diagnosis with a previous hysterectomy were estimated to have become menopausal 6 months following chemotherapy. For women over 52 years of age, time of menopause was estimated to be age 52. For 21 patients incomplete histories prevented a precise estimation of age at menopause.

Results

The women in the tamoxifen-treated and observation group were similar with respect to age and height (Table 1). The two groups also reported similar frequencies of smoking, regular exercise, alcohol consumption, and history of osteoporosis or unexpected fractures. Patients in the tamoxifen group, however, were significantly more likely than observation patients to be more recently diagnosed ($p = 0.0001$), postmenopausal at diagnosis

($p = 0.003$), and of greater years postmenopausal ($p = 0.012$). This group was also slightly heavier than the observation women. BMD at the lumbar spine and radius was similar between tamoxifen-treated and observation patients (Table 2). For the tamoxifen-treated patients, the BMD values were 106% of those expected for matched normals [15]. The control group as whole had spine and radius BMD of about 103% and 99% of expected, based on similar age women. Greater BMD was significantly influenced by younger age, greater weight and height, premenopausal status, and fewer years since menopause (Table 3). Therefore, regression analyses were conducted to adjust for these underlying risk differences in the two study groups.

Among postmenopausal patients, mean (adjusted for age, weight, years menopausal) BMD of the spine was 1.113 g/cm^2 in tamoxifen patients, and 1.109 g/cm^2 in the observation patients (Table 4). Radius BMD was also similar in tamoxifen-treated (0.634 g/cm^2), and untreated (0.615 g/cm^2) patients. These differences were not statistically significant. No relationship was found between increasing duration of tamoxifen therapy and bone mineral density. The effect of tamoxifen was also examined according to whether patients' menopause was natural, surgical, or a result of therapy. Type of menopause did not modify the magnitude of the observed BMD difference (Table 4).

For 20 patients, menopausal status at the time of

Table 1. Selected characteristics of tamoxifen treated and observed patients.

Characteristic	Group				
	Tamoxifen (n = 48)		Observation (n = 37)		p-value[1]
	mean	(S.D)	mean	(S.D)	
Age (years)	52.9	(10.1)	51.5	(6.6)	0.45
Weight (kilograms)	73.9	(12.9)	70.1	(14.5)	0.21
Height (centimeters)	162.2	(7.1)	162.4	(7.5)	0.89
Years since diagnosis	4.9	(1.7)	6.6	(1.6)	0.001
Menopausal status at diagnosis					
Premenopausal	56.3%		86.5%		0.003
Postmenopausal	43.8%		13.5%		
Menopausal status at study					
Premenopausal	4.2%		5.4%		0.43
Postmenopausal	66.6%		73.0%		
Unknown[2]	27.1%		21.6%		
Years postmenopausal[3]	10.78	(7.6)	6.98	(3.2)	0.012

[1] From two-sample t-test for comparison of means and X^2 for comparison of proportions.
[2] The menopausal status of this younger aged group (<52 years) treated prior to age 40 cannot be determined.
[3] Includes all women known to be postmenopausal naturally, surgically, or as a result of therapy (n = 60).

Table 2. Unadjusted bone mineral density for spine and radius among tamoxifen-treated and observation women.

	Mean (S.E.) Bone Mineral Density (g/cm^2)			
	Tamoxifen (n = 48)	Observation (n = 37)	p-value[1]	95% Confidence interval for difference (T-NT)
Lumbar spine	1.129 (0.21)	1.126 (0.023)	0.93	[−0.059 to 0.065]
Radius	0.650 (0.011)	0.634 (0.011)	0.31	[−0.017 to 0.048]

[1] From two sample t-test.

BMD evaluation was not known; for an additional 4 patients menopause had not yet occurred. In order to evaluate the impact of their exclusion on previous analyses, we included all study patients in a regression model adjusted for age and weight only (Table 4). The adjusted BMD means were slightly greater than among postmenopausal patients. However, no significant differences were observed between the tamoxifen-treated and observation groups.

Discussion

In this retrospective study of breast cancer subjects treated continuously for two years or never treated with tamoxifen, we found no evidence for an adverse effect of tamoxifen on the BMD of the trabecular bone of the lumbar spine or the compact bone of the radius.

In interpreting these findings, however, several limitations should be considered. First, a signif-

Table 3. The effect of selected patient characteristics on bone mineral density at the spine and radius.[1]

	Spine			Radius		
	Coefficient	SE[2]	p-value	Coefficient	SE[2]	p-value
Age	−0.0036	0.0017	0.04	−0.0034	0.0001	<0.001
Weight	0.0037	0.0010	<0.001	0.0016	0.0001	0.006
Height	0.0049	0.0021	0.021	0.0027	0.0011	0.026
Currently menopausal	−0.2065	0.0733	0.007	−0.0511	0.0379	0.18
Years since menopause	−0.0056	0.0029	0.069	−0.0030	0.0015	0.05

[1] From univariate regression analyses.
[2] Standard error of the coefficient.

Table 4. Adjusted estimates for bone mineral density at spine and radius according to type of menopause.

	Mean (adjusted) Bone Mineral Density (g/cm^2)			
	Tamoxifen	Observation	p-value	95% confidence interval for difference (T-NT)
Postmenopausal patients[1,2]	(n = 33)	n = 27)		
Spine	1.113	1.109	0.93	[−0.070 to 0.077]
Radius	0.634	0.615	0.30	[−0.018 to 0.056]
Surgical menopause[1]	(n = 5)	n = 4)		
Spine	1.079	1.115	0.84	[−0.491 to 0.420]
Radius	0.632	0.541	0.25	[−0.097 to 0.279]
Post chemotherapy menopause[1]	(n = 10)	n = 16)		
Spine	1.132	1.152	0.72	[−0.131 to 0.093]
Radius	0.661	0.641	0.46	[−0.034 to 0.074]
Natural menopause[1]	(n = 11)	n = 1)		
Spine	1.049	1.137	0.40	[−0.319 to 0.144]
Radius	0.604	0.668	0.49	[−0.269 to 0.143]
All patients[3]	(n = 48)	n = 37)		
Spine	1.125	1.132	0.81	[−0.066 to 0.052]
Radius	0.650	0.634	0.24	[−0.011 to 0.041]

[1] Adjusted for age, weight, and years since menopause.
[2] Includes postmenopausal patients with estimated time of menopause.
[3] Adjusted for age, weight.

icantly greater proportion of eligible tamoxifen-treated patients agreed to participate in this study than patients who were not treated with tamoxifen (67.1% vs. 49.3%). The influence of this selection variable is unknown. Second, patients who received tamoxifen differed from observation patients with respect to several important characteristics that are known to influence bone density. While regression techniques were employed to control for these differences, this standardization may have been inadequate due to the presence of other unmeasured or unknown confounding factors. Finally, the limited size of this study necessarily restricts our evaluation of tamoxifen effects on bone density. Although the modest differences between the two groups were not statistically significant, the confidence intervals show that a meaningful difference cannot be ruled out. Further, because of the small number of patients in certain subgroups, one cannot exclude the possibility of an important tamoxifen effect among some women.

Target tissues in humans are affected differently by tamoxifen. The drug exhibits both estrogenic and antiestrogenic actions, but one type of response usually predominates [1]. Given the structure of the molecule, a large portion of which looks like an estrogen, this is not surprising. The antiestrogenic properties of the drug are exploited to treat breast and uterus carcinomas [16]. In bone, however, tamoxifen may be estrogenic. If tamoxifen is indeed bone preserving, this would be a particularly salutary effect. Consideration of longer term tamoxifen therapy is being increasingly advocated [5, 6] and supported by clinical data [5, 7]. The case for tamoxifen as a long-term chemosuppressive agent would also be stronger were a favorable effect on bone to be shown [8]. Definitive proof of the lack of adverse effects or the favorable effects of tamoxifen on bone can only come from a prospective double blind, placebo-controlled trial. We are currently conducting such a study in postmenopausal women with node negative breast cancer.

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