Association Between Osteoporosis and Micro-Calcification in Postmenopausal Women with Breast Cancer

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Research Article

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Abstract

Purpose: Our study draws the association between osteoporosis and micro-calcification in postmenopausal patients with breast cancer.

Patients and methods: A retrospective study was conducted of postmenopausal patients, who had undergone the diagnostic procedure of both mammography and bone mineral density (BMD) evaluation from 2014-2017. Possible confounding factors such as: age at which cancer was diagnosed, menopausal age, length of menopause, serum calcium, breast composition on mammography, breast arterial calcification, diabetes mellitus, hypertension and family history on the basis of medical interview conducted. Logistic regression analyses were performed to evaluate the association between BMD and micro-calcification in breast cancer.

Results: The study included 352 postmenopausal breast cancer patients (mean age 62.0±6.6 years), out of which 165(46.9%) patients exhibited micro-calcification, and 40(11.4%) patients show osteoporosis. Patients with micro-calcification were significantly more likely to be younger, have dense breast tissue, shorter length of menopause, without diabetes mellitus or hypertension, but have osteoporosis compared to patients without micro-calcification. Multivariate logistic regression analyses showed that patients with micro-calcification were more likely to have osteoporosis and dense breast tissue as compared with patients without micro-calcification.

Conclusion: The results of our retrospective study suggest that breast cancers discovered in the form of micro-calcification are more often associated with osteoporosis.

Keywords: Breast Cancer; Micro-Calcification; Osteoporosis; Postmenopausal

Introduction

Mammography has highly reliability in diagnosis of breast cancer worldwide. According to the difference of X-ray attenuation, we could find breast vascular calcifications and micro-calcification in tumors. Breast vascular calcifications have little help in diagnosis of breast cancer, but it may associate with cardiovascular diseases [1-3]. Meanwhile, some investigators studied the association between breast vascular calcifications and osteoporosis because, several epidemiological studies have documented an association between clinical cardiovascular disease and reduced BMD [4-6]. However, the association between breast vascular calcifications and osteoporosis has been conflicting [7-9].

As we known, micro-calcification as one of the major signs of breast cancer plays a crucial role in breast cancer diagnosis. According to the shape and distribution of calcification, breast cancer can be classified and diagnosed. Mammography is superior to breast ultrasound and MRI in displaying micro-calcification. In the past, we thought that micro-calcification in breast cancer was attributed by the necrosis of the cancer tissue. However, in recent years, some studies reported that its formation may be similar to the formation of bone tissue [10]. These results prompt us to

speculate the association between micro-calcification in lesions and osteoporosis. On the other side, assessment of BMD is a very important part of postmenopausal breast cancer, especially for those pursuing endocrine therapy. Therefore, if our data allow us to conclude that micro-calcification in lesions detected on mammograms are adequate for identifying postmenopausal breast cancer patients with osteoporosis, it is of great importance for the assessment of BMD by micro-calcification in clinical applications.

To our knowledge, there are no published studies that have explored the association between micro-calcification in lesions and osteoporosis among postmenopausal breast cancer patients. The primary purpose of our study was to determine whether there is an association between the presence of micro-calcification in lesions on mammography and reduced BMD.

Subjects and Methods

Study subjects

This retrospective study was conducted at Tianjin Medical University Cancer Institute and Hospital. The study cohort consisted of 352 postmenopausal women with breast cancer who underwent routine mammography before surgery from January 2014 to December 2017 and who also had been referred for Dual-Energy X-Ray Absorptiometry (DXA) scan before endocrine therapy. Subjects were excluded if they were not yet menopausal or patients with negative hormone receptors or had bone metastasis before BMD examination. Possible confounding factors such as: age at which cancer was diagnosed, menopausal age, length of menopause, serum calcium, breast composition on mammography, breast arterial calcification, diabetes mellitus, hypertension and family history on the basis of medical interview conducted.

BMD and micro-calcification in lesions measurements

Mammography was obtained in two standard projections, craniocaudal and mediolateral oblique, for each breast. Two radiologists, blinded to the subject's clinical data, reviewed each mammogram for the presence of micro-calcification of the lesions. According to the Breast Imaging Reporting and Data System (BI-RADS) developed by The American College of Radiology (ACR), breast compositions were classified as follows: a. almost entirely fatty; b. scattered areas of fibro-glandular density; c. heterogeneously dense; d. extremely dense

Bone density was measured in accordance with established osteoporosis screening guidelines of World Health Organization. Dual-energy x-ray absorption-metric scans were classified as: normal (T score ≥ 1.0 SD), osteopenia (T score -1.0 to -2.5 SD), and osteoporosis (T score ≤ 2.5 SD).

Statistical analysis

The data were stratified by the presence of micro-calcification. Comparisons were made using the χ^2 test for categorical data and the Student's t test for continuous data.

Univariate and multivariate logistics analysis were employed to determine whether low BMD independently connects micro-calcification in lesions. Statistical significance was set at P < 0.05, and data were analyzed using SPSS version 19.0.

Results

Table 1 shows characteristics of the study cohort. The mean

age of the women was 62.0±6.6 years old, and mean length of post-menopause was 11.7±7.0 years. Because of cardiomyopathy or lung and liver metastasis, 3(0.9%) of 352 cases were not treated by operation. 37(10.5%) of 352 cases were operated after neoadjuvant chemotherapy. And 312(88.6%) of 352 cases were treated by operation first. Among 312 cases, there were 16(5.1%) cases with in situ carcinoma and 296(94.5%) cases with invasive carcinoma. Lymph node metastasis was found in 94(30.1%) cases. At last, 291 case of invasive carcinoma were treated with adjuvant chemotherapy after operation.

Table 1: Characteristics of the study population. Data are given as mean ± standard deviation or frequency (%).

Risk Factor	Mean±SD or n (%)
Age at diagnosis (years)	62.0±6.6
Age at menopause (years)	50.3±3.4
Length of post-menopause (years)	11.7±7.0
Serum Calcium (mmol/L)	2.35±0.10
Micro-calcification in breast cancer positive	165(46.9%)
Breast Composition	
a or b	182(51.7%)
c or d	170(48.3%)
Breast arterial calcification positive	86(24.4%)
Bone Mineral Density	
Normal/ Osteopenia	312(88.6%)
Osteoporosis	40(11.4%)
Diabetes mellitus	56(15.9%)
Hypertension	136(38.6%)
Family history	122(34.7%)

Table 2: Comparison between the groups with and without micro-calcifications in lesions in terms of clinical parameters.

	Without Micro-Calcification	With Micro-Calcification	Value	t/p
Age at diagnosis (years)	63.2±6.5	60.7±6.4	3.599	0.000*
Age at menopause(years)	50.3±3.5	50.3±3.3	0.116	0.907
Length of post-menopause (years)	12.8±7.0	10.4±6.9	3.289	0.001*
Serum Calcium(mmol/L)	2.36±0.11	2.34±0.10	0.763	0.446
Breast Composition				
a or b	113(60.4%)	69(41.8%)	12.157	0.000*
c or d	74(39.6%)	96(58.2%)		
Breast Arterial Calcification				
negative	137(73.3%)	129(78.2%)	1.149	0.284
positive	50(26.7%)	36(21.8%)		
Bone Mineral Density				
Normal/ Osteopenia	172(92.0%)	140(84.8%)	4.424	0.035*
Osteoporosis	15(8.0%)	25(15.2%)		
Diabetes Mellitus				
no	149(79.7%)	147(89.1%)	5.804	0.016*
yes	38(20.3%)	18(10.9%)		
Hypertension				
no	102(54.5%)	114(69.1%)	7.822	0.005*
yes	85(45.5%)	51(30.9%)		
Family History				
no	121(64.7%)	109(66.1%)	0.071	0.79
yes	66(35.3%)	56(33.9%)		

Of all patients, about 165(46.9%) cases have micro-calcification in lesion, including 8 cases with in situ carcinoma and 157 cases with invasive carcinoma. In addition, 40(11.4%) cases present osteoporosis.

Table 2 shows the comparison between the group with micro-calcification and that without micro-calcification in terms of some clinical parameters. Statistically significant differences between

the two groups were found for the following variables: age, length of post-menopause, breast composition, bone mineral density, diabetes mellitus and hypertension ($p < 0.05$).

Logistic regression analysis revealed that only breast composition on mammography and BMD exhibited a statistically significance. Table 3 shows the details of this result.

Table 3: Multivariate adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for predictors of micro-calcification.

	OR (95% CI)	P
Hypertension	0.765(0.473-1.238)	0.275
Diabetes mellitus	0.642(0.340-1.212)	0.171
Age at diagnosis (years)	0.964(0.899-1.035)	0.314
Length of post-menopause (years)	0.989(0.927-1.056)	0.741
Breast composition	1.834(1.167-2.882)	0.009*
Bone mineral density	2.412(1.175-4.953)	0.016*

(* $p<0.05$)

Discussion

Breast cancers in old patients often had a more favorable prognosis than cancers in younger patients [11], but they were more likely to combine with systemic diseases. Osteoporosis is a very common disease all over the world, in which a reduction in bone density can lead to an increased risk of fractures. Osteoporosis is also associated with acute and chronic pain, which can significantly reduce the quality of life [12]. Especially in postmenopausal breast cancer, we should pay more attention on BMD. Because of the high positive rate of hormone receptor in postmenopausal breast cancer [11], endocrine therapy is not only an important or even the only treatment for patients who cannot tolerate chemotherapy or surgery, but also an important part of adjuvant therapy after surgery. Aromatase inhibitors are preferred for endocrine therapy in postmenopausal patients. However, one of the biggest side effects of aromatase inhibitors is bone loss. In addition, the decrease of hormone level in elderly women also leads to the loss of bone mass. As a result, postmenopausal breast cancer patients who treated with aromatase inhibitor are more likely to have osteoporosis.

With the spread of breast cancer screening, mammography as the classic screening method provides more information than the diagnosis of breast cancer. Several investigations showed that breast vascular calcification was associated with an increased risk of cardiovascular disease event [1,2]. Osteoporosis, the same as breast vascular calcification, was found to be an independent predictor of future cardiovascular outcomes in postmenopausal women [13]. It sparked the interest in conducting studies with the purpose of exploring the association between the presence of breast vascular calcification on routine mammography and reduce BMD. However, those studies have yielded conflicting results [7-9].

Micro-calcification in breast cancer is also regularly observed at mammography. Indeed, about 50% of non-palpable breast cancers are detected by mammography exclusively through the study of micro-calcification [14]. What is more, it is reported that 90% of ductal carcinoma in situ has micro-calcification on mammography [15,16]. Some studies investigated the properties of breast cancer microenvironment, and they found that bone-related proteins

(such as BMP-2, OPN, and osteonectin) in breast cancer may be involved in the formation of micro-calcification. Breast cancer cells close to micro-calcifications expressed higher levels of bone mineralization markers, and these lesions were characterized by the presence of breast-osteoblast-like cells [17,18]. These data suggest that the micro-calcification on mammogram may be an informative way to identify women at BMD. Based on it, we conducted a retrospective study of 352 postmenopausal breast cancer patients, who had both mammography before surgery and BMD evaluation before endocrine therapy, to investigate the association of micro-calcification positive rate in breast lesions with osteoporosis.

We found that patients with micro-calcification were significantly more likely to be younger, have dense breast tissue, shorter length of menopause, without diabetes mellitus or hypertension, but have osteoporosis compared to patients without micro-calcification. Specifically, we have documented an independent association between micro-calcification and osteoporosis, a relationship that remained significant after adjustment for potential confounders. Our results are consistent with previous studies investigating the association between osteoporosis and vascular or valvular calcification [5,19,20]. In 1966, Bernstein revealed that there may be some associations between osteoporosis and abdominal aortic calcification [21]. The first longitudinal data from the Framingham Study showed that women with the greatest of bone loss had the highest incidence of aortic calcification over a 25-yr follow-up [5].

There are several potential limitations of this study. First, the study sample size was small and this was a single-center study. Second, subjects were selected in a retrospective manner from breast cancer patients, so some important factors for osteoporosis diagnosis could not be collected, such as vitamin D deficiency. Finally, patient's BMD was measured only before endocrine therapy, because universal screening for osteoporosis in women under the age of 65 years is not recommended unless certain risk factors were present [7].

In summary, our study showed an independent association between micro-calcification and osteoporosis. And the link between micro-calcification and osteoporosis may lead to the early identification of subjects at higher risk for osteoporosis, especially for postmenopausal breast cancer patients pursuing endocrine therapy. However, more clinical studies are needed to further clarify the pathophysiological correlation between micro-calcification and osteoporosis.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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