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Bone Health in Premenopausal Chinese Patients after Adjuvant Chemotherapy for Early Breast Cancer

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Keywords
Osteoporosis · Osteopenia · Cytotoxic treatment

Abstract
Background: In this cohort study, the objectives were to determine bone mineral density (BMD) and potential associated factors for bone health among young premenopausal patients after adjuvant chemotherapy. ***Methods:*** Eligibility criteria included premenopausal Chinese aged <45 years who had received adjuvant chemotherapy. At study entry, background demographics and menstrual history were collected; BMD was measured. Factors associated with reduced BMD and fracture risk were analyzed. ***Results:*** A total of 271 patients entered the study. The median time from breast cancer diagnosis to study entry was 5.0 years. The median ages at breast cancer diagnosis and at study entry were 41 and 47 years, respectively. The median BMDs for femoral neck (FN) and lumbar spine (LS) were 0.72 and 0.91 g/cm^2, respectively; 40.2% had abnormal Z-scores (defined as ≤–1) and 50.2% had osteopenia/osteoporosis of either FN or LS. On multivariate analyses, factors that were identified to have a positive association with bone health (higher BMD) included higher family income (OR [95% CI] for LS = 1.573 [1.091–2.268]), taller stature (OR for LS = 2.975 [1.723–5.137]), and higher BMI (OR for FN = 2.156 [1.599–2.907]), while negatively associated factors included longer interval since last adjuvant treatment (OR for LS: 0.435 [0.250–0.757]), peri-/postmenopausal status at study entry (OR for LS = 0.443 [0.255–0.768]; OR for FN = 0.353 [0.205–0.609]), and having received adjuvant tamoxifen (OR for FN = 0.452 [0.243–0.841]). ***Conclusion:*** About 5 years after breast cancer diagnosis and adjuvant chemotherapy, >50% of premenopausal patients who had received adjuvant chemotherapy were detected to have osteopenia/osteoporosis and 40% had abnormal Z-scores for FN/LS.

Background

Breast cancer is the most common female malignancy in China, with an age-standardized rate of 27.96 per 100,000 population [1]; it is also the commonest female cancer in Hong Kong, with a relatively higher corresponding figure of 64.6 per 100,000 population. Over 80% of newly diagnosed breast cancer patients have early-stage disease [2]. For women with early-stage breast cancer who have undergone curative surgery, adjuvant therapies have shown to improve disease-free and overall survival; for the latter, it has been noted that young patients have an increased probability of receiving adjuvant cyto-

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toxic chemotherapy [3]. Adjuvant chemotherapy is well known to be associated with immediate as well as long-term toxicities, which may affect the quality of life and well-being of cancer survivors [4–7]. One of the chemotherapy-related long-term toxicities among premenopausal patients is hormonal changes with ovarian failure, which may lead to chemotherapy-related amenorrhoea (CRA) and early menopause. In our earlier report on young premenopausal Chinese patients after adjuvant chemotherapy, over 90% were reported to have developed CRA, while one-third subsequently developed menopause before the age of 45 [8].

Oestrogen deficiency as a result of ovarian dysfunction is a key factor that can lead to accelerated bone loss and subsequent increased incidences of fractures [9]. Earlier studies had reported that premenopausal breast cancer patients who received CMF chemotherapy (consisting of cyclophosphamide, methotrexate, and fluorouracil) and subsequently entered menopause had lower bone mineral density (BMD) when compared to those who did not develop menopause [10–15]. Other studies on women who had received relatively modern chemotherapeutic regimens including anthracyclines and taxanes had reported mean bone loss of 5% in the lumbar spine (LS) over a 12-month period [16–19]. These findings have been based on Caucasian patient populations and are limited by small patient numbers, with most studies involving less than 50 patients; in addition, all apart from one study [20] had short follow-up of 1–2 years post-chemotherapy. Further, while data on BMD with or without T-scores have been commonly reported, data on Z-score for premenopausal breast cancer patients after adjuvant chemotherapy has been limited. Z-score has been regarded as a more accurate parameter for comparison as it represents the standard deviation (SD) in BMD relative to the expected BMD range for women of similar age, and is recommended by the International Society for Clinical Densitometry as the preferred assessment parameter for BMD in premenopausal women [21, 22].

In this cohort study on Chinese women with early breast cancer in Hong Kong, the objectives were to (1) determine the BMD, Z-scores, and T-scores based on dual energy X-ray absorptiometry (DXA) scanning among young premenopausal breast cancer patients after adjuvant chemotherapy, and (2) identify potential factors associated with these parameters.

Patients and Methods

Between September 2008 and February 2011, eligible breast cancer patients who were attending the breast cancer follow-up clinic at the Prince of Wales Hospital were approached for study enrolment. Eligibility criteria included female of Chinese ethnicity, a history of stage I–III breast cancer within 3–10 years, and premenopausal with age younger than 45 years when receiving adjuvant chemotherapy at the time of breast cancer diagnosis. Patients were excluded if they had evidence of disease recurrence. Patients who received ovarian ablation as part of the endocrine therapy or had hysterectomy prior to breast cancer diagnosis were also excluded. Eligible patients identified during their follow-up visits consented to the study. The study was approved by the Joint CUHK-NTEC Clinical Research Ethics Committee of the Chinese University of Hong Kong and Hong Kong Hospital Authority.

Data Collection

Clinical details at the time of breast cancer diagnosis were retrieved from individual patient's medical records. These included patient's age at breast cancer diagnosis, tumour characteristics, and information on treatment she received for her breast cancer (type of breast surgery, details of adjuvant radiotherapy, chemotherapy, tamoxifen and trastuzumab, and history of corticosteroid premedication during chemotherapy). Individual patient's body height and weight, measured by clinic staff at the time of diagnosis and at study entry, were also retrieved from the medical records. At study entry, patients' demographics (education level, employment history, level of family income, smoking and alcohol history, family history of breast cancer, and number of live births before breast cancer diagnosis) as well as medical history were collected. Each patient was asked to complete a study questionnaire in which they recalled their menstruation history with the assistance of a research assistant within the same hospital visit; details of the questions asked have been described in a previous report [8].

BMD (grams per square centimeter) measurements of the LS and femoral neck (FN) were obtained by DXA using Hologic Delphi W (S/N 70354) system. Z- and T-scores were calculated with the Hologic manufacturer's reference ranges for LS and FN.

Definitions

CRA was defined as amenorrhoea for ≥3 months during and within 12 months after the completion of adjuvant chemotherapy [8]. Menopause was defined in line with World Health Organization (WHO) criteria as 12 months of amenorrhoea with last menstrual period ≥12 months after chemotherapy and before study entry [23].

Body mass index (BMI) was categorized according to the WHO criteria for Asians. BMI categories included underweight, normal weight, overweight, and obesity, which were respectively defined as <18.5, 18.5–<23, 23–<25, and ≥25.0 [24].

Z-score is the number of SDs away from the mean bone density of a person of the same age, race, and gender [21]. For the purpose of this study, Z-scores of less than or equal to –1 were defined as abnormal. T-score is defined as the number of SDs away from the mean bone density of a young adult with peak bone density. Osteoporosis was defined by the WHO [25] as a BMD below a T-score of 2.5 SDs below the mean value of peak bone mass expected for a young healthy female adult either in the spine and/or the hip. Osteopenia was defined as a T-score between –1 and –2.5 SD.

Fracture risk of individual patients was being assessed by adopting Fracture Risk Assessment Tool (FRAX®) for Chinese [26]. This tool incorporates multiple factors including BMD of FN, based on which the 10-year probability of major osteoporotic hip fracture was calculated.

Statistical Analysis

Statistical analysis was performed by SAS version 9.3. Clinical characteristics data were summarized as patient number (*n*) and percentage (%) for categorical variables, and mean and SD for continuous variables.

Table 1. Patients' background demographic and clinical characteristics at the time of breast cancer diagnosis (n = 271)

	Patients	%
Age at diagnosis		
≤35 years	39	14.4
36–40 years	81	29.9
41–45 years	151	55.7
Age at time of study entry		
≤40 years	32	11.8
41–45 years	74	27.3
46–50 years	142	52.4
>50 years	23	8.5
Education		
Primary	44	16.3
Secondary	181	67.0
Tertiary	27	10.0
Higher qualification	18	6.7
Marital status		
Single	42	15.5
Married/partner	209	77.1
Divorced/separated	15	5.5
Widowed	5	1.9
Employment		
Full-time employment	124	45.8
Part-time employment	44	16.2
Unemployed/retired	103	38.0
Family income*		
<HKD 5,000	26	9.6
HKD 5,000–25,000	143	52.8
HKD 25,000–50,000	83	30.6
HKD 50,000	19	7.0
Weight at diagnosis ≥median	136	50.2
Height at diagnosis ≥median	138	50.9
Weight at study entry ≥median	140	51.7
Height at study entry ≥median	139	51.3
BMI at study entry (according to HK BMI)		
Underweight (<18.5)	11	4.1
Normal (18.5–22.9)	120	44.2
Overweight (23.0–24.9)	59	21.8
Obese (>25)	81	29.9
Stage of breast cancer		
Stage I	86	31.8
Stage II	160	59.0
Stage III	25	9.2
Breast surgery		
Lumpectomy	94	34.7
Mastectomy	177	65.3
Axillary lymph node dissection	267	98.5
Received adjuvant radiotherapy	180	66.4
Adjuvant chemotherapy regimen		
Anthracycline-containing	177	65.3
Anthracycline- and taxane-containing	72	26.6
Others (taxane-containing, non-anthracycline + non-taxane containing)	22	8.1
Adjuvant chemotherapy regimen		
Taxane-containing	77	28.4
Non-taxane-containing	194	71.6
Duration of adjuvant chemotherapy >64 days	184	67.9
Time since last adjuvant treatment (only include chemotherapy/radiotherapy or trastuzumab)		
3 to <5 years	153	56.5
5 to <10 years	118	43.5
Ever received adjuvant tamoxifen	205	75.7
On adjuvant tamoxifen at study entry	110	40.6

Table 1 (continued)

	Patients	%
Received adjuvant trastuzumab	8	3.0
Use of traditional Chinese medicine since diagnosis	80	29.5
Having experienced chemotherapy-related amenorrhoea	247	91.1
Menopausal status at study entry		
Premenopausal	109	40.2
Peri-/postmenopausal	162	59.8
Menopausal before age <45 for "postmenopausal" patients	91	33.6

* HKD, Hong Kong dollars; HKD 1 is equivalent to USD 0.128.

Baseline continuous variables were compared by Student's *t* test or Mann-Whitney U test as appropriate, and categorical variables were compared by chi-square test.

Univariate logistic regression was performed to identify any potential factors associated with BMD, Z-score, and T-score post-chemotherapy. The odds ratio (OR) and corresponding 95% confidence interval (CI) were provided. Stepwise multivariate logistic regression analysis that included significant factors was conducted.

All statistical tests were two-sided, and p values less than 0.05 were regarded as significant.

Results

In total, 300 breast cancer patients were approached for study entry, 14 of them declined participation. As a result, 286 patients consented to participate in this study. Two patients failed to meet inclusion criteria as they received neoadjuvant therapy for their stage IIIb breast cancers. Four patients withdrew with the reason that they did not have time to perform the study tests after consent. As a result, 280 eligible patients entered the study, amongst whom 271 underwent DXA assessment. Table 1 shows the patients' background demographics, tumour characteristics, and anticancer treatments received at breast cancer diagnosis.

The median age at breast cancer diagnosis was 41 years (range: 24–45). Adjuvant chemotherapy regimens included anthracycline-containing (65.3%), anthracycline-taxane-containing (26.6%), taxane-containing (1.8%), and non-anthracycline/non-taxane-containing (6.3%) regimens. Two hundred and five patients (75.7%) also received adjuvant tamoxifen; 180 (66.4%) received adjuvant radiotherapy.

The median time from breast cancer diagnosis to study entry was 5.04 years (range: 2.96–9.94). The median age at study entry was 47 years (range: 28–54). At the time of the study, 110 (40.5%) patients were still on adjuvant tamoxifen therapy.

Two hundred and forty-seven of the 271 patients (91.1%) had experienced CRA; the median period of CRA was 9.0 months. Of the 247 who had CRA, 82 did not regain their menstruation and went into menopause; for the remaining two-thirds who resumed their menstruation, 45 developed menopause, 95 remained to be premenopausal, and 25 were considered to be peri-menopausal at study entry. Of the 24 patients who did not experience CRA, 3 subsequently became peri-menopausal and 7 developed menopause. Thus, at study entry, 28 were peri-menopausal and 134 patients were postmenopausal; of the latter, 68% were younger than 45 at the time of menopause.

Body Weight, Body Height, and BMI at Breast Cancer Diagnosis and at Study Entry

At breast cancer diagnosis, the median weight and height of patients were 54.6 kg (range: 39.0–89.0) and 159 cm (range: 141–175), respectively; at study entry, the corresponding figures were 56.2 kg (range: 39.5–92.6) and 157 cm (range: 143–172), respectively. At study entry, 4.1% were underweight, 44.2% were normal, 21.8% were overweight, and the remaining 29.9% were obese.

Bone Health Assessment with DXA

The median BMD of FN was 0.72 g/cm^2 (interquartile range [IQR]: 0.66–0.70), that of LS was 0.91 g/cm^2 (IQR: 0.83–1.01).

The median Z-scores for FN and LS were 0.00 (IQR: –0.7 to +0.8) and –0.40 (IQR: –1.2 to +0.3), respectively. One hundred and nine patients (40.2%) had abnormal Z-scores for either FN or LS; abnormal Z-scores for FN and LS were detected in 55 (20.3%) and 89 patients (32.8%), respectively. One hundred and thirty-eight patients (50.9%) had discordant Z-scores between FN and LS; only 35 patients (12.9%) had abnormal Z-scores for both FN and LS.

The median T-scores for FN and LS were –0.30 (IQR: –1.0 to +0.5) and –0.80 (IQR: –1.5 to +0.2), respectively.

Table 2. Univariate and multivariate analyses on factors associated with higher bone mineral densities (above median) for lumbar spine, by stepwise logistic regression

	Univariate analysis			Multivariate analysis		
	OR	95% CI for OR	*p*	OR	95% CI for OR	*p*
Age at breast cancer diagnosis	0.778	0.560–1.082	0.1358			
≤35 years	1	–	–			
36–40 years	0.580	0.266–1.264	0.1708			
41–45 years	0.540	0.263–1.110	0.0936			
Age at time of study entry	0.681	0.503–0.924	0.0135			
≤40 years	1	–	–			
41–45 years	1.207	0.521–2.796	0.6608			
46–50 years	0.603	0.278–1.306	0.1994			
>50 years	0.415	0.137–1.254	0.1191			
Education	1.108	0.797–1.542	0.5417			
Primary	1	–	–			
Secondary	1.081	0.562–2.080	0.8146			
Tertiary	1.231	0.473–3.200	0.6701			
Higher qualification	1.429	0.476–4.286	0.5246			
Marital status	0.780	0.494–1.232	0.2873			
Single	1	–	–			
Married/partner	1.294	0.665–2.518	0.4472			
Divorced/separated	0.807	0.243–2.675	0.7529			
Widowed	–	–	0.9794			
Employment	0.904	0.696–1.174	0.4487			
Full-time employment	1	–	–			
Part-time employment	0.440	0.215–0.904	0.0247			
Unemployed/retired	0.834	0.494–1.408	0.4977			
Family income	1.649	1.181–2.302	0.0033	1.573	1.091–2.268	0.0152
<HKD 5,000	1	–	–			
HKD 5,000–25,000	1.446	0.604–3.461	0.4079			
HKD 25,000–50,000	2.862	1.141–7.180	0.0251			
HKD 50,000	3.238	0.943–11.117	0.0619			
Height at diagnosis ≥median	2.354	1.446–3.833	0.0006	2.975	1.723–5.137	<0.0001
Weight at study entry ≥median	2.510	1.539–4.095	0.0002			
Height at study entry ≥median	2.021	1.246–3.279	0.0044			
BMI at study entry (according to HK BMI)	1.584	1.212–2.069	0.0008			
Underweight (<18.5)	1	–	–			
Normal (18.5–22.9)	1.717	0.433–6.801	0.4416			
Overweight (23.0–24.9)	3.627	0.873–15.062	0.0762			
Obese (>25)	4.083	1.007–16.553	0.0488			
Stage of breast cancer	1.333	0.892–1.990	0.1607			
Stage I	1	–	–			
Stage II	1.146	0.678–1.939	0.6106			
Stage III	2.142	0.853–5.378	0.1047			
Breast surgery						
Lumpectomy vs. mastectomy	0.597	0.360–0.989	0.0454			
Axillary lymph node dissection vs. nil	0.316	0.032–3.080	0.3215			
Received adjuvant radiotherapy	1.457	0.877–2.422	0.1461			
Adjuvant chemotherapy regimen	1.078	0.742–1.566	0.6936			
Anthracycline-containing	1	–	–			
Anthracycline- and taxane-containing	1.308	0.755–2.267	0.3376			
Others (taxane-containing, non-anthracycline + non-taxane containing)	0.923	0.379–2.246	0.8592			
Duration of adjuvant chemotherapy >64 days	0.800	0.480–1.333	0.3907			
Time since last adjuvant treatment (only include chemotherapy/radiotherapy or trastuzumab)						
"3 to <5 years" vs. "5 to <10 years"	0.549	0.337–0.892	0.0155	0.435	0.250–0.757	0.0032
Ever received adjuvant tamoxifen	0.636	0.363–1.114	0.1137			
On adjuvant tamoxifen at study entry	1.637	1.004–2.669	0.0480			
Received adjuvant trastuzumab	0.614	0.144–2.621	0.5100			
Use of traditional Chinese medicine since diagnosis	1.617	0.955–2.739	0.0737			
Having experienced chemotherapy-related amenorrhoea	1.250	0.539–2.899	0.6025			
Menopausal status at study entry						
Peri-/postmenopausal vs. premenopausal	0.431	0.262–0.708	0.0009	0.443	0.255–0.768	0.0038
Menopause before age 45	0.488	0.291–0.818	0.0065			

Table 3. Univariate and multivariate analyses on factors associated with higher bone mineral densities (above median) for femoral neck, by stepwise logistic regression

	Univariate analysis			Multivariate analysis		
	OR	95% CI for OR	*p*	OR	95% CI for OR	*p*
Age at breast cancer diagnosis	0.800	0.576–1.112	0.1848			
≤35 years	1	–	–			
36–40 years	0.448	0.204–0.985	0.0457			
41–45 years	0.510	0.246–1.057	0.0702			
Age at time of study entry	0.767	0.569–1.035	0.0830			
≤40 years	1	–	–			
41–45 years	1.294	0.561–2.983	0.5451			
46–50 years	0.684	0.317–1.476	0.3330			
>50 years	0.679	0.231–1.994	0.4810			
Education	0.990	0.712–1.376	0.9519			
Primary	1	–	–			
Secondary	0.905	0.474–1.739	0.7648			
Tertiary	0.765	0.294–1.995	0.5841			
Higher qualification	1.196	0.399–3.585	0.7498			
Marital status	0.869	0.553–1.366	0.5426			
Single	1	–	–			
Married/partner	1.270	0.653–2.470	0.4816			
Divorced/separated	0.807	0.243–2.675	0.7259			
Widowed	0.303	0.031–2.941	0.3029			
Employment	0.827	0.636–1.075	0.1578			
Full-time employment	1	–	–			
Part-time employment	0.570	0.284–1.145	0.1143			
Unemployed/retired	0.691	0.409–1.168	0.1678			
Family income	1.216	0.882–1.675	0.2321			
<HKD 5,000	1	–	–			
HKD 5,000–25,000	1.088	0.471–2.515	0.8439			
HKD 25,000–50,000	0.985	0.407–2.384	0.9736			
HKD 50,000	3.267	0.909–11.743	0.0698			
Weight at diagnosis ≥median	2.835	1.732–4.640	<0.0001			
Height at diagnosis ≥median	1.213	0.753–1.955	0.4268			
Weight at study entry ≥median	3.033	1.848–4.977	<0.0001			
Height at study entry ≥median	1.327	0.823–2.140	0.2454			
BMI at study entry (according to HK BMI)	1.999	1.511–2.643	<0.0001	2.156	1.599–2.907	<0.0001
Underweight (<18.5)	1	–	–			
Normal (18.5–22.9)	2.423	0.500–11.732	0.2715			
Overweight (23.0–24.9)	6.562	1.301–33.086	0.0227			
Obese (>25)	8.999	1.816–44.586	0.0071			
Stage of breast cancer	0.919	0.617–1.368	0.6759			
Stage I	1	–	–			
Stage II	0.804	0.476–1.359	0.4154			
Stage III	0.987	0.405–2.407	0.9771			
Breast surgery						
Lumpectomy vs. mastectomy	0.777	0.471–1.283	0.3244			
Axillary lymph node dissection vs. nil	–	–	0.9812			
Received adjuvant radiotherapy	0.978	0.591–1.619	0.9304			
Adjuvant chemotherapy regimen	1.202	0.827–1.749	0.3352			
Anthracycline-containing	1	–	–			
Anthracycline- and taxane-containing	1.017	0.640–1.915	0.7159			
Others (taxane-containing, non-anthracycline + non-taxane containing)	1.599	0.650–3.932	0.3064			
Duration of adjuvant chemotherapy >64 days	0.747	0.448–1.246	0.2634			
Time since last adjuvant treatment (only include chemotherapy/radiotherapy or trastuzumab)						
"3 to <5 years" vs. "5 to <10 years"	0.659	0.406–1.069	0.0909			
Ever received adjuvant tamoxifen	0.456	0.257–0.808	0.0072	0.452	0.243–0.841	0.0121
On adjuvant tamoxifen at study entry	1.131	0.696–1.838	0.6182			
Received adjuvant trastuzumab	3.213	0.637–16.209	0.1576			
Use of traditional Chinese medicine since diagnosis	1.131	0.671–1.907	0.6434			
Having experienced chemotherapy-related amenorrhoea	1.250	0.539–2.899	0.6025			
Menopausal status at study entry						
Peri-/postmenopausal vs. premenopausal	0.431	0.262–0.708	0.0009	0.353	0.205–0.609	0.0002
Menopause before age 45	0.839	0.506–1.390	0.4944			

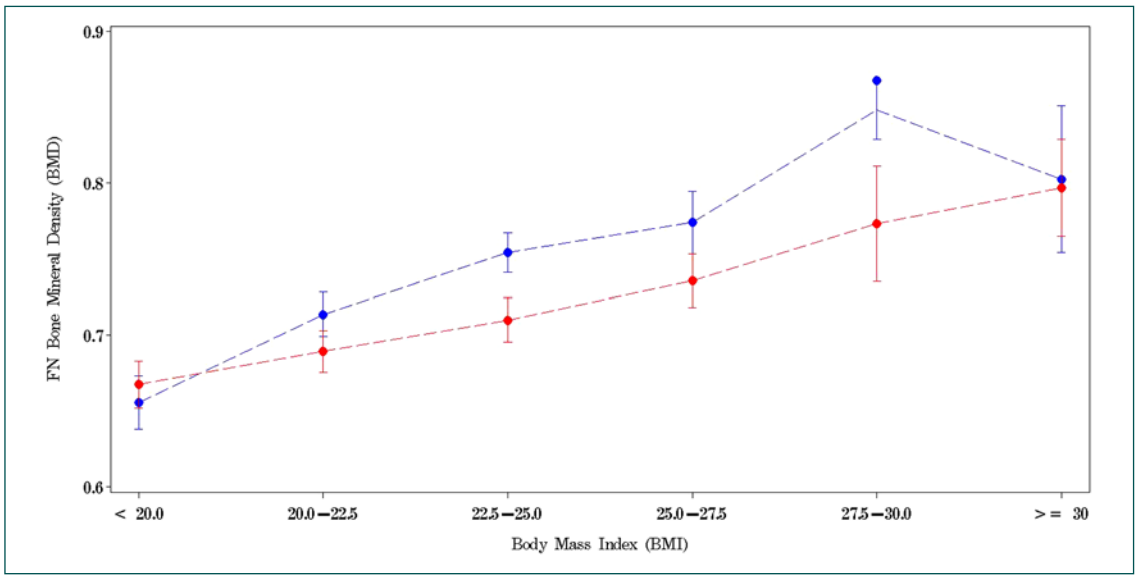

Fig. 1. Bone mineral density of femoral neck (FN) versus body mass index. Blue line, pre-/perimenopausal; red line, postmenopausal.

Osteopenia/osteoporosis of either FN or LS occurred in 136 patients (50.2%); 67 patients (24.7%) had osteopenia/osteoporosis of FN and 122 (45.0%) had osteopenia/osteoporosis of LS. Ninety-six patients (35.4%) had discordant T-scores between FN and LS; 53 patients (19.6%) had osteopenia/osteoporosis for both FN and LS. A total of 17 patients (6.3%) had osteoporosis at LS, and no patient was detected to have osteoporosis at FN. FRAX scores ranged from 0 to 4%, with a median score of 0.2%.

Analysis for Risk Factors Associated with Abnormalities Detected in DXA

Univariate and multivariate analyses on factors associated with higher BMD (defined as above median BMD) of LS are listed in Table 2. Patients with higher family income (OR = 1.573, 95% CI = 1.091–2.268, $p = 0.0152$) and having taller stature (OR = 2.975, 95% CI = 1.723–5.137, $p < 0.0001$) were significantly associated with higher BMD, while longer time interval since last adjuvant treatment (excluding endocrine therapy) (OR = 0.435, 95% CI = 0.250–0.757, $p = 0.0032$) and peri-/postmenopausal status (OR = 0.443, 95% CI = 0.255–0.768, $p = 0.0038$) were significantly and inversely associated with higher BMD.

Table 3 shows the outcomes of univariate and multivariate analyses on factors associated with higher BMD of FN. Higher BMI (OR = 2.156, 95% CI = 1.599–2.907, $p < 0.0001$) was significantly associated with higher BMD (Fig. 1), while having ever received adjuvant tamoxifen (OR = 0.452, 95% CI = 0.243–0.841, $p = 0.0121$) and peri-/postmenopausal status (OR = 0.353, 95% CI = 0.205–0.609, $p = 0.0002$) were significantly and inversely associated with higher BMD.

Univariate and multivariate analyses on factors associated with abnormal Z-scores of FN and/or LS are shown in Table 4. Being married/having partner/divorced/separated was shown to be significantly associated with higher risk of abnormal Z-scores (OR = 1.869, 95% CI = 1.203–3.166, $p = 0.0312$), while higher weight at study entry was significantly associated with lower risk of abnormal Z-scores (OR = 0.182, 95% CI = 0.106–0.312, $p < 0.0001$).

Table 5 illustrates the outcomes of univariate and multivariate analyses on factors associated with osteopenia/osteoporosis of FN and/or LS. Taller body stature (OR = 0.510, 95% CI = 0.303–0.858, $p = 0.0111$) and higher BMI (OR = 0.491, 95% CI = 0.366–0.658, $p < 0.0001$) at study entry were significantly associated with lower risk of osteopenia/osteoporosis. Longer duration of adjuvant chemotherapy (OR = 1.754, 95% CI = 1.004–3.063, $p = 0.0482$) and peri-/postmenopausal status at study entry (OR = 2.502, 95% CI = 1.463–4.280, $p = 0.0008$) were significantly associated with lower risk of osteopenia/osteoporosis.

Table 6 shows the factors that were identified on univariate and multivariate analyses to be associated with increased risk of hip fracture based on FRAX score. Higher BMI (OR = 0.498, 95% CI = 0.370–0.669, $p < 0.0001$) was significantly associated with lower fracture risk while having undergone lumpectomy (OR = 1.918, 95% CI = 1.099–3.349, $p = 0.0220$), and longer time interval since last adjuvant treatment (OR = 1.784, 95% CI = 1.053–3.022, $p = 0.0313$) and peri-/postmenopausal status at study entry (OR = 1.985, 95% CI = 1.162–3.391, $p = 0.0121$) were significantly associated with higher risk of fracture.

Table 4. Univariate and multivariate analyses on factors associated with Z-scores (≤–1) of femoral neck and/or lumbar spine, by stepwise logistic regression

	Univariate analysis			Multivariate analysis		
	OR	95% CI for OR	*p*	OR	95% CI for OR	*p*
Age at breast cancer diagnosis	0.890	0.639–1.240	0.4914			
≤35 years	1	–	–			
36–40 years	2.154	0.972–4.773	0.0588			
41–45 years	1.113	0.529–2.344	0.7773			
Age at time of study entry	0.853	0.631–1.153	0.3009			
≤40 years	1	–	–			
41–45 years	0.730	0.316–1.686	0.4617			
46–50 years	0.806	0.373–1.741	0.5824			
>50 years	0.400	0.125–1.277	0.1219			
Education	1.484	1.055–2.089	0.0235			
Primary	1	–	–			
Secondary	2.237	1.066–4.695	0.0332			
Tertiary	2.870	1.039–7.927	0.0419			
Higher qualification	3.091	0.982–9.734	0.0538			
Marital status	1.739	1.074–2.815	0.0245	1.869	1.203–3.166	0.0312
Single	1	–	–			
Married/partner	1.317	0.655–2.650	0.4394			
Divorced/separated	1.750	0.527–5.812	0.3608			
Widowed	–	–	0.9788			
Employment	0.886	0.678–1.157	0.3736			
Full-time employment	1	–	–			
Part-time employment	1.154	0.277–2.306	0.6854			
Unemployed/retired	0.776	0.453–1.329	0.3559			
Family income	1.022	0.739–1.413	0.8959			
<HKD 5,000	1	–	–			
HKD 5,000–25,000	1.327	0.554–3.179	0.5260			
HKD 25,000–50,000	1.311	0.523–3.285	0.5639			
HKD 50,000	1.102	0.321–3.783	0.8775			
Weight at diagnosis ≥median	0.249	0.148–0.418	<0.0001			
Height at diagnosis ≥median	0.758	0.466–1.233	0.2646			
Weight at study entry ≥median	0.193	0.114–0.328	<0.0001	0.182	0.106–0.312	<0.0001
Height at study entry ≥median	0.577	0.353–0.942	0.0278			
BMI at study entry (according to HK BMI)	0.422	0.311–0.572	<0.0001			
Underweight (<18.5)	1	–	–			
Normal (18.5–22.9)	0.281	0.058–1.356	0.1139			
Overweight (23.0–24.9)	0.083	0.016–0.425	0.0028			
Obese (>25)	0.059	0.012–0.299	0.0006			
Stage of breast cancer	0.862	0.574–1.296	0.4740			
Stage I	1	–	–			
Stage II	0.950	0.558–1.618	0.8510			
Stage III	0.654	0.255–1.679	0.3769			
Breast surgery						
Lumpectomy vs. mastectomy	1.601	0.950–2.700	0.0774			
Axillary lymph node dissection vs. nil	–	–	0.9822			
Received adjuvant radiotherapy	0.646	0.388–1.077	0.0941			
Adjuvant chemotherapy regimen	0.870	0.591–1.279	0.4782			
Anthracycline-containing	1	–	–			
Anthracycline- and taxane-containing	1.103	0.633–1.920	0.7299			
Others (taxane-containing, non-anthracycline + non-taxane containing)	0.547	0.204–1.465	0.2301			
Duration of adjuvant chemotherapy >64 days	1.430	0.842–2.428	0.1862			
Time since last adjuvant treatment (only include chemotherapy/radiotherapy or trastuzumab)						
"3 to <5 years" vs. "5 to <10 years"	0.913	0.559–1.490	0.7151			
Ever received adjuvant tamoxifen	1.139	0.644–2.013	0.6555			
On adjuvant tamoxifen at study entry	1.049	0.640–1.720	0.8485			
Received adjuvant trastuzumab	1.505	0.368–6.149	0.5694			
Use of traditional Chinese medicine since diagnosis	0.789	0.460–1.352	0.3887			
Having experienced chemotherapy-related amenorrhoea	0.882	0.372–2.094	0.7759			
Menopausal status at study entry						
Peri-/postmenopausal vs. premenopausal	1.458	0.883–2.407	0.1408			
Menopause before age 45	1.446	0.867–2.410	0.1575			

Table 5. Univariate and multivariate analyses on factors associated with osteopenia/osteoporosis of femoral neck and/or lumbar spine, by stepwise logistic regression

	Univariate analysis			Multivariate analysis		
	OR	95% CI for OR	*p*	OR	95% CI for OR	*p*
Age at breast cancer diagnosis	1.393	0.999–1.943	0.0504			
≤35 years	1	–	–			
36–40 years	2.675	1.192–6.003	0.0171			
41–45 years	2.534	1.196–5.372	0.0153			
Age at time of study entry	1.339	0.999–1.809	0.0569			
≤40 years	1	–	–			
41–45 years	0.927	0.401–2.141	0.8590			
46–50 years	1.523	0.703–3.298	0.2585			
>50 years	2.000	0.672–5.951	0.2128			
Education	1.014	0.730–1.410	0.9330			
Primary	1	–	–			
Secondary	1.235	0.642–2.375	0.5275			
Tertiary	0.914	0.351–2.385	0.8546			
Higher qualification	1.143	0.383–3.412	0.8109			
Marital status	1.420	0.894–2.255	0.1374			
Single	1	–	–			
Married/partner	0.935	0.482–1.815	0.8429			
Divorced/separated	1.500	0.453–4.965	0.5068			
Widowed	–	–	0.9791			
Employment	0.992	0.764–1.288	0.9510			
Full-time employment	1	–	–			
Part-time employment	1.694	0.840–3.417	0.1409			
Unemployed/retired	0.968	0.574–1.633	0.9027			
Family income	0.794	0.576–1.096	0.1604			
<HKD 5,000	1	–	–			
HKD 5,000–25,000	0.786	0.338–1.830	0.5771			
HKD 25,000–50,000	0.682	0.280–1.660	0.3992			
HKD 50,000	0.428	0.127–1.441	0.1705			
Weight at diagnosis ≥median	0.353	0.216–0.578	<0.0001			
Height at diagnosis ≥median	0.613	0.379–0.990	0.0454			
Weight at study entry ≥median	0.310	0.189–0.510	<0.0001			
Height at study entry ≥median	0.527	0.325–0.854	0.0092	0.510	0.303–0.858	0.0111
BMI at study entry (according to HK BMI)	0.537	0.408–0.707	<0.0001	0.491	0.366–0.658	<0.0001
Underweight (<18.5)	1	–	–			
Normal (18.5–22.9)	0.370	0.077–1.791	0.2168			
Overweight (23.0–24.9)	0.152	0.030–0.768	0.0227			
Obese (>25)	0.117	0.024–0.581	0.0087			
Stage of breast cancer	0.945	0.635–1.406	0.7785			
Stage I	1	–	–			
Stage II	1.158	0.685–1.956	0.5838			
Stage III	0.698	0.283–1.726	0.4369			
Breast surgery						
Lumpectomy vs. mastectomy	1.498	0.905–2.478	0.1159			
Axillary lymph node dissection vs. nil	–	–	0.9813			
Received adjuvant radiotherapy	0.802	0.484–1.329	0.3917			
Adjuvant chemotherapy regimen	0.923	0.635–1.341	0.6737			
Anthracycline-containing	1	–	–			
Anthracycline- and taxane-containing	0.967	0.559–1.672	0.9035			
Others (taxane-containing, non-anthracycline + non-taxane containing)	0.806	0.331–1.961	0.6345			
Duration of adjuvant chemotherapy >64 days	1.687	1.007–2.825	0.0471	1.754	1.004–3.063	0.0482
Time since last adjuvant treatment (only include chemotherapy/radiotherapy or trastuzumab)						
"3 to <5 years" vs. "5 to <10 years"	1.416	0.875–2.294	0.1571			
Ever received adjuvant tamoxifen	1.393	0.797–2.434	0.2443			
On adjuvant tamoxifen at study entry	0.683	0.420–1.112	0.1255			
Received adjuvant trastuzumab	1.679	0.393–7.171	0.4840			
Use of traditional Chinese medicine since diagnosis	0.800	0.474–1.350	0.4028			
Having experienced chemotherapy-related amenorrhoea	0.686	0.293–1.603	0.3842			
Menopausal status at study entry						
Peri-/postmenopausal vs. premenopausal	2.205	1.343–3.622	0.0018	2.502	1.463–4.280	0.0008
Menopause before age 45	1.630	0.979–2.713	0.0601			

Table 6. Univariate and multivariate analyses on factors associated with increased risk of hip fracture based on FRAX® score

	Univariate analysis			Multivariate analysis		
	OR	95% CI for OR	*p*	OR	95% CI for OR	*p*
Age at breast cancer diagnosis	1.220	0.875–1.702	0.2416			
≤35 years	1	–	–			
36–40 years	2.195	0.979–4.921	0.0564			
41–45 years	1.893	0.893–4.014	0.0961			
Age at time of study entry	1.334	0.985–1.808	0.0629			
≤40 years	1	–	–			
41–45 years	0.696	0.299–1.623	0.4019			
46–50 years	1.117	0.516–2.417	0.7797			
>50 years	2.411	0.797–7.288	0.1191			
Education	0.930	0.667–1.297	0.6711			
Primary	1	–	–			
Secondary	1.012	0.525–1.953	0.9704			
Tertiary	1.346	0.517–3.505	0.5426			
Higher qualification	0.625	0.625–1.960	0.4203			
Marital status	1.088	0.692–1.711	0.7135			
Single	1	–	–			
Married/partner	0.952	0.489–1.853	0.8846			
Divorced/separated	1.060	0.325–3.456	0.9237			
Widowed	1.817	0.275–12.025	0.5356			
Employment	1.101	0.847–1.432	0.4715			
Full-time employment	1	–	–			
Part-time employment	2.431	1.200–4.923	0.0136			
Unemployed/retired	1.188	0.699–2.018	0.5252			
Family income	0.989	0.718–1.362	0.9457			
<HKD 5,000	1	–	–			
HKD 5,000–25,000	1.619	0.677–3.873	0.2790			
HKD 25,000–50,000	1.844	0.738–4.606	0.1902			
HKD 50,000	0.675	0.183–2.481	0.5535			
Weight at diagnosis ≥median	0.409	0.250–0.668	0.0004			
Height at diagnosis ≥median	0.806	0.499–1.301	0.3770			
Weight at study entry ≥median	0.389	0.238–0.637	0.0002			
Height at study entry ≥median	0.655	0.404–1.060	0.0848			
BMI at study entry (according to HK BMI)	0.559	0.424–0.738	<0.0001	0.498	0.370–0.669	<0.0001
Underweight (<18.5)	1	–	–			
Normal (18.5–22.9)	0.272	0.056–1.311	0.1046			
Overweight (23.0–24.9)	0.123	0.024–0.622	0.0113			
Obese (>25)	0.099	0.020–0.493	0.0047			
Stage of breast cancer	1.144	0.767–1.708	0.5095			
Stage I	1	–	–			
Stage II	1.165	0.686–1.979	0.5710			
Stage III	1.282	0.524–3.134	0.5859			
Breast surgery						
Lumpectomy vs. mastectomy	1.828	1.091–3.062	0.0220	1.918	1.099–3.349	0.0220
Axillary lymph node dissection vs. nil	–	–	0.9717			
Received adjuvant radiotherapy	0.747	0.450–1.239	0.2589			
Adjuvant chemotherapy regimen	0.837	0.573–1.224	0.3595			
Anthracycline-containing	1	–	–			
Anthracycline- and taxane-containing	0.876	0.504–1.522	0.6383			
Others (taxane-containing, non-anthracycline + non-taxane containing)	0.662	0.264–1.657	0.3783			
Duration of adjuvant chemotherapy >64 days	1.398	0.832–2.349	0.2055			
Time since last adjuvant treatment (only include chemotherapy/radiotherapy or trastuzumab)						
"3 to <5 years" vs. "5 to <10 years"	1.764	1.085–2.869	0.0222	1.784	1.053–3.022	0.0313
Ever received adjuvant tamoxifen	1.712	0.963–3.045	0.0671			
On adjuvant tamoxifen at study entry	0.727	0.445–1.188	0.2037			
Received adjuvant trastuzumab	0.403	0.080–2.035	0.2716			
Use of traditional Chinese medicine since diagnosis	0.822	0.485–1.394	0.4666			
Having experienced chemotherapy-related amenorrhoea	0.593	0.245–1.436	0.2470			
Menopausal status at study entry						
Peri-/postmenopausal vs. premenopausal	1.963	1.190–3.237	0.0082	1.985	1.162–3.391	0.0121
Menopause before age 45	1.252	0.755–2.077	0.3837			

Conclusion

Clinical follow-up of cancer survivors had previously focused on survival and early detection of cancer recurrence. With the development of appropriate adjuvant therapies, survival outcome of breast cancer patients has increased, and as a result, longer survivals are expected. With increased survival, it is anticipated that long-term toxicities associated with cancer treatments may become more evident; these include effects on physical morbidities and psychosocial symptoms. As the incidence of breast cancer among young Asian females has been noted to be rapidly increasing, information on these aspects among the studied population is of particular interest.

Most of the earlier studies assessing BMD in breast cancer patients had been confined to the first year after adjuvant chemotherapy, in which bone loss was reported to be between 2 and 5% [11, 13, 15, 17, 18, 20, 27]. There is very limited data on long-term follow-up of bone health status among premenopausal patients after adjuvant cytotoxic treatment. In the study reported by Vehmanen et al. [13], follow-up DXA 5 years after adjuvant chemotherapy revealed BMD loss of 5% in the FN and 10% in the LS. Changes in BMD have been reported to vary according to the menstrual status of women after chemotherapy. While it has been reported that bone loss showed no sign of recovery after chemotherapy, partial recovery of BMD has been reported in 70% of patients who were treated with a finite period of goserelin [20]. In their follow-up study, Vehmanen et al. [28] reported BMD changes at 10 years to be 5% for those who continued to have regular menses, while it was three-fold greater for those who had irregular menses or remained amenorrhoeic. However, the fact that the study only included 29 patients who received CMF, a regimen rarely used in contemporary adjuvant protocol nowadays, greatly limited the generalizability of the findings.

Although BMD decrease has been consistently reported after chemotherapy, it could not be ascertained whether such a decrease was related to the natural history of loss of BMD in the general population associated with increasing age, as the BMD of the patients concerned have rarely been compared with women of similar age. To our knowledge, the current study is one of the first to include a large number of premenopausal Chinese patients in order to assess the long-term bone health after modern-day adjuvant chemotherapy. With over 90% of the studied population having received anthracycline- and/or taxane-containing chemotherapy, the present study has shown that 40% had abnormal Z-scores for FN and/or LS, while 50% developed osteopenia/osteoporosis at a relatively young age.

Based on multivariate analyses, the present study has identified a number of factors that were associated with poorer bone health in terms of BMDs, Z-scores, T-scores, and FRAX scores. Higher family income, taller stature, and higher BMI at study entry were associated with higher BMD, while longer time interval since last adjuvant treatment, peri-/postmenopausal status at study entry, and having received adjuvant tamoxifen were associated with lower BMD. In addition, abnormal Z-scores were associated with marital status and higher weight at study entry. Further, taller stature and higher BMI at study entry were associated with a lower risk, while longer duration of adjuvant chemotherapy and peri-/postmenopausal status at study entry were associated with higher risk of osteopenia/osteoporosis. Moreover, having undergone breast-conserving surgery, longer interval since chemotherapy and peri-/postmenopausal status were associated with higher risk, while higher BMI at study entry was associated with lower risk of hip fracture based on FRAX assessment. Apart from chemotherapy, the use of adjuvant tamoxifen, a selective oestrogen receptor modulator, exerts distinctive bone effects between pre- and postmenopausal women; while it improves bone health in the latter [29], it has been associated with increased bone loss in premenopausal women due to its partial antagonistic effect [30].

The study has a number of limitations. For instance, history of administration of bone medication including bisphosphonates, denosumab, calcium, and vitamin D was not collected. There was also lack of follow-up information on occurrence of fractures and serial assessments of BMD. Nonetheless, the identified potential risk factors associated with poorer bone health provide a good rationale for encouraging lifestyle changes to patients after breast cancer diagnosis [31]. In many developing countries, educational status and economical level are major influential factors of reaching healthcare resources and preventative interventions. As such, interventional studies with lifestyle modifications to improve general health status including aspects on bone health are valuable and may enable the provision of useful information to health care providers to avoid long-term negative impacts of anticancer treatments.

Statement of Ethics

This research project was designed in accordance with the national law and the World Medical Association Declaration of Helsinki (1964) with its ethical principles for medical research involving human subjects and subsequent amendments. Furthermore, the subjects have given their informed consent.

Disclosure Statement

The authors declare no conflicts of interest.

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Author Contributions

W.Y. contributed to the study conception, design, writing of the manuscript, acquisition of data, and analysis. C.H.W.Y. and F.K.F.M. participated in the statistical analysis and drafting of the manuscript. E.P., Y.L., J.J.S.S., J.K., R.Y.W.N., C.C.H.Y., and L.L. participated in the data collection and drafting of the manuscript. G.S.L. contributed to the study conception and design and writing of the manuscript. All authors read and approved the final manuscript.

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