Peptides 51 (2014) 86–90

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Preoperative serum visfatin levels and prognosis of breast cancer among Chinese women

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ARTICLE INFO

Article history:
Received 27 October 2013
Received in revised form
13 November 2013
Accepted 13 November 2013
Available online 21 November 2013

Keywords:
Visfatin
Breast cancer
Prognosis
Biomarker

ABSTRACT

Visfatin is identified a pro-inflammatory cytokine and its serum level is increased in various cancers. This study aimed to evaluate the prognostic value of preoperative serum visfatin level in breast cancers. Preoperative serum visfatin levels of 248 patients with breast cancer and serum visfatin levels of 100 healthy individuals and 100 benign women controls were determined using enzyme-linked immunosorbent assay. Unfavorable outcome was defined as first local recurrence, distant metastasis, second primary cancer of another organ, or death from any cause. Disease-free survival was defined as the time between surgery and the date of unfavorable outcome whichever appeared first. Overall survival was defined from surgery to death for any cause. The association of serum visfatin level with outcomes including mortality, unfavorable outcome, disease-free survival and overall survival was investigated by univariate and multivariate analyses. Preoperative serum visfatin level was substantially higher in patients than in healthy subjects and benign controls respectively. Elevated preoperative serum level of visfatin was identified an independent predictor of mortality, unfavorable outcome, disease-free survival and overall survival. Receiver operating characteristic curve analysis showed that serum level visfatin had high predictive value for mortality and unfavorable outcome. Thus, our results suggest that high preoperative serum visfatin level is associated with poor patient outcomes as well as may play a role as prognostic biomarker in breast cancer survival.

1. Introduction

Breast cancer (BC) is the most common cancer in women worldwide [18]. The incidence of BC is increasing at a surprisingly rapid pace [15]. Many established prognostic factors for breast cancer exist including tumor size, nodal status, histologic grade, histologic type, and hormone receptor status [15,18]. Visfatin is a 52-kDa adipokine originally found in the visceral fat and also in other tissues and plays an important role in the inflammation, in a variety of metabolic and stress responses as well as in the cellular energy metabolism [3,8,10,13,19]. Visfatin has been recently implicated in the tumorigenesis and/or metastasis of various cancers [2,14,16]. Increased expression of visfatin is closely associated with the pathogenesis of colon, brain, pancreas, liver, stomach, and prostate cancers [2,14,16]. Interestingly, serum visfatin is significantly elevated in patients with BC [5] and can discriminate between postmenopausal BC patients with early cancer stage and those with late stage [4]. Moreover, high expression of visfatin in BC tissues was reported to be associated with more malignant cancer behavior as well as adverse prognosis [12]. Thus, serum visfatin level may be a promising prognostic tool in BC. This study was designed to verify the association between the preoperative serum levels of visfatin and BC outcomes.

2. Materials and methods

2.1. Study population

This study evaluated 248 patients with histologically confirmed incident BC between January 2005 and January 2008 at The Central Hospital of Wenzhou City, China. This study had excluded the patients who had prior history of any type of cancer, stage 0 or IV BC (multi-cancer or metastatic disease at diagnosis, distant organ metastasis, and in situ BC) as well as who had missing of follow-up, unavailable blood sample and incomplete clinical information. This study also included 100 healthy women controls and 100 benign women controls with breast benign diseases. This study was permitted by Ethnic Committee in The Central Hospital of Wenzhou

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0196-9781/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.peptides.2013.11.010

City. All participants provided their written informed consent to participate in this study and to publish these case details.

2.2. Assessment

This study collected information on demographic factors and clinical information on the patients with respect to hormone receptor status, lymph node status, histologic grade, nuclear grade, tumor-mode-metastasis stage, and tumor size. All patients received radical mastectomy or modified radical mastectomy. Adjuvant treatment with radiotherapy, chemotherapy and hormone therapy was based on international guidelines.

2.3. Follow-up

After surgery, patients were followed up every 3 months for 3 years and thereafter every 6 months until January 2013. Unfavorable outcome was defined as first local recurrence, distant metastasis, second primary cancer of another organ, or death from any cause during follow-up. Disease-free survival (DFS) was defined as the time between surgery and the date of first local recurrence, distant metastasis, second primary cancer of another organ, or death from any cause whichever appeared first during follow-up. Patients known to be alive with no evidence of disease were censored at the last follow-up date. Overall survival (OS) was defined from surgery to death for any cause, and patients who were alive were censored at date of last follow-up visit.

2.4. Immunoassay methods

One day before surgery, peripheral venous blood was obtained for visfatin assessment of patients with BC and controls with benign breast diseases. Peripheral blood samples were taken for healthy individuals at study entry. Samples were placed on ice, centrifuged at 3000 × *g*, and serum aliquoted and frozen at −70 °C. Serum visfatin levels were measured using a commercial enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA) according to manufacturer's instructions. All samples were assayed in duplicate. The person carrying out the assays was completely blinded to the clinical information.

2.5. Statistical analysis

All statistical analyses were performed with the use of computer software (SPSS 15.0 from SPSS Inc., Chicago, IL, USA and MedCalc 9.6.4.0. from MedCalc Software, Mariakerke, Belgium). The results were reported as counts (percentage) for the categorical variables, mean ± standard deviation for the continuous variables. Chi-square tests (or Fisher exact tests) and t tests were performed for intergroup comparisons. To analyze association of visfatin to unfavorable outcome and mortality during follow-up, multivariate analysis was performed in a binary logistic-regression model with calculated odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic curves were used to describe the predictive values with the estimated optimal cut-off point and the calculated area under curve. DFS and OS were estimated using the Kaplan–Meier method and the intergroup differences in survival time were tested using the log-rank test. Multivariate Cox's proportional hazard analysis was carried out to compare and identify independent prognostic factors for DFS and OS and to calculate hazard ratios (HR) and 95% CI. All significant parameters in the univariate analysis were entered into a multivariate model. All *P* values less than 0.05 were considered as statistically significant with a 2-tailed test.

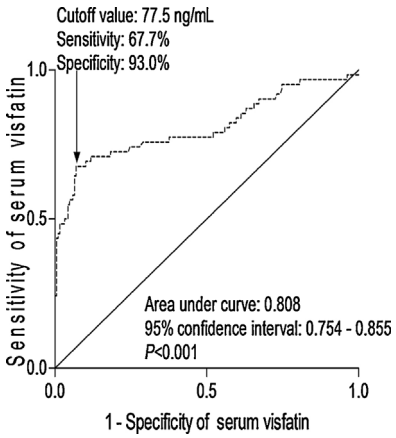

Fig. 1. The receiver operating characteristic curve analysis of serum visfatin level for mortality in breast cancer.

3. Results

3.1. Study population characteristics

This study included 248 BC patients and 100 healthy women individuals and 100 benign women controls. There were not statistically significant differences in age among three groups. Clinical information on patients was shown in Table 1. Serum visfatin levels in all patients (65.6 ± 16.9 ng/mL; range, 41.2–123.7 ng/mL), were markedly higher than those in healthy controls (37.2 ± 9.6 ng/mL; range, 15.4–63.0 ng/mL; $P < 0.001$) and in benign women controls (36.9 ± 9.5 ng/mL; range, 17.7–59.7 ng/mL; $P < 0.001$). In addition, serum visfatin levels were bifurcated at mean value (65.6 ng/mL). Values of >65.6 ng/mL indicated high levels of serum visfatin, and values of <65.6 ng/mL indicated low levels of serum visfatin.

3.2. Mortality prediction

Table 1 showed that some risk factors were correlated with mortality of BC women during follow-up. A multivariate analyses selected serum visfatin level (OR, 1.089; 95% CI, 1.062–1.116; $P = 0.001$) and lymph node status (positive versus negative) (OR, 2.203; 95% CI, 1.091–4.791; $P = 0.002$) as the independent predictors for mortality of BC women during follow-up. Fig. 1 showed that serum visfatin level had high predictive value for mortality of BC women.

3.3. Adverse event prediction

Table 1 showed that some risk factors were correlated with unfavorable outcome of BC women during follow-up. A multivariate analyses selected serum visfatin level (OR, 1.080; 95% CI, 1.056–1.105; $P = 0.003$) and lymph node status (positive versus negative) (OR, 2.102; 95% CI, 1.076–4.658; $P = 0.005$) as the independent predictors for unfavorable outcome of BC women during follow-up. Fig. 2 showed that serum visfatin level had high predictive value for unfavorable outcome of BC women.

3.4. DFS analysis

Table 2 showed that some risk factors were correlated with DFS of BC women during follow-up. A multivariate analyses selected serum visfatin level (high versus low) (HR, 3.695; 95% CI, 2.288–5.968; $P = 0.008$) and lymph node status (positive versus negative) (HR, 2.718; 95% CI, 1.121–5.633; $P = 0.009$) as the independent predictors for DFS of BC women during follow-up. Fig. 3