Rapid Communication

Stem Cell INVESTIGATION

CD133 mRNA may be a suitable prognostic marker for human breast cancer

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Abstract: Breast cancer is the most commonly malignant cancers in women. CD133 protein is a widely used marker for isolating cancer stem cell (CSC). Its expression is associated with the prognosis of many cancers. However, whether *CD133* mRNA could be used as an independent prognostic factor for breast cancer remains inconsistent in previous studies. In this study, I used the Gene Expression-Based Outcome for Breast Cancer Online algorithm (GOBO) software to analysis the prognostic roles of *CD133* mRNA in the subtypes of breast cancer. I found that *CD133* mRNA is associated with distant metastasis free survival (DMFS) in the patient with all tumors, ER-positive tumors, tamoxifen (TAM) tumors, LN-negative tumors, ER-positive/LN-negative tumors, ER-negative tumors, grade 2 tumors, HER2 enriched tumors, and untreated tumors. These results could provide a molecular target for the subtypes of breast cancer. In this study, I conclude that *CD133* mRNA may be a suitable prognostic marker for human breast cancer.

Keywords: Breast cancer; CD133; prognosis; Gene Expression-Based Outcome for Breast Cancer Online algorithm (GOBO); bioinformatic analyses

Received: 21 July 2017; Accepted: 17 October 2017; Published: 07 November 2017.

doi: 10.21037/sci.2017.10.03

View this article at: http://dx.doi.org/10.21037/sci.2017.10.03

Introduction

Breast cancer is the first cause of cancer death in women (1). It is a heterogeneous disease that has been divided into two main types with five subtypes, according to hormone receptor (HR) expression (negative or positive) and epithelial cellular origin (basal or luminal) (2). The HR-negative group has three subtypes: (I) with human epidermal growth factor receptor-2 (HER2) overexpression; (II) normal-like; and (III) basal subtype with positive absent HR (estrogen receptor and progesterone receptor) and absent HER2 expression (triple-negative subtype) (2). The major causes of treatment failure for patients with breast cancer are tumor metastasis (3). Recent years, cancer stem cells (CSCs) are considered to be the origin of tumor metastasis and recurrence (4).

CD133 (prominin-1) is a transmembrane glycoprotein that localizes to membrane protrusions of both cancer cells and normal cells (5). It has been intensively used to isolate CSCs in various solid tumors (6). To our knowledge, the prognostic role of CD133 in breast cancer has not been well established. CD133 expression showed no statistical association with the survival rate of the patients with triple-negative breast cancer (7). However, CD133 expression is an independent poor prognostic factor for invasive breast cancer (8). In this study, we used the Gene Expression-Based Outcome for Breast Cancer Online algorithm (GOBO, http://co.bmc.lu.se/gobo) that developed by Ringnér and colleagues in Lund University Canceromics Branch (Sweden) (9) to analysis the prognostic roles of *CD133* mRNA in the subtypes of breast cancer.

Methods

GOBO is a publicly available database that including tumor tissue gene expression data and clinical information from 1881 breast cancer subjects. The correlations of CD133 transcript with molecular subtypes, histological grades, and clinical outcomes in breast cancer patients was

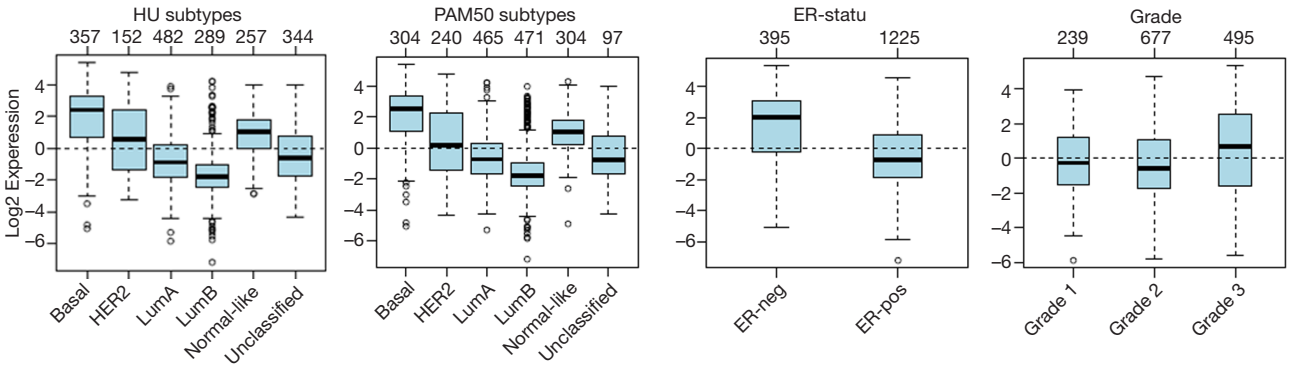

Figure 1 Gene Expression-Based Outcome for Breast Cancer Online algorithm (GOBO) analyses of CD133 transcript among subtypes of breast cancer.

analyzed by using GOBO. The calculated P values were adjusted for multiple testing by applying a False Discovery Rate adjustment (FDR =0.2). P values less than 0.05 were considered statistically significant.

Results

CD133 mRNA is associated with the survival rate of breast cancer patients

The highest *CD133* mRNA was observed in basal tumors (P<0.00001, *Figure 1*). ER-negative tumors showed a higher *CD133* mRNA than ER-positive ones (P<0.00001, *Figure 1*). The level of *CD133* mRNA was higher in grade 3 tumor than that in grade 1 and grade 2 tumors (P<0.00001, *Figure 1*). Low *CD133* mRNA was a bad prognostic factor for distance metastasis free survival (DMFS) in the patient with all tumors (P=1e-05), ER-positive tumors (P=0.005), ERBB2 tumors (P=0.011), tamoxifen (TAM) tumors (P=0.004), LN-negative tumors (P=1e-05), ER-positive/LN-negative tumors (P=0.004), ER-negative tumors (P=0.008), grade 2 tumors (P=0.009), HER2 enriched tumors (P=3e-05), and untreated tumors (P=0.001) (*Figure S1*). High *CD133* mRNA is a good indicator for RFS of all tumors (P=0.013), ER-positive tumors (P=0.008), HER2 enriched tumors (P=0.048), and LN-positive tumors (P=0.022) (*Figure 2*). After adjustment for age, tumor size, tumor grade, ER-status, and LNstatus, the Kaplan-Meier survival analyses were supported by the corresponding multivariate analyses (*Figure 2* and *Figure S1*).

Discussion

CD133 protein has been used as a marker to identify CSC in many solid tumors, including breast cancer (6). CD133 overexpression was significantly correlated with LN metastasis, ER negativity, PR negativity, HER2 positivity, non-luminal subtype, and chemotherapy (8). In this study, we confirmed that that *CD133* mRNA is associated with DMFS in the patient with all tumors, ER-positive tumors, ERBB2 tumors, TAM tumors, LN-negative tumors, ER-positive/LN-negative tumors, ER-negative tumors, grade 2 tumors, HER2 enriched tumors and untreated tumors. Many previous studies showed that CD133 protein expression was correlated with a poor survival time of breast cancer (5,8,10). However, breast cancer is a heterogeneous disease. There was often a controversy whether CD133 was a suitable marker for the subtypes of breast cancer. Liu *et al.* (11) found that CD133 overexpression was associated with poor prognosis of invasive carcinoma. Lin *et al.* (12) found that CD133 overexpression correlated with negative hormone status and perineural invasion and there was a trend towards correlation with HER2-amplified status in invasive carcinoma. Obviously, the opposite trend of CD133 protein and mRNA was observed in predicting the prognosis of breast cancer. Human CD133 protein is a five transmembrane single-chain glycoprotein that containing two large extracellular and two small intracellular loops (13). The nature of CD133's epitope is a main factor that influenced the antibody binding (14). Both micromilieu and drug treatment could affect CD133 stability and its transport to the cell surface (15,16). We speculate that the different prognostic value may be due to different stem cell characteristics in subtypes of breast cancer. Therefore, the results of the present study require validation via *in vivo* and *in vitro* studies.

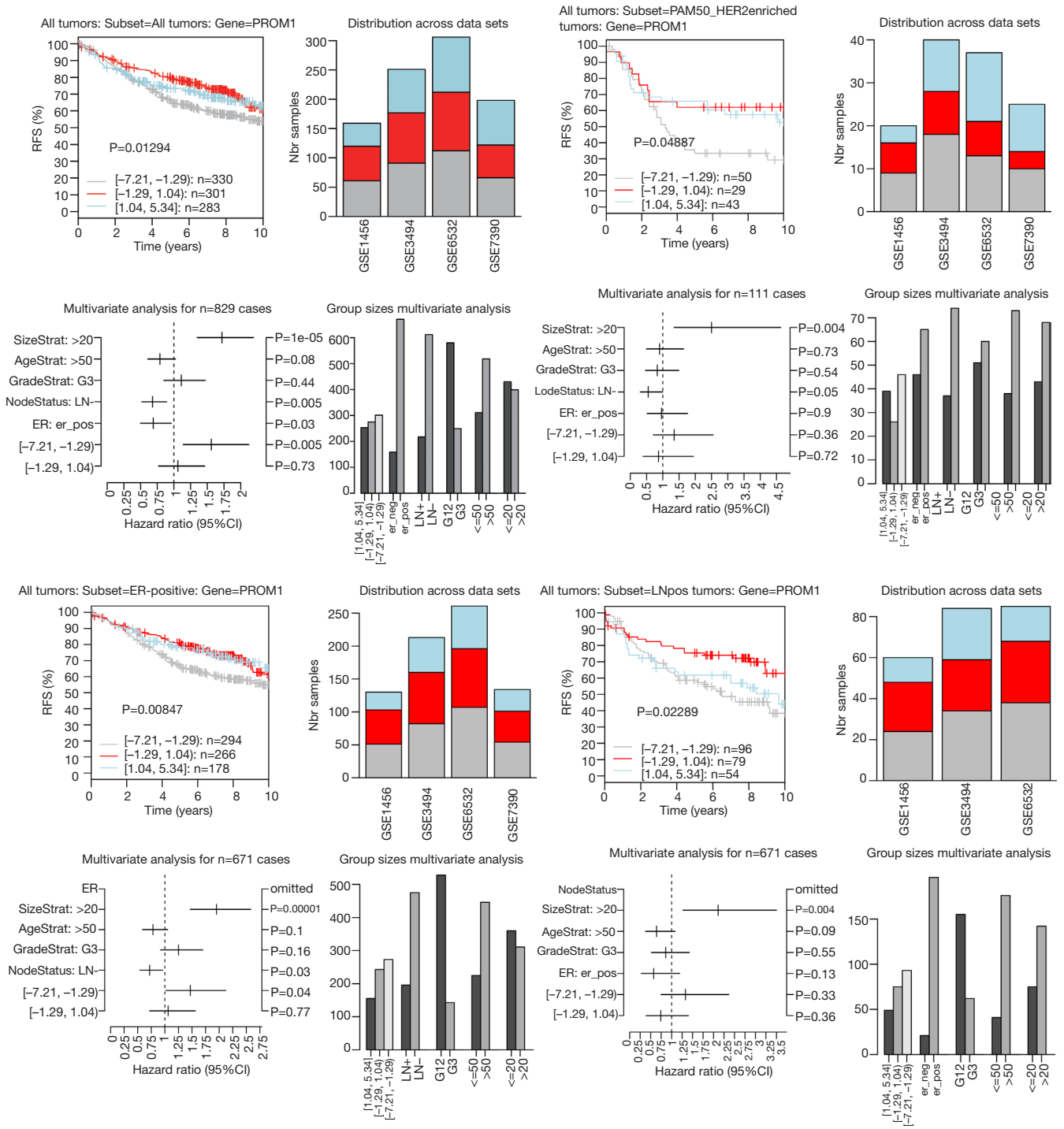

Figure 2 Kaplan Meier analysis of relapse free survival (RFS) in patients with the subtypes of breast cancer expressing high (blue line), intermediate (red line), and low (gray line) *CD133* mRNA.

In summary, based on the results showed above, *CD133* mRNA may be suitable for predicting the prognosis of breast cancer, but not CD133 protein. In this study, we provide an overview of prognostic roles of *CD133* mRNA in the subtypes of breast cancer. It can provide a choice of molecular target therapy in the clinic.

Acknowledgements

Funding: This study was supported by National Natural Scientific Foundation of China (No. 81502558) and Talents Introduction Projects of Liaoning Medical University.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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doi: 10.21037/sci.2017.10.03
Cite this article as: Xia P. *CD133* mRNA may be a suitable prognostic marker for human breast cancer. Stem Cell Investig 2017;4:87.

Supplementary

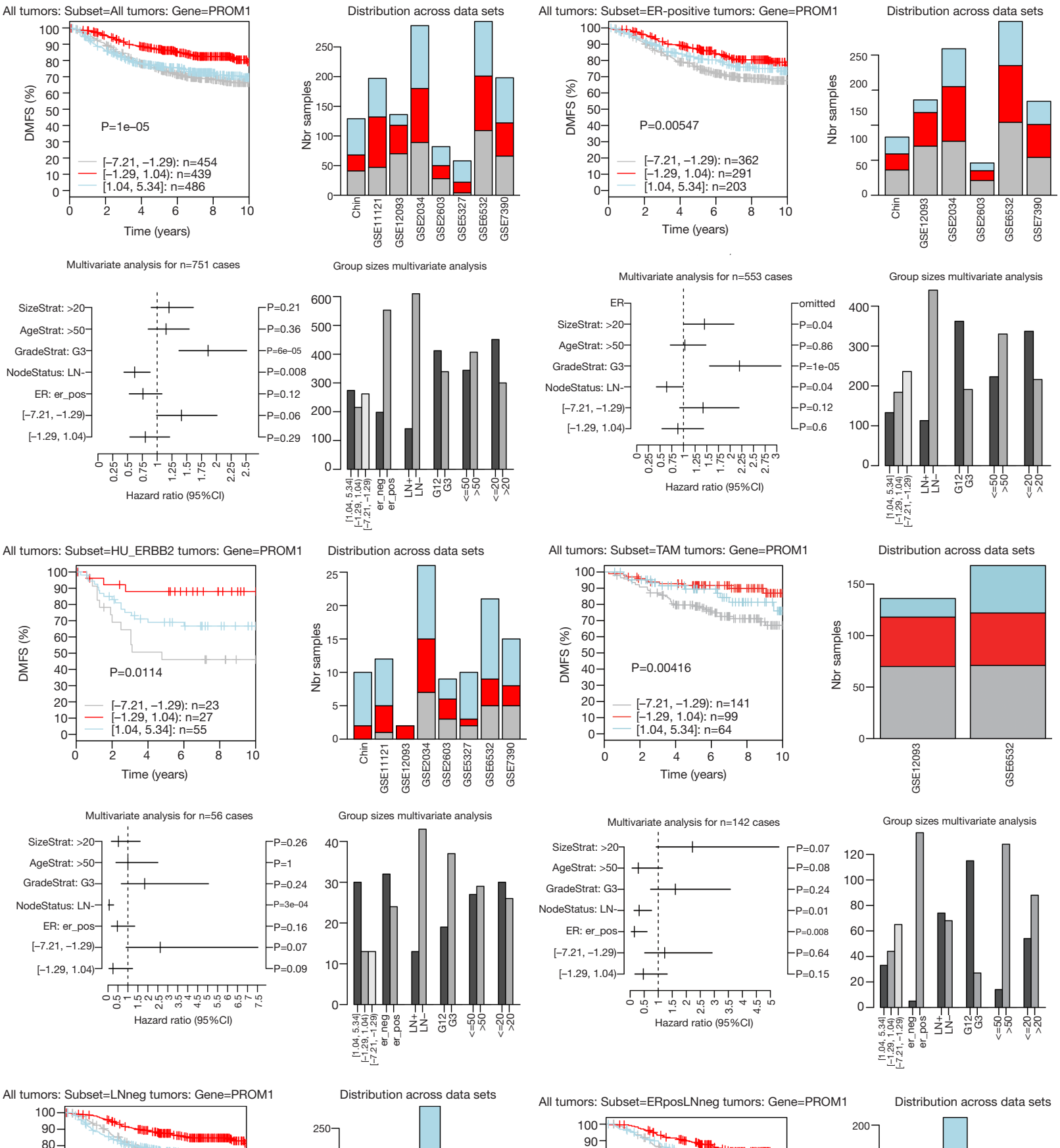

Figure S1 Kaplan Meier analysis of distance metastasis free survival (DMFS) in patients with the subtypes of breast cancer expressing high (blue line), intermediate (red line), and low (gray line) *CD133* mRNA.