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Cortical and trabecular bone at the radius and tibia in postmenopausal breast cancer patients: A Peripheral Quantitative Computed Tomography (pQCT) study

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Abstract

Bone morbidity associated with antineoplastic treatment is a significant health concern for postmenopausal breast cancer patients. Trials have demonstrated that adjuvant therapy with an Aromatase Inhibitor is associated with an increase in musculoskeletal disorders and bone fractures. The objective of this study was to utilize Peripheral Quantitative Computed Tomography (pQCT) to assess *in vivo* trabecular and cortical volumetric bone at peripheral skeletal sites in healthy postmenopausal women and breast cancer patients prescribed Anastrozole. Fifty-eight women were recruited for this study: 27 breast cancer patients and 31 healthy control participants. pQCT measurements were taken at distal and diaphyseal sites of the radius and tibia using a Stratec XCT-2000 pQCT scanner. Bone measurement values for total density and total content at the 4% radius; total and cortical content as well as cortical density at the 20% radius; total density at the 4% tibia; and cortical density at the 38% tibia were found to be significantly lower in breast cancer patients. Moreover, the duration of time on Anastrozole showed a significant negative correlation with the following measurements: total content at the 4% radius ($r=-0.36$, $p<0.01$); total content ($r=-0.33$, $p<0.05$), cortical content ($r=-0.34$, $p<0.05$) and cortical density ($r=-0.44$, $p<0.01$) at the 20% radius; as well as cortical density ($r=-0.39$, $p<0.01$) and cortical content ($r=-0.27$, $p<0.05$) at the 38% tibia. Overall, the breast cancer patients demonstrated significantly lower values for volumetric bone density and content at the radius and tibia compared with healthy postmenopausal women. Furthermore, this novel study found adverse effects from Anastrozole treatment primarily in cortical bone.

Keywords

Breast cancer; Postmenopausal women; Anastrozole; Peripheral Quantitative Computed; Tomography (pQCT); Cortical bone; Trabecular bone

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Introduction

The cessation of ovarian function with the onset of menopause is an important factor in the pathogenesis of bone fragility. Estrogen exerts a multitude of actions on bone tissues and is integral to bone health; thus, estrogen withdrawal during menopause leads to accelerated bone loss and the increased risk of fracture. After menopause, intrinsic production of estrogen from androgens largely occurs in non-ovarian tissues such as fat, muscle, skin, and liver, as a result of the activity of the aromatase enzyme complex. There is evidence to suggest that even these low levels of circulating estrogens have protective effects on the skeleton [1]. Since many antineoplastic treatments have been found to reduce residual circulating estrogen levels dramatically, cancer-associated bone morbidity is of particular concern to postmenopausal women. Aromatase Inhibitors (AIs), including Anastrozole, have become increasingly prevalent in the treatment of patients with estrogen-receptor positive breast carcinoma, and evidence indicates an increase in fracture risk and bone loss in patients prescribed AIs [2–9]. In order to improve therapy, it is important to carefully evaluate the pathophysiology of AIs on skeletal health, with attention to the particular effects of these medications on cortical and trabecular bone.

Peripheral Quantitative Computed Tomography (pQCT) allows for the separate study of cortical and trabecular bone; this technology was developed to provide simultaneous information on geometric properties and volumetric density, specifically for appendicular bone. pQCT presents a means of assessing bone strength and fracture risk beyond the scope of current dual energy X-ray absorptiometry determinations, while also providing a means of examining the response of mature bone to various treatment regimens. Bone response can be detected via changes in geometry and increased, decreased, or redistributed mineral mass, which ultimately impact bone strength and risk of fracture. The aim of this study was to assess cortical and trabecular density, mass, and geometry at proximal and distal sites of the radius and tibia in women with a history of breast cancer, all prescribed Anastrozole, and to compare these results with measurements taken from healthy postmenopausal women.

Materials and methods

Study participants

Healthy postmenopausal females were recruited from staff and outpatients at McMaster University Medical Center (Hamilton, Ontario). Postmenopausal breast cancer patients were recruited from the Juravinski Cancer Center (Hamilton, Ontario). Postmenopausal status was determined by self-report and natural menopause was defined as the age at which menses ceased for at least 12 months. All cancer patients had completed treatment for Stage I or II breast cancer and had been taking Anastrozole for a period of 8 to 512 days (mean = 185 days) prior to study entry. A prior diagnosis of osteoporosis or other metabolic bone diseases served as exclusion criteria. Fifty-eight women were recruited for this study: 27 breast cancer patients and 31 healthy control participants. All participants gave informed, written consent prior to taking part in this study. The study was reviewed and approved by the Hamilton Health Sciences Research Ethics Board.

Medical history assessment

All study participants completed a questionnaire to document age, age at menopause, race/ethnicity, height, body weight, and to provide a general health/medical history profile. Additional self-reported information on smoking habit, time spent exercising, family history of osteoporosis, use of medications, fracture history, and intake of dietary supplements was also assessed.

Peripheral Quantitative Computed Tomography (pQCT)

pQCT measurements were taken at 2 sites of the radius and 3 sites of the tibia using a Stratec XCT-2000 pQCT scanner (Stratec Medizintechnik, Pforzheim, Germany). The device is a translate-rotate, small-bore computed tomography scanner that acquires a trans-axial image. The X-ray source (58 kV, 180 μ A) is collimated to produce a narrow fan beam with an effective width of 2.3 mm. The total radiation dose associated with each examination is less than 2 μ Sv. Images were acquired with an in-plane voxel dimension of 0.2 mm (0.008 mm³). To ensure machine stability, the pQCT device was assessed daily based on a quality control phantom (Stratec Medizintechnik, Pforzheim, Germany), which includes soft tissue equivalent material.

Scanning procedure

For each participant, the non-dominant arm or leg was selected for measurement on the basis of whether the patient was right- or left-handed. Exceptions were made when the non-dominant arm or leg had been fractured within the last 10 years. The participants were seated on a stationary chair, adjusted to the appropriate height, and were offered the use of a foot stool and cushion to optimize comfort. For the radius scans, the length of the bone from the humeroradial joint cleft to the styloid process was measured. For the tibia scans, the length of the bone from the distal end of the medial malleolus to the medial knee joint cleft was measured. A radial or tibial adjustable clamp was used to support the limb and to limit motion during the scans. Care was taken to ensure that the limb being scanned was well supported and centered appropriately in the imaging field.

The scanner was positioned on the distal radius or distal tibia and a coronal computed radiograph (scout view) was carried out for the operator to manually locate a reference line on the distal end of either the radius or the tibia. The measurement sites were located proximal to this reference line by a distance corresponding to 4% (distal radius) and 20% (diaphyseal radius) of the forearm length, and 4% (distal tibia) and 38% (diaphyseal tibia) of the tibia length. For muscle, subcutaneous fat, and bone cross-sectional area, the measurement site was at 66% of the length of the tibia, where the largest calf diameter is typically located. For this site, the device was manually positioned and the scan was performed without a scout scan. Each scan required approximately 90 s, with some variability depending upon the cross-sectional size of the forearm or lower leg.

Measurement parameters

Image analysis and the selection of threshold values were performed using the manufacturer's software, version 5.40. The following parameters were determined at the selected bone sites: (i) the mass of mineralized tissue in the cortical region, the trabecular

region, and the overall cross-sectional region (bone mineral content in mg); (ii) the size of the cross-sectional area of bone (area in mm²); and (iii) volumetric bone mineral density (vBMD in mg/cm³). These parameters included total vBMD (TOT_DEN), trabecular vBMD (TRAB_DEN), cortical vBMD (CRT_DEN), total content (TOT_CNT), trabecular content (TRAB_CNT), cortical content (CRT_CNT), total cross-sectional area (TOT_A), cortical cross-sectional area (CRT_A), cortical thickness (CRT_THK), endocortical circumference (ENDO_CIR), periosteal circumference (PERI_CIR), polar moment of inertia (PMI), polar moment of resistance (PMR), and polar stress strain index (SSI).

To define the outer boundary of the bone and to distinguish trabecular bone from cortical bone, the pQCT system uses a contour algorithm that detects the periosteal surface of the bone based on a threshold of 280 mg/cm³. After detecting the outer bone contour, there is concentric peeling of the outer 55% of voxels until a central area covering 45% of the total bone cross-sectional area remains. From this central area, TRAB_DEN and TRAB_CNT were determined. The actual relative cross-sectional area of the trabecular compartment is considerably larger than 45%; however, the resolution of the pQCT system is not sufficient to trace the exact border between trabecular and cortical bone. Therefore, this geometric definition of trabecular bone involves some margin of safety to exclude cortical bone from the trabecular region of interest (ROI). In the cortical compartment, many voxels are only partially occupied by cortical bone. At a threshold of 710 mg/cm³, the number of such voxels that are included in the analysis is equivalent to the number excluded. In this study, cortical bone parameters were only determined at the diaphyseal sites of the radius and tibia.

For the analysis of muscle cross sectional area, the ROI was defined to include the entire matrix (skin, subcutaneous tissue, muscle and bone). Within this ROI, the total area of the muscle was determined with the threshold set at 40 mg/cm³, and the total bone was assessed at the threshold of 710 mg/cm³. Next, the total area of skin and subcutaneous fat was identified using a threshold of -100 mg/cm³. Subsequently, the total bone area and total areas of skin and subcutaneous fat were deducted from the ROI to yield the total muscle area found between the thresholds of 40 mg/cm³ and 710 mg/cm³. No additional volume was removed from inside the muscle with this approach.

Data analysis

Quantitative analysis was performed for the cohort as a whole and statistical analysis was also conducted to compare the healthy and breast cancer patient subgroups. Descriptive statistics including the number of subjects (*n*), mean, and standard deviation (SD) values were calculated for each variable. Tests for normality were conducted on all the data sets, and 2-sided *t*-tests were used for inter-group comparisons. Any data patterns associated with independent variables were determined; in all cases the Pearson correlation coefficient (*r*) value is reported. All calculations were conducted on the original data in accordance with the valid application of the test of significance; differences were considered significant at *p*<0.05.

Results

Participant characteristics

The anthropometric characteristics of the study participants are provided in Table 1 with separate analysis given for the participant subgroups. The mean age of all participants was 60 ± 8 years (range 46 to 81) and within the subgroups, 58 ± 7 years for healthy postmenopausal women and 62 ± 9 years for breast cancer participants. There were no significant differences between the two populations with respect to age, mass, height, body mass index (BMI), or number of biological children. The mean BMI value was 27 ± 5.4 kg/m^2 (range 18.5 to 39.8 kg/m^2). BMI values reflect that these women as a group were overweight ($\text{BMI} > 25$), with 23% ($n=6$ controls and $n=7$ breast cancer patients) classified as obese ($\text{BMI} > 30$). The mean age at menopause was similar for both subgroups; 49 ± 7 years for healthy postmenopausal women and 48 ± 6 years for breast cancer patients. The mean years since menopause was higher in the breast cancer group at 14 ± 9 versus 9 ± 9 years, however, this difference was not statistically significant. One participant in each subgroup did not submit her age at menopause, thus, the sample size for this parameter is $n=26$ for the breast cancer participants and $n=30$ for the healthy control participants. Twenty-three participants had undergone surgical hysterectomy ($n=8$ healthy postmenopausal women and $n=15$ breast cancer participants), and fourteen had undergone surgical ovariectomy ($n=7$ for each subgroup); the mean ages for these surgeries were 45 years and 44 years, respectively.

Ninety-five percent of the study participants were Caucasian, there was one participant each of Hispanic, Asian and African-American ethnicity. Seventy-nine percent of participants stated that they had never fractured a bone as an adult. It is important to note that fragility fractures will have been underestimated, as no radiographic assessment was made for asymptomatic vertebral fractures. For those that had experienced a fracture, the sites involved were those typically associated with traumatic fractures such as the clavicle, phalanges, fibula, and coccyx. Three participants had fractures that may have been due to bone fragility; two at the radius and one at the ankle. With respect to a family history of osteoporosis, participants were asked to indicate if anyone in their immediate family had ever shown signs of bone loss. Fifty percent indicated that in their recollection a member of their family had been diagnosed with osteoporosis or had shown symptoms of the disease. Approximately 10% fewer breast cancer participants (55% healthy controls in comparison with 44% breast cancer participants) reported a family history of osteoporosis. Of all the participants, 40% indicated that their mother had either been diagnosed with osteoporosis, developed a stoop with age (loss of height) or had fractured her hip or wrist, 10% indicated that their father had developed osteoporosis or exhibited a loss of height, and 9% indicated that either their sister or brother had incurred a loss of height.

With respect to cigarette smoking, 3% of the healthy controls were current smokers and 39% had smoked regularly in the past; 15% of the breast cancer participants were current smokers and 33% had smoked regularly in the past. Fifty-two percent of the healthy controls and 67% of the breast cancer participants regularly consumed coffee on a daily basis (mean of 2 cups per day), and 35% of the healthy controls and 33% of the breast cancer participants regularly consumed some form of alcohol on a daily basis (mean of 2 servings per day).

Calcium, vitamin D, and multivitamin supplements were assessed separately at any dose as long as the supplements were taken regularly. Sixty-one percent of the healthy controls and all of the breast cancer participants regularly took calcium supplements; 42% of the healthy controls and 96% of the breast cancer participants took separate vitamin D supplements with 58% of the healthy controls and 44% of the breast cancer participants taking multivitamin supplements. With respect to physical activity, 55% reported that they did participate in some form of regular physical activity (one or more times per week for 15 min or longer). When investigating the subgroups separately, this proportion was shown to be much higher for the healthy controls (71%) than for the breast cancer participants (37%). Overall, the breast cancer patients participated in less strenuous sports and weight-bearing activities than the post-menopausal controls. However, only 11% considered themselves to be a lot less active than their peers and 19% somewhat less active, whereas 48% rated themselves about the same, 15% deemed themselves somewhat more active and 7% regarded themselves as a lot more active.

Distal radius and tibia

Table 2 lists the pQCT variables measured at the 4% distal radius in the healthy postmenopausal subjects and the breast cancer patients. Also given in the table, where applicable, is the statistical significance of the difference between the measured parameters for these two subgroups. One scan at the 4% radius site of a breast cancer patient displayed an inadequately high level of motion artifact; this scan had to be excluded from further analysis for this reason. Therefore, at the 4% radius site, the sample size of breast cancer patients was $n=26$. The mean value for TOT_DEN at the distal radius was 359 mg/cm³ in the healthy control subjects; results were significantly lower ($p<0.05$) in the breast cancer patients at 319 mg/cm³. The results for TOT_CNT were also significantly different ($p<0.01$) between the two groups with mean values of 103 mg and 91 mg for the healthy and breast cancer participants respectively. Table 3 displays the pQCT variables measured at the 4% distal tibia. The mean value for TOT_DEN at the distal tibia was 297 mg/cm³ in the healthy control participants; results were significantly lower ($p<0.05$) in the breast cancer patients at 276 mg/cm³.

Diaphyseal radius and tibia

Table 4 displays the descriptive statistics of pQCT derived density, mass, area, and geometry at the 20% diaphyseal site of the non-dominant radius. At this site, the TOT_CNT and CRT_CNT were significantly lower ($p<0.05$) in the breast cancer patients. The mean TOT_CNT measured 95 mg in the control participants and 89 mg in the breast cancer patients. The mean values for CRT_CNT were 89 mg and 82 mg for each group respectively. The mean CRT_DEN values were also significantly lower ($p<0.01$) in the breast cancer patients, at 1227 mg/cm³ as compared with 1270 mg/cm³ for the healthy controls. Table 5 displays the descriptive statistics at the 38% diaphyseal site of the non-dominant tibia. One scan at the 38% site of a breast cancer patient displayed an inadequately high level of motion artifact; this scan was excluded from further analysis for this reason. Therefore, at the 38% tibia site, the sample size of breast cancer patients was $n=26$. At this site, only the CRT_DEN values showed a significantly lower ($p<0.01$) result for the breast cancer patients.

The mean CRT_DEN was measured as 1209 mg/cm³ in the control participants and 1173 mg/cm³ in the breast cancer patients.

Muscle, subcutaneous fat, and bone cross-sectional area

pQCT scans were performed on the non-dominant tibia at the 66% site; positioning at this site was occasionally difficult due to the size of the leg aperture in relation to the diameter of a subject's calf. Table 6 lists the results for muscle, fat, and bone area in healthy postmenopausal women ($n=31$) and breast cancer patients ($n=27$) assessed at the 66% tibia site. There were no statistically significant differences between the two subject populations for these parameters at this site.

Correlation analysis—skeletal sites and anthropometric characteristics

To further explore the relationships between differing skeletal site measurements, correlation analyses were conducted to determine if there were any patterns of association connecting the four measurement sites (4% radius and tibia, 20% radius, and 38% tibia) to the anthropometric characteristics of the study participants. In the course of this analysis, several interesting findings were revealed. Only the 20% radius showed significant negative correlations with both age and years since menopause, and these were significant for TOT_DEN ($r=-0.32$ and $r=-0.31$ respectively), TOT_CNT ($r=-0.37$ and $r=-0.31$ respectively), CRT_DEN ($r=-0.40$ and $r=-0.35$ respectively), and CRT_CNT ($r=-0.42$ and $r=-0.36$ respectively). The measurements significantly associated with height were at the 38% tibia, TOT_CNT ($r=0.35$) and CRT_CNT ($r=0.28$). The 4% sites of the radius and tibia showed significant positive correlations with mass and BMI. At the primarily cortical bone sites, the 20% radius and 38% tibia, TOT_CNT ($r=-0.32$ and $r=-0.36$ respectively) and CRT_CNT ($r=-0.31$ for both sites) measurements significantly negatively correlated with the number of biological children in the sample population. Time on Anastrozole showed significant negative correlation with the following measurements: TOT_CNT at the 4% radius ($r=-0.36$), TOT_CNT ($r=-0.33$), CRT_CNT ($r=-0.34$) and CRT_DEN ($r=-0.44$) at the 20% radius and CRT_DEN ($r=-0.39$) and CRT_CNT ($r=-0.27$) at the 38% tibia. When these data were adjusted for all the other variables, the significant association with time on Anastrozole persisted for all sites. Each cell in Table 7 displays the Pearson correlation coefficient (r) between the intersecting variables and the associated p -values.

Discussion

The primary aim of this study was to apply pQCT technology in an assessment of skeletal density, content, and geometry at the radius and tibia, with a focus on the effects of menopause and breast cancer therapy on trabecular and cortical bone. In examining the difference between participant sub-groups for each bone variable, certain patterns emerge. It appears that total and cortical bone content measurements are generally reduced in women with a history of breast carcinoma. Furthermore, comparisons of scans of the radius show a greater degree of difference between the two cohorts than scans of the tibia. The variables that were found to be significantly lower in the breast cancer patients were: TOT_DEN and TOT_CNT at the 4% radius; TOT_DEN at the 4% tibia; CRT_DEN, TOT_CNT, and CRT_CNT at the 20% radius; and CRT_DEN at the 38% tibia. As such, the breast cancer

patients demonstrated lower total and cortical bone density and content values, which may predispose them to an increased risk of osteoporosis and fracture. Interestingly, in this study, despite significant differences in CRT_DEN between the two cohorts, the PMR and SSI were not significantly different at the diaphyseal radius or tibia between the two cohorts. SSI is calculated using the cortical volumetric density and the cross-sectional moment of inertia. This parameter is an important validated biomechanical bone strength indicator that is related to breaking force [10]. More detailed study is required to confirm the significance of these findings in the context of changes in bone health which occur during the postmenopausal aging process, and to further evaluate bone changes in women that have undergone various therapy regimens for breast cancer.

When the variables that demonstrated significant differences between the two groups were investigated further, regression analysis revealed several notable observations. TOT_CNT at the 4% radius ($r=-0.36$); TOT_CNT ($r=-0.33$), CRT_CNT ($r=-0.34$) and CRT_DEN ($r=-0.44$) at the 20% radius; and CRT_DEN ($r=-0.39$) and CRT_CNT ($r=-0.27$) at the 38% tibia demonstrated significant negative correlations with days on Anastrozole. The largest trials to date, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Breast International Group (BIG) 1–98 trials, results have shown that adjuvant therapy with an AI (Anastrozole or Letrozole) is associated with a significant increase in musculoskeletal disorders and fractures as compared with Tamoxifen. In the ATAC trial ($n=6186$), after a median follow-up of 68 months, the overall fracture rates were 11.0% and 7.7% in the Anastrozole and Tamoxifen groups respectively ($p=0.001$) [3]. Similarly, in the BIG 1–98 trial comparing Letrozole with Tamoxifen ($n=4895$), after a median follow-up of 51 months, clinical fractures occurred more frequently in the AI group than in the Tamoxifen group, 8.6% versus 5.8% ($p<0.001$) [4,5]. In the ATAC trial, a prospectively designed sub-protocol ($n=203$) assessed changes in BMD and bone biomarkers [2]. BMD was lost at the lumbar spine (median 4.1% loss) and total hip (median 3.9% loss) after two years of Anastrozole treatment. Increased bone remodeling was also observed, urinary N-telopeptide (NTX) increased by 15% and bone alkaline phosphatase (ALP) increased by 20% after one year of treatment [2]. In contrast, decreased bone remodeling was observed with Tamoxifen. In the ABCSG trial 8 and ARNO 95 trial ($n=3199$), postmenopausal women who had completed 2 years of adjuvant Tamoxifen were randomized to receive Anastrozole or Tamoxifen for the remainder of their adjuvant treatment [6]. The study likewise noted significantly more fractures in the patients treated with Anastrozole than those on Tamoxifen ($p=0.015$). The NCIC CTG MA-17 trial, a placebo-controlled trial of Letrozole after standard adjuvant Tamoxifen, found that those on Letrozole experienced more cases of patient-reported osteoporosis (5.3% vs 4.6% for placebo, $p=0.003$) [7]. This study also included a bone sub-protocol ($n=226$) to evaluate bone turnover markers and BMD in postmenopausal women randomly assigned to MA-17 [8]. After two years, patients receiving Letrozole showed a significant decrease in total hip BMD (-3.6% vs. -0.7% , $p=0.044$) and lumbar spine BMD (-5.35% vs. -0.7% , $p=0.008$). Letrozole increased NTX at 6, 12, and 24 months ($p=0.054$, $p<0.001$, and $p<0.016$ respectively) [8]. In the Intergroup Study or IES, Exemestane was assessed after 2–3 years of Tamoxifen therapy; women were randomized to complete a total of 5 years of Tamoxifen or to switch to Exemestane for the remainder of the 5 years [9]. In a bone sub-protocol for this study, after a median follow-up of 58 months, there was a trend

for more clinical fractures in the Exemestane group than in the Tamoxifen group (7% vs 5%, $p=0.003$) [9]. Prior use of Tamoxifen in all these trials complicates their interpretation; it is likely that shortly following cessation of Tamoxifen therapy, bone turnover increases and bone loss is accelerated. Nonetheless, results of available clinical studies indicate that all three third-generation AIs affect bone turnover, BMD, and fracture risk. These data raise concerns about the long-term effects of AIs on skeletal integrity. The present study suggests that the effects of Anastrozole on bone integrity and fracture risk may be related to the role this medication has in reducing cortical bone content and density.

In the present study, the 20% radius was significantly negatively correlated with age and years since menopause for TOT_DEN, TOT_CNT, CRT_DEN, and CRT_CNT, whereas the 4% radius site did not show a significant association with these variables. As the majority of fractures of the distal radius occur within 1.6 and 3.0 cm of the tip of the radial styloid process [11], an intact trabecular network appears to be crucial for maintaining maximum bone strength [12]. Given the common fracture occurrence at this site among postmenopausal women [13], a fracture in a bone high in trabecular content is considered to be one of the earliest clinical manifestations of primary (type I) osteoporosis, and early recognition of this manifestation allows the time for preventive measures to take place [14]. As this study demonstrates, the content and density of the cortical envelope also warrants attention when assessing fracture risk at the radius. Great differences in turnover between different bones and regions within bones place constraints on the capacity of biochemical indices to capture the behavior of the overall skeleton from a single bone site. However, a prior forearm fracture has been shown to be associated with an approximately twofold increase in the likelihood of a subsequent hip, radial or humeral fracture [15–20]. Thus, measurements of cortical bone density and content at the radius and tibia could potentially be applicable in the prediction of hip fracture risk. Interestingly, of the primarily cortical bone sites, the 20% radius and 38% tibia, TOT_CNT ($r=-0.32$ and $r=-0.36$ respectively) and CRT_CNT ($r=-0.31$ for both sites) measurements showed a significant, inverse association with the number of biological children in the sample population. This suggests that the formation of the fetus or subsequent breastfeeding practices may affect cortical bone throughout the body. This also merits further research in the interest of evaluating the roles of peak bone density in determining fracture risk.

A few limitations to this study should be noted. First, the sample was not representative of the total population; the study was exploratory and based on a sample of convenience from one geographical area. It consisted primarily of middle-class, English-speaking women who were relatively well educated and had access to both professional and media sources of health information. In addition, other factors which may have led to differences in exposure to estrogen, and the extent to which these women reached peak bone mass before menopause, were not examined. Moreover, the majority of women (55%) did participate in some form of physical activity on a regular basis; however, this included only 37% of the breast cancer participants versus 71% of the healthy postmenopausal women. Intervention trials investigating the effects of weight-bearing physical activity on bone mass have found positive results only with high intensity exertion, and the degree to which such activity may have had a protective effect on the bones of the healthy controls remains to be studied.

Absorptiometry and other diagnostic tools, together with recently introduced clinical approaches to osteoporosis, have opened up new possibilities for the prompt treatment of osteoporotic fractures, the prevention of further fractures, and above all, primary prevention of fractures. It is foreseeable that osteoporosis will present a significant challenge to an aging population of breast cancer survivors, unless effective early detection and intervention strategies are developed and implemented. The interrelationships between skeletal sites and the clinical benefits of individual cortical and trabecular bone analyses need to be more fully determined before direct implementation for the assessment of fracture risk in the general population. A definitive framework for the interpretation of cortical and trabecular bone measurements can only be established through continued investigation in this area. Given that breast cancer survivors are a growing population and that breast cancer has become a chronic disease for many women, preventing bone loss through the evaluation of cortical and trabecular bone density and content may play a significant role in reducing co-morbidity and in improving health-related quality of life.

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Table 1

Anthropometric data of the study participants.

Variable ^a	All participants (n=58)	Healthy postmenopausal women (n=31)	Breast cancer patients (n=27)
Age (years)	60±8	58±7	62±9
Age at menopause ^b (years)	49±6	49±7	48±6
Years since menopause ^b (years)	11±9	9±9	14±9
Height (m)	1.63±0.06	1.62±0.06	1.64±0.07
Mass (kg)	71.4±13.6	69.3±12.1	73.8±15.0
Body mass index (kg/m ²)	27.0±5.4	26.5±5.1	27.6±5.7
Number of biological children	2±0.1	2±0.2	2±0.2

^aData expressed as the mean±SD.^bData set consists of n=26 breast cancer patients, n=30 healthy postmenopausal women, and n=56 total participants.

Table 2

Bone variables at the 4% radius.

Variable ^a	All participants (n=57)	Healthy postmenopausal women (n=31)	Breast cancer patients (n=26)
<i>Density (mg/cm³)</i>			
TOT_DEN	341±72	359±71	319±69 *
TRAB_DEN	175±37	182±39	167±35
<i>Mass (mg)</i>			
TOT_CNT	97±16	103±16	91±13 **
TRAB_CNT	23±6	24±7	22±5
<i>Area (mm²)</i>			
TOT_A	292±48	292±45	292±51

*
 $p < 0.05$ and**
 $p < 0.01$ for 2 sample *t*-test.^aData expressed as the mean ±SD;

Abbreviations: TOT_DEN, total density; TRAB_DEN, trabecular density; TOT_CNT, total content; TRAB_CNT, trabecular content; TOT_A, total area.

Table 3

Bone variables at the 4% tibia.

Variable ^a	All participants (n=58)	Healthy postmenopausal women (n=31)	Breast cancer patients (n=27)
<i>Density (mg/cm³)</i>			
TOT_DEN	287±40	297±42	276±34 *
TRAB_DEN	226±36	230±38	222±33
<i>Mass (mg)</i>			
TOT_CNT	286±38	291±40	281±35
TRAB_CNT	102±17	102±18	102±17
<i>Area (mm²)</i>			
TOT_A	1003±109	986±108	1022±109

*
p<0.05 for 2 sample t-test.

^aData expressed as the mean±SD;

Abbreviations: TOT_DEN, total density; TRAB_DEN, trabecular density; TOT_CNT, total content; TRAB_CNT, trabecular content; TOT_A, total area.

Table 4

Bone and geometric variables at the 20% radius.

Variable ^a	All participants (n=58)	Healthy postmenopausal women (n=31)	Breast cancer patients (n=27)
<i>Density (mg/cm³)</i>			
TOT_DEN	867±123	895±118	834±122
CRT_DEN	1250±42	1270±38	1227±34 ^{**}
<i>Mass (mg)</i>			
TOT_CNT	92±11	95±10	89±12 [*]
CRT_CNT	86±12	89±10	82±12 [*]
<i>Area (mm²)</i>			
CRT_A	69±8	70±7	67±9
<i>Geometry</i>			
CRT_THK (mm)	2.4±0.4	2.4±0.3	2.3±0.4
PERI_CIR (mm)	37±3	37±3	37±3
ENDO_CIR (mm)	22±4	21±4	23±4
PMI (mm ³)	1534±412	1558±413	1507±417
PMR(mm ³)	203±38	206±37	200±41
SSI (mm ³)	211±41	217±38	204±43

*
 $p < 0.05$ and**
 $p < 0.01$ for 2-sample *t*-test.^aData expressed as the mean ±SD;

Abbreviations: TOT_DEN, total density; CRT_DEN, cortical density; TOT_CNT, total content; CRT_CNT, cortical content; CRT_A, cortical area; CRT_THK, cortical thickness; PERI_CIR, periosteal circumference; ENDO_CIR, endosteal circumference; PMI, polar moment of inertia; PMR, polar moment of resistance; SSI, stress-strain index.

Table 5

Bone and geometric variables at the 38% tibia.

Variable ^a	All participants (n=57)	Healthy postmenopausal women (n=31)	Breast cancer patients (n=26)
<i>Density (mg/cm³)</i>			
TOT_DEN	846±100	852±110	838±89
CRT_DEN	1192±34	1209±29	1173±28 **
<i>Mass (mg)</i>			
TOT_CNT	333±35	340±37	326±31
CRT_CNT	310±33	317±32	301±32
<i>Area (mm²)</i>			
CRT_A	260±26	262±25	257±28
<i>Geometry</i>			
CRT_THK (mm)	4.7±0.7	4.7±0.7	4.7±0.7
PERI_CIR (mm)	71±6	71±7	70±4
ENDO_CIR (mm)	41±9	42±10	41±7
PMI (mm ³)	20274±3895	20570±4041	19921±3763
PMR (mm ³)	1394±191	1414±204	1370±175
SSI (mm ³)	1383±193	1421±209	1337±166

**
p<0.01 for 2 sample t-test.

^aData expressed as the mean ±SD;

Abbreviations: TOT_DEN, total density; CRT_DEN, cortical density; TOT_CNT, total content; CRT_CNT, cortical content; CRT_A, cortical area; CRT_THK, cortical thickness; PERI_CIR, periosteal circumference; ENDO_CIR, endosteal circumference; PMI, polar moment of inertia; PMR, polar moment of resistance; SSI, stress-strain index.

Table 6

Cross-sectional muscle, subcutaneous fat, and bone area at the 66% tibia.

Variable ^a	All participants (n=58)	Healthy postmenopausal women (n=31)	Breast cancer patients (n=27)
Area (mm ²)			
Total muscle	5588±575	5669±577	5496±571
Total fat	4907±1403	4868±1247	4951±1586
Total bone ^b	327±39	331±33	323±44

^aData expressed as the mean±SD.^bIncludes total tibia and fibula.

Table 7

Pearson correlation coefficients and *p*-values between skeletal sites and anthropometric characteristics.

Variable (<i>n</i> =58)	Pearson correlation coefficients and <i>p</i> -values (ns=not significant; * <i>p</i> <0.05, ** <i>p</i> <0.01)															
	4% Radius TOT_DEN	4% Radius TOT_CNT	4% Radius TRAB_DEN	4% Radius TRAB_CNT	4% Tibia TOT_DEN	4% Tibia TOT_CNT	4% Tibia TRAB_DEN	4% Tibia TRAB_CNT	20% Radius TOT_DEN	20% Radius TOT_CNT	20% Radius CRT_DEN	20% Radius CRT_CNT	38% Tibia TOT_DEN	38% Tibia TOT_CNT	38% Tibia CRT_DEN	38% Tibia CRT_CNT
Age (years)	-0.18 ns	-0.21 ns	0.10 ns	0.13 ns	-0.03 ns	0.04 ns	0.08 ns	0.13 ns	-0.32 *	-0.37 **	-0.40 **	-0.42 **	0.08 ns	-0.27 *	-0.22 ns	-0.24 ns
Height (m)	-0.05 ns	0.11 ns	-0.13 ns	-0.03 ns	-0.06 ns	0.15 ns	0.00 ns	0.17 ns	0.00 ns	0.13 ns	0.15 ns	0.15 ns	-0.25 ns	0.35 **	-0.05 ns	0.28 *
Mass (kg)	0.31 *	0.38 **	0.21 ns	0.17 ns	0.38 **	0.48 **	0.28 *	0.33 *	0.13 ns	0.07 ns	0.05 ns	0.10 ns	0.06 ns	0.26 *	0.02 ns	0.24 ns
Body mass index (kg/m ²)	0.31 *	0.32 *	0.26 *	0.17 ns	0.41 **	0.40 **	0.29 *	0.25 *	0.11 ns	0.00 ns	-0.02 ns	0.02 ns	0.16 ns	0.10 ns	0.05 ns	0.10 ns
Years since menopause (years)	-0.13 ns	-0.17 ns	0.04 ns	0.04 ns	-0.07 ns	0.11 ns	0.12 ns	0.25 ns	-0.31 *	-0.31 *	-0.35 **	-0.36 *	0.00 ns	-0.23 ns	-0.23 ns	-0.22 ns
Age at menopause (years)	0.01 ns	0.02 ns	0.07 ns	0.08 ns	0.10 ns	-0.03 ns	-0.01 ns	-0.10 ns	0.10 ns	0.06 ns	0.05 ns	0.05 ns	0.09 ns	-0.01 ns	0.06 ns	-0.02 ns
Number of children	-0.04 ns	-0.21 ns	-0.04 ns	-0.14 ns	-0.18 ns	0.02 ns	-0.06 ns	-0.10 ns	-0.11 ns	-0.32 *	-0.22 ns	-0.31 *	0.07 ns	-0.36 **	-0.17 ns	-0.31 *
Time on Anastrozole (days)	-0.23 ns	-0.36 **	-0.15 ns	-0.19 ns	-0.21 ns	-0.19 ns	-0.09 ns	-0.07 ns	-0.17 ns	-0.33 *	-0.44 **	-0.34 *	-0.07 ns	-0.24 ns	-0.39 **	-0.27 *