Original Study

Magnetic Resonance Spectroscopy-Detected Change in Marrow Adiposity Is Strongly Correlated to Postmenopausal Breast Cancer Risk

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Abstract

Previous ex vivo studies described marrow adipocytes influencing cancer bone metastasis. The prognosis of marrow adiposity on breast cancer risk remains elusive. We hypothesized that marrow adiposity and leptin levels would be associated with breast cancer risk. We found marrow fat expansion, but not circulating leptin is a predictor of postmenopausal breast cancer risk and clinicopathological characteristics of breast cancer.

Purpose: To determine whether marrow fat fraction (FF) is correlated with postmenopausal breast cancer risk and clinicopathological characteristics of breast cancer. **Methods:** Fifty-six patients with newly diagnosed and histologically confirmed postmenopausal breast cancer and 56 healthy controls underwent serologic test and magnetic resonance spectroscopy–based FF measurements. Data were analyzed by logistic multivariate regression models to determine the independent predictors of breast cancer risk and clinicopathological characters of breast cancer. **Results:** Patients with breast cancer had higher FF than that of the controls. Marrow FF showed positive association with serum leptin levels ($r = 0.607$, $P < .001$) in the cases, but no relationship was found in the controls. In the univariate analysis, both levels of leptin and marrow FF were significantly associated with breast cancer risk and clinicopathological characteristics of breast cancer. In the multivariable model with adjustment for established breast cancer risk factors, serum leptin was a significant predictor of breast cancer risk (OR 1.746; 95% CI, 1.226-2.556) and clinicopathological characteristics of breast cancer including TNM, tumor size, lymph node status, and histological grade (OR 1.461-1.695); but when marrow FF was additionally added to the regression model, marrow FF but not leptin levels was observed to be an independent risk factor for breast cancer risk (OR 1.940; 95% CI, 1.306-2.910) and clinicopathological characteristics of breast cancer (OR 1.770-1.903). **Conclusion:** Marrow adiposity is a predictor of postmenopausal breast cancer risk and clinicopathological characteristics of breast cancer.

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Introduction

Breast cancer metastasis is responsible for most breast cancer mortality. Bone is the most preferred site for distant metastasis of breast cancer and bone metastasis is an incurable complication of breast cancer, affecting 70% to 80% of advanced patients.[1]

Both marrow adipocytes and osteoblasts arise from common multipotent progenitor cells, known as bone marrow mesenchymal stromal cells (MSCs). The associations of marrow fat with other adipose tissue depots are complicated. Marrow fat may play crucial roles in modulation of hemopoiesis, metabolic homoeostasis, and osteogenesis.[2,3] Previous study showed that marrow fat cells appear to be capable of translocating stored lipids to the metastatic tumor cells. These adipocyte-supplied lipids serve as an energy source for cancer cells, a process suggested to increase tumor cell proliferation,

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motility, and invasion.[4,5] Recent ex vivo studies describe marrow fat cells influencing cancer bone metastasis, particularly breast and prostate cancer[6-8]; however, the prognosis of marrow adiposity on modulating tumor colonization and macro-metastasis in the skeleton remains largely unexplored.

Marrow adipocytes store quantities of fat and produce adipokines, such as leptin and adiponectin, which are known for their roles in the regulation of energy metabolism through endocrine-, paracrine-, and autocrine-mediated pathways.[9] Adipokines also have been studied on cancer cells and are implicated in proliferation of breast, prostate, and lung cancers[10-12]; however, there have been some controversies in the currently available data. Some,[13-15] but not all studies[16,17] showed that there exist associations between breast cancer incidence and adipokines, in particular leptin.

Because there exists a clear association between levels of leptin and marrow adiposity,[9,18] we hypothesized that elevated marrow fat content as measured by magnetic resonance spectroscopy (MRS) and serum leptin would be associated with increased risk for breast cancer and clinicopathological characteristics of breast cancer in postmenopausal females.

Material and Methods

Study Populations

Fifty-six postmenopausal patients (mean age, 63.0 ± 8.5 years) with more than 1 year since menopause (YSM) who were newly diagnosed and histologically confirmed breast cancer with no prior surgical, chemotherapy, or radiotherapy treatment between May 2013 and June 2016 were enrolled in this study. Diagnosis of breast cancer was confirmed histologically in each case and estrogen receptor status was determined. Tumors were classified as receptor-positive status according to the following criteria: ≥ 10% of positive histologically stained cells, an any "plus-system" description, ≥ 20 fmol/mg, an Allred score of ≥ 3, an immunoreactive score of ≥ 2, or an H-score of ≥ 10.[19] The staging of breast cancer was determined according to the TNM system, and histological grade was determined according to the modified Scarff–Bloom–Richardson criteria.[20] The healthy control individuals (n = 56) were age and body mass index (BMI) matched with the cases. All control participants were confirmed free from benign or malignant breast diseases by physical examination and mammography. Furthermore, the key exclusion criteria were as follows: (1) any disease known to affect bone metabolism, such as previous or current malignant tumor (except for breast cancer), exposure to chemo-radiotherapy, diabetes mellitus, chronic renal failure, thyroid and parathyroid diseases, vitamin D deficiency; (2) any previous or current use of medications known to affect bone metabolism, such as bisphosphonate, glucocorticoid, hormone replacement therapy, or calcium or vitamin D supplementation; and (3) any confounding factor that had the potential to interfere with the interpretation of the findings, such as hip or lumbar spine fracture.

For all participants, comprehensive questionnaires were used to collect medical information, including demographics (such as age, YSM, height, body weight, and BMI), alcohol consumption, smoking status, physical activity, detailed medical history, use of medications, as well as family history of breast cancer and other cancers. Physical activity was assessed using the International Physical Activity Questionnaire short form, with data reported as Metabolic Equivalent of Task hours per week.[21] Written informed consent was obtained for all individual participants included in the study according to a protocol approved by a local research ethics committee and in accordance with the 2008 Helsinki declaration.

Serologic Analysis

Blood samples were collected from an overnight fast of at least 8 hours. Routine biochemical parameters, such as fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, were determined immediately after blood was drawn and plasma samples were stored at −20°C for further analyses. Serum leptin was determined by an enzyme-linked immunosorbent assay kit (Diagnostic Systems Laboratories Inc, Webster, TX). Levels of estradiol and insulin were assayed using a radioimmunoassay kit (Union Medical & Pharmaceutical Technology Tianjin Ltd, Tianjin, China); the intraassay and interassay coefficients of variation were less than 10%, respectively.

Marrow Fat Measurements

Magnetic resonance imaging (MRI) examinations were performed on a MAGNETOM Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). The images were acquired with the participant in the supine position using the standard spine-array receive coil. Sagittal T1- and T2-weighted turbo spin-echo sequences were used for morphological assessments of the lumbar region to exclude any confounders such as wedging of vertebrae, vertebral hemangiomas, end plate depression, and silent compression fractures.

To quantify marrow fat fraction (FF), a tri-plane gradient echo localizer pulse sequence of the lumbar spine was used to guide positioning of a volume of interest (1.5 × 1.5 × 1.5 cm^3) within the third vertebral body, and then single-voxel proton MRS data were acquired using the PRESS pulse sequence without water suppression with the following image parameters: repetition time, 3000 ms; echo time (TE), 30 ms; bandwidth, 2000 Hz; flip angle, 90°; data points, 1024; number of acquisitions, 64. Six outer volume saturation bands were used to eliminate unwanted signal contamination from outside the voxel. Moreover, we applied default autoshimming as provided by the manufacturer. The acquisition time for the bone marrow MRS scan was 3 minutes 24 seconds.

A commercially available imaging workstation (Siemens Syngo B17) was used for postprocessing of MRS data. Spectral assignments were based on previous studies,[22,23] and only clearly identifiable peaks were measured. All spectra have shown a water peak located at 4.65 ppm and a lipid peak (bulk methylene) located at 1.30 ppm. FF value was calculated according to the following equation: $FF = (AUC_{lipid}/[AUC_{lipid} + AUC_{water}]) \times 100\%$, where AUC_{lipid} and AUC_{water} referred to the peak area under the lipid and water curve, respectively.

Statistical Analysis

Categorical data are described using frequencies and percentages. Continuous data are described using means ± SD. Normality of data was assessed using the Shapiro-Wilk test. Differences in the baseline characteristics between groups were evaluated using the χ^2 test for categorical data and Student's *t*-test or Wilcoxon rank sum test for