A meta- and bioinformatics analysis of maspin expression levels influencing the prognosis of patients with breast cancer

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Abstract. Maspin is a serine protease inhibitor that is encoded by the human SERPINB5 gene. As a tumor inhibitor, it can inhibit the growth of tumor cells, increase adhesion between tumor cells and inhibit tumor angiogenesis. In the present study, a meta- and bioinformatics analysis was performed through the PubMed and China National Knowledge Infrastructure databases including entries added until up to March 20, 2023. It was found that compared with normal breast tissue, maspin expression was downregulated in breast cancer tissue. Maspin expression was negatively associated with lymph node metastasis. According to Kaplan-Meier plotter, it was found that lower maspin expression was negatively associated with the overall and distant metastasis-free survival rate of patients with estrogen receptor-positive, luminal A and grade 2 breast cancer. High expression of maspin was also positively associated with the relapse-free survival rate of patients of the luminal A subtype. Low maspin expression was positively associated with the post-progression and distant metastasis-free survival rate of the progesterone receptor-negative subtype. According to the GEPIA database, SERPINB5 mRNA expression was higher in normal than breast cancer tissues and negatively correlated with the TNM stage. High expression of maspin was also positively associated with the overall survival rate. In the UALCAN database, it was found that the mRNA and promoter methylation levels of SERPINB5 were higher in normal than in breast cancer tissues. These findings suggest that the expression of maspin may serve as a potential marker to indicate the occurrence, subsequent progression and even prognosis of breast cancer.

Introduction

Maspin, a serine protease inhibitor that is encoded by the human SERPINB5 gene, is a tumor suppressor that was discovered in 1994 (1). As a tumor inhibitor, it can impair the growth of tumor cells, increase adhesion between tumor cells and inhibit tumor angiogenesis (2). The SERPINB5 gene is mainly distributed on human chromosome 18q21.3f9, with a cDNA sequence of 2,548 bp and a coding protein containing 375 amino acids. This protein belongs to the serine protease inhibitor superfamily-ovalbumin subfamily, which includes an amino-bound terminal methionine and a carboxyl-bound terminal valine. The eight cysteine residues present in it can form two or more disulfide bonds to form a stable tertiary structure. It has a stable and specific three-dimensional structure that can inhibit the activity of serine protease (3). Maspin inhibits tumor metastasis by reducing the ability of tumor cells to move and invade, increasing intercellular adhesion (4).

Silencing of the maspin gene leads to a decrease in Bax-mediated cell apoptosis and tumor suppression, resulting in a weakened inhibitory effect on cancer cells (5). Maspin can act on fibroblast growth factor and vascular endothelial growth factor, blocking cell mitosis and pipeline formation, inhibiting the transfer of cultured endothelial cells to the matrix and thus inhibiting the growth of tumors in blood vessels (6). Yin *et al* (7) found that maspin delayed Ca^{2+} reduction-induced disengagement through a new interaction with urokinase type plasmin activator/urokinase type plasmin. Endsley *et al* (8) discovered that maspin, as a bridge between the plasmin activator system and β1 integrin, promotes cell adhesion, also in breast epithelial cells. Studies have found that maspin can increase cell adhesion and reduce cell mobility. Maspin can inhibit cell mobility by regulating the activities of G protein Racl and Pakl (p21 active kinase), and regulate cell adhesion through phosphoinositol 3 kinase and extracellular signal regulated kinase pathways (9). It can also inhibit the regulatory effect of urokinase-type plasminogen activator around cells on protein hydrolysis and cell movement, thereby blocking cell infiltration and movement (10). Maspin expression is directly regulated by wild-type p53 and there is a p53 binding site upstream of the maspin promoter. p53 can directly bind to this site to regulate the expression of its mRNA. When wild-type p53 binds to the p53 binding site of maspin, it activates the maspin promoter and enhances transcription (11).

In order to examine the expression of maspin in breast cancer, a meta-analysis was conducted in the present study, and the odds ratio (OR) of risk factors affecting abnormal expression of maspin, including TNM stage and lymph node metastasis, was analyzed. Furthermore, a bioinformatics

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analysis was used to estimate the relationship between maspin expression and prognosis.

Materials and methods

Identification of eligible studies and data extraction. A publication search was performed using PubMed (https://www.ncbi.nlm.nih.gov/) and the China National Knowledge Infrastructure (CNKI; https://www.cnki.net/) database updated on March 20, 2023. The following search terms were used: ('maspin') AND ('breast') AND ('cancer' OR 'carcinoma'). The inclusion criteria were as follows: i) Patients with breast cancer; ii) immunohistochemical staining was used to detect the expression of maspin; and iii) none of the patients received chemotherapy or radiotherapy before surgery. The exclusion criteria for articles were as follows: i) Abstract, case report, meeting abstract or review; ii) protein blotting and reverse transcription PCR (RT-PCR) were used to detect the expression of maspin; and iii) duplicate publications. Meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist (12). The results of Egger's test indicated no significant publication bias in the present meta-analysis.

Data extraction and quality score assessment. The main information in the article was extracted by two reviewers (SS and HYM). As presented in Table I, the main information included in the article was as follows: Name of first author, year of publication, country, antibody supplier, number of cases and controls, expression change and quality assessment score. The quality of the research articles included was independently evaluated by two reviewers based on the Newcastle-Ottawa scale (NOS) (13).

Bioinformatics analysis. The prognostic value of SERPINB5 mRNA expression in breast cancer was evaluated using the Kaplan-Meier plotter database (http://www.kmplot.com). The expression of SERPINB5 mRNA in breast cancer and normal breast tissue and its relationship with clinical characteristics were obtained from the GEPIA (gepia.cancer-pku.cn/) and UALCAN (UALCAN.path.uab.edu/) databases.

Statistical analysis. Revman (version 5.3; the Cochrane Collaboration) was used for meta-analysis. According to the clinicopathological parameters of patients with breast cancer, the ratio and 95% confidence interval were used to estimate the expression of maspin. If heterogeneity was not significant, a fixed-effects model (Mantel-Haenszel method) is used. Otherwise, a random-effects model was used (DerSimonian and Laird methods). The I^2 test was used to quantify heterogeneity effects. Based on three cutoff values (25, 50 and 75%), heterogeneity was classified as low, moderate or high. Funnel plots were used to evaluate publication bias, and Begg's and Egger's tests were used to evaluate compliance with funnel plots. A two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Characteristics of eligible studies. As presented in Fig. 1, 26 articles on the relationship between maspin expression and clinicopathological characteristics of breast cancer evaluated by immunohistochemical methods were retrieved from PubMed and CNKI (14-39). Only 11 of these articles contained an analysis of normal breast tissues (15,17-21,24-28). The clinicopathological parameters included in the articles were lymph node metastasis, TNM staging, estrogen receptor (ER) expression, progesterone receptor (PR) expression and human EGFR2 (HER2) expression.

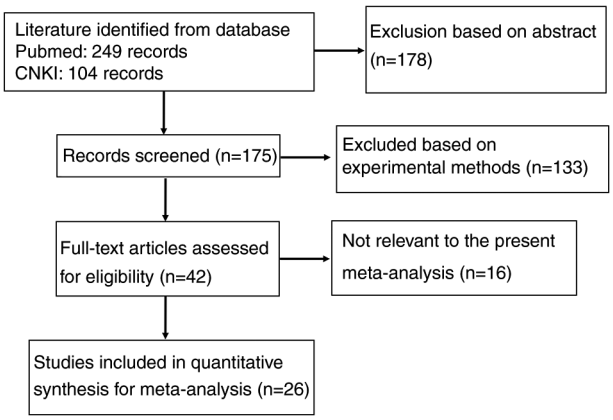

Figure 1. Flow diagram of article selection. CNKI, China National Knowledge Infrastructure.

Forest plot of OR for the association between maspin expression and the clinicopathological parameters of patients with breast cancer. The association between maspin expression and cancer susceptibility of normal breast tissue reported in 11 studies with 818 cancers and 397 controls was analyzed. It was found that maspin expression was downregulated in breast cancer compared with normal breast tissue (P<0.00001, Fig. 2). Maspin expression was not significantly associated with the TNM stage (P>0.05, Table II). Lower maspin expression was found in lymph node metastasis of breast cancer (P<0.05, Table II). Maspin expression was not significantly associated with ER-positive (P>0.05, Table II), PR-positive (P>0.05, Table II) or HER2-positive (P>0.05, Table II) patients with breast cancer.

Publication bias. As indicated in Fig. 3, heterogeneity testing was conducted on the included articles. In the sensitivity analysis, one study was removed from the summary analysis each time and the impact of each single study on the summary results was thereby evaluated. The results of Egger's test indicated no significant publication bias in the present meta-analysis.

Clinicopathological and prognostic significance of SERPINB5 expression in breast cancers. As indicated in Fig. 4, the analysis with the Kaplan-Meier plotter database indicated that lower SERPINB5 expression was positively associated with the overall survival rate of patients with ER-positive (P<0.05, Fig. 4A and B), luminal A (P<0.05, Fig. 4C) and grade 2 (P<0.05, Fig. 4D) breast cancer. Patients with luminal A breast cancer with high SERPINB5 mRNA expression had a longer relapse-free survival time than those with low SERPINB5 expression (P<0.05, Fig. 4E) and until the end of the follow-up time (100-200 months), there was an advantage.

Table I. Main characteristics of eligible studies.

First author	Year	Country	Antibody supplier	Cases, n	Controls, n	Risk of cancer	Quality (NOS standard)	(Refs.)
Liu	2005	China	Santa Cruz Biotechnology, Inc.	137	-	NS	8	(14)
Liu	2004	China	Santa Cruz Biotechnology, Inc.	104	10	Down	8	(15)
Hu	2006	China	MXB Biotechnologies	34	-	NS	8	(16)
Zhang	2014	China	Lab Vision	60	20	Down	8	(17)
Liu	2013	China	Dako	96	25	Down	8	(18)
Sun	2014	China	Nevomarkers	98	96	Down	8	(19)
Yang	2009	China	Mindray	65	12	Down	7	(20)
Ding	2007	China	Lab Vision	82	15	Down	8	(21)
Cao	2006	China	MXB Biotechnologies	40	-	NS	7	(22)
Zhu	2007	China	Novoprotein	57	-	NS	8	(23)
Chen	2015	China	Nevomarkers	60	35	Down	8	(24)
Pei	2011	China	Nevomarkers	53	34	Down	8	(25)
Fang	2009	China	MXB Biotechnologies	30	30	Down	8	(26)
Zhang	2012	China	Nevomarkers	90	90	Down	8	(27)
Zhang	2022	China	MXB Biotechnologies	80	30	Down	8	(28)
Liu	2008	China	Nevomarkers	60	-	NS	8	(29)
Wang	2005	China	BD Pharmingen	21	-	NS	8	(30)
Wakahara	2017	Japan	Leica Biosystems	164	-	NS	7	(31)
Tuncel	2020	Turkey	Abcam	200	-	NS	7	(32)
Feng	2008	China	Lab Vision	80	-	NS	7	(33)
Helal	2017	Egypt	Santa Cruz Biotechnology, Inc.	45	-	NS	7	(34
Lee	2006	China	Nevomarkers	80	-	NS	8	(35)
Kim	2002	Korea	BD Pharmingen	162	-	NS	7	(36)
Umekita	2003	Japan	BD Pharmingen	92	-	NS	7	(37)
Joensuu	2009	Finland	Dako	73	-	NS	7	(38)
Prasad	2009	India	BD Pharmingen	59	-	NS	7	(39)

NOS, Newcastle-Ottawa scale.

The post-progression survival rate of patients with basal-like carcinoma or HER2-positive carcinoma in the SERPINB5 mRNA high expression group was lower than that in the low expression group (P<0.05, Fig. 4F and H), but the opposite was found in patients with PR-negative breast cancer (P<0.05, Fig. 4G). There appeared to be a negative relationship between low SERPINB5 mRNA expression and the distant metastasis-free survival rate of patients with ER-positive (P<0.05, Fig. 4I and J), luminal A (P<0.05, Fig. 4K) and PR-negative (P<0.05, Fig. 4L) breast cancer.

According to the GEPIA database, SERPINB5 mRNA expression was higher in normal tissues than breast cancer (P<0.05, Fig. 5A) and negatively correlated with TNM staging (P<0.05, Fig. 5B). High expression of maspin was also positively associated with the overall survival rate (P<0.05, Fig. 5C). In addition, SERPINB5 mRNA expression was also higher in normal tissues than breast cancer (P<0.05, Fig. 6A) in the UALCAN database. There appeared to be a positive relationship between low SERPINB5 mRNA expression and lymph node metastasis (P<0.05, Fig. 6B), gender (P<0.05,

Table II. Meta-analysis of the association between maspin expression and clinicopathological parameters of patients with breast cancer.

	Heterogeneity		Test for overall effect	
Clinicopathological features	I^2 (%)	P-value	Odds ratio (95% CI)	P-value
TNM staging (I-II/III-IV)	67	<0.001	1.07 (0.69-1.65)	0.770
Lymph node metastasis (LN+/LN-)	60	<0.001	0.36 (0.24-0.54)	<0.001
ER (+/-)	61	0.002	1.26 (0.77-2.07)	0.360
PR (+/-)	70	<0.001	1.08 (0.55-2.09)	0.830
HER2 (+/-)	77	<0.001	1.50 (0.48-4.71)	0.490

TNM, tumor-nodes-metastasis; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human EGFR2.

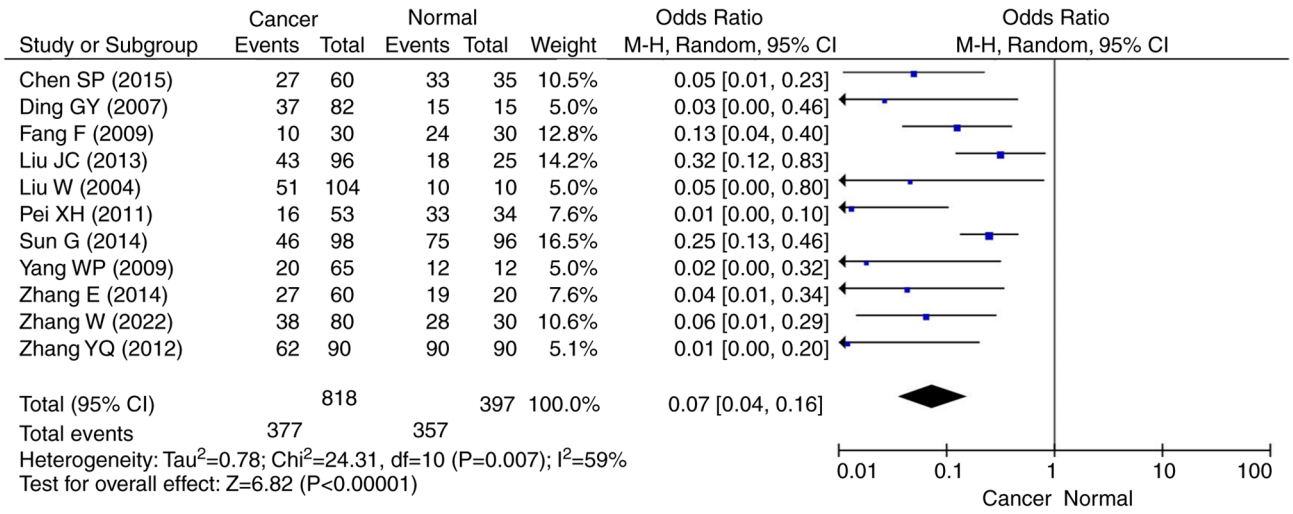

Figure 2. Forest plot of odds ratio for the association between maspin expression and the clinicopathological parameters of patients with breast cancer. Cancer vs. Normal M-H, Mantel-Haenszel; df, degrees of freedom.

Fig. 6C) and tumor protein 53 mutation (P<0.05, Fig. 6D) in patients with breast cancer. The promoter methylation level of SERPINB5 was higher in normal tissue than breast cancer tissue (P<0.05, Fig. 6E). The promoter methylation level of SERPINB5 was also associated with patients' gender (P<0.05, Fig. 6F).

Discussion

The occurrence and development of breast cancer is a process involving multiple genes and steps. The biological characteristics of malignant tumors are invasive growth and metastasis, and its mechanism comprises abnormal changes of gene structure and function in cells caused by genetic defects and epigenetic changes (40). The expression of maspin mRNA in the human breast cancer cell line MDA-M-B-435S is low, but after the treatment with 5-aza-2'-deoxycytidine, the expression of maspin mRNA was significantly increased, which suggests that the decreased expression of maspin in breast cancer cells may, at least in part, be caused by abnormal methylation or deacetylation of the promoter region (41). Maspin can significantly inhibit the proliferation of glioma cells, causing them to stagnate in the S phase, indicating that maspin may have tumor suppressor gene characteristics in glioma. In glioma, the inhibition of maspin expression is related to the methylation of its promoter CpG island; 5-Aza-2'-deoxycitydine (5-aza-dC) was able to restore the transcription of maspin in glioma cell lines (42). When the recombinant maspin gene was used to treat breast cancer cell lines, it was found that their ability to transfer through laminin, type IV collagen and gelatin matrix was significantly lower than that of control cells, and this inhibitory effect could be blocked by maspin antibodies, which showed that maspin is able to increase cell adhesion and inhibit tumor metastasis and growth (9). In order to study the clinicopathological and prognostic significance of maspin in breast cancer, 26 articles that met specific inclusion criteria were analyzed in the present study and the quality of these articles was scored according to the NOS.

Previous studies have found that the synthesis of nitric oxide (NO) in endothelial cells is related to the maspin gene. NO can induce a decrease in maspin expression, thereby reducing the motility and invasiveness of tumor cells and increasing cell apoptosis (43). Khalkhali-Ellis *et al* (44) and

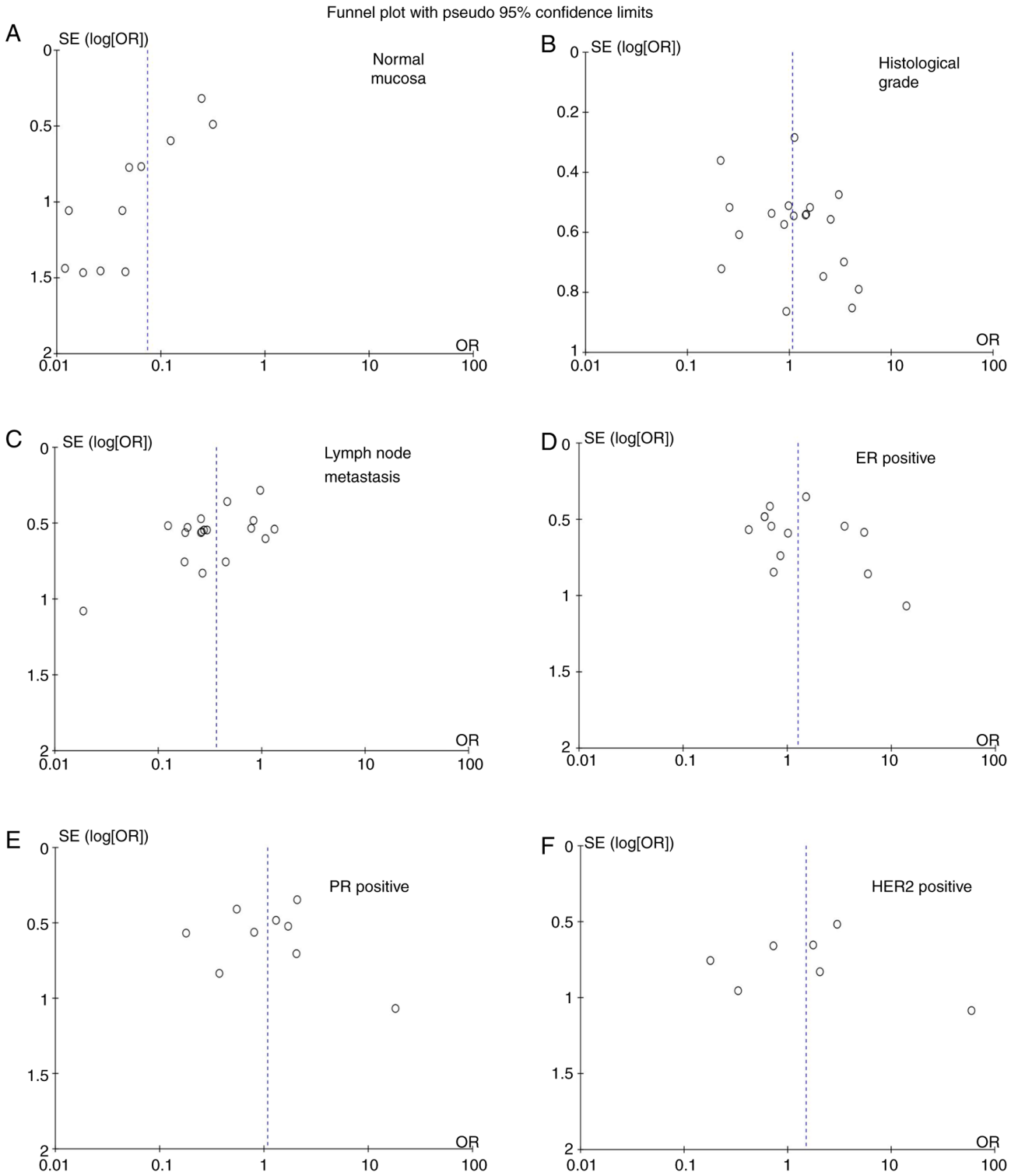

Figure 3. Funnel plot for testing publication bias between maspin expression and breast cancer. (A) Cancer vs. normal, (B) histological grade, (C) lymph node metastasis, (D) ER-positive, (E) PR-positive and (F) HER2-positive. ER, estrogen receptor; PR, progesterone receptor; HER2, human EGFR2; SE, standard error; OR, odds ratio.

Lim *et al* (45) also found that the synthesis of NO is related to maspin gene in breast cancer cells and human neuroepithelial tumor cells. Jiang *et al* (46) proved that γ citric acid can upregulate the expression of maspin and inhibit the motility of colon cancer, breast cancer and melanoma cell lines. Yin *et al* (47) found that glutathione S-transferase interacts most with maspin. After maspin transfection or recombinant maspin protein intervention, breast cancer and prostate cancer cell lines showed higher glutathione S-transferase activity and lower reactive oxygen species products. This effect was reduced when the maspin gene is knocked out or glutathione S-transferase is inhibited, which indicates that the interaction between maspin and glutathione S-transferase may have a role in reducing oxidative stress of cells (47).

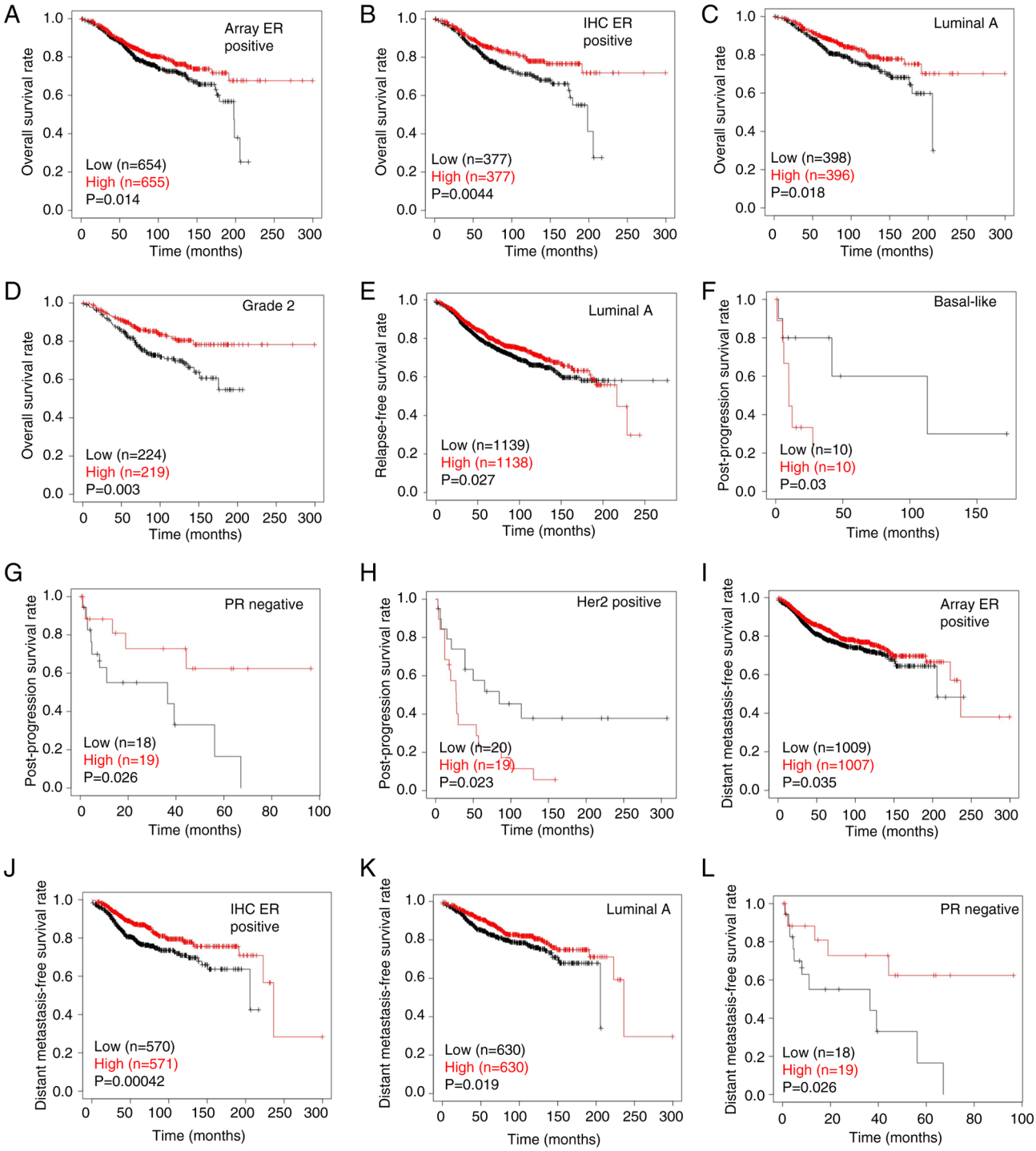

Figure 4. Clinicopathological and prognostic significance of SERPINB5 expression in breast cancers according to the Kaplan-Meier plotter database. Overall survival rate: (A) Array ER-positive, (B) IHC ER-positive, (C) luminal A, (D) grade 2. Relapse-free survival rate: (E) Luminal A. Post-progression survival rate: (F) Basal-like, (G) PR-negative, (H) HER2-positive. Distant metastasis-free survival rate: (I) Array ER-positive, (J) IHC ER-positive, (K) luminal A, (L) PR-negative. ER, estrogen receptor; PR, progesterone receptor; HER2, human EGFR2; IHC, immunohistochemistry.

The expression of maspin protein in oral squamous cell carcinoma is lower than that in normal oral tissue and the low expression of maspin is related to lymph node metastasis in oral squamous cell carcinoma (48). The present meta-analysis found that the low expression of maspin in breast cancer tissue was associated with lymph node metastasis. Maspin gene expression in gastric cancer tissue was significantly lower than that in adenoma tissue and its low expression was significantly associated with histological type, tumor stage and invasion depth, indicating that loss of the maspin gene is associated with the occurrence and progression of gastric cancer. At the same time, it was found that when the methylation inhibitor 5-aza-2'-deoxycytidine was used to treat eight gastric cancer cell lines with the loss of maspin gene expression, re-expression of the maspin gene was found in five cell lines, indicating that DNA methylation has a role in the loss of maspin gene expression, which led to tumor progression and invasion (49). Zheng *et al* (50) found through bioinformatics

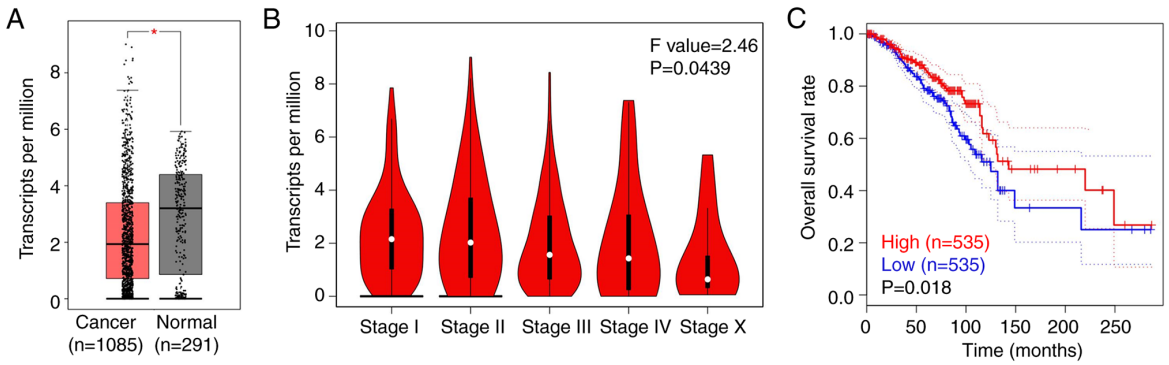

Figure 5. Clinicopathological and prognostic significance of SERPINB5 expression in breast cancers according to the GEPIA databases. SERPINB5 mRNA expression was (A) higher in normal than in breast cancer tissues, and (B) negatively correlated with the TNM stage. (C) High expression of maspin was also positively associated with the overall survival rate. *P<0.05.

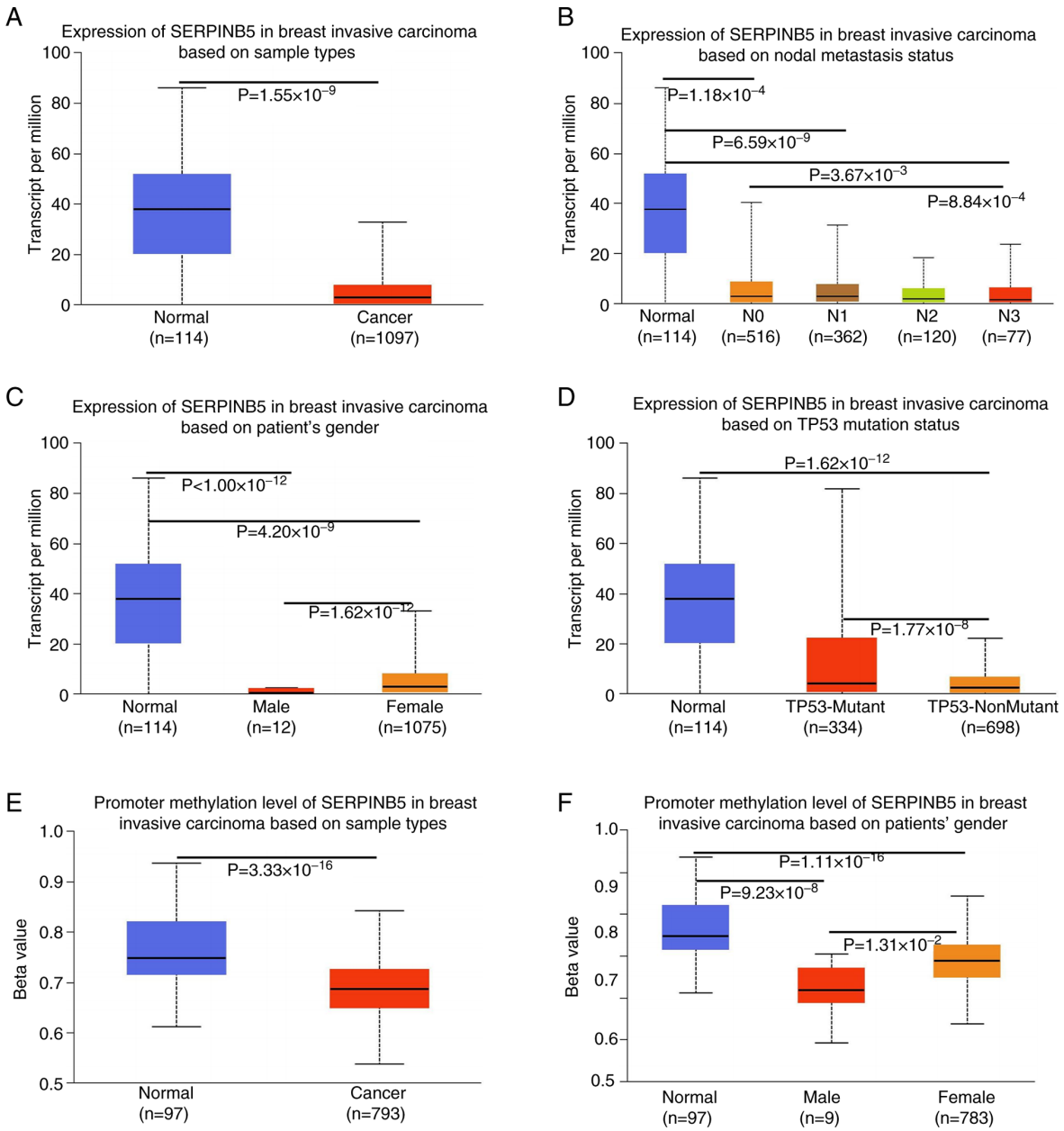

Figure 6. Clinicopathological and prognostic significance of SERPINB5 expression in breast cancers according to the UALCAN database. (A) SERPINB5 mRNA expression was higher in normal than in breast cancer tissues. Relationship between SERPINB5 mRNA expression and (B) lymph node metastasis, (C) gender and (D) TP53 mutation in patients with breast cancer. (E) Promoter methylation level of SERPINB5 in normal and breast cancer tissue. (F) Association of promoter methylation level of SERPINB5 with patients' gender. TP53, tumor protein 53.

databases that the expression of maspin in gastric cancer tissue was lower than that in normal gastric tissue. Through the UALCAN database, it was found that the methylation level of SERPINB5 promoter of maspin in normal tissues was higher than that in breast cancer tissues. The results of this study are thus consistent with those of other studies.

Maspin expression levels gradually decrease in normal endometrium, atypical endometrial hyperplasia and endometrial cancer. As the level of malignant biological behavior in endometrial cancer increases, the expression of maspin decreases. At the same time, maspin protein is lowly expressed in endometrial cancer with high pathological staging and poor differentiation, and vice versa (51). According to research, overexpression of maspin is associated with better overall survival in esophageal and oral squamous cell carcinoma (52,53). Zheng *et al* (50) found that SERPINB5 mRNA expression is positively associated with overall survival and progression-free survival in patients with gastric cancer, and even after stratification based on clinical and pathological characteristics. The results of the present bioinformatics analysis showed that the expression of maspin mRNA was positively associated with the overall survival rate of patients with breast cancer. This is contrary to the report by Lu *et al* (54) on lung adenocarcinoma. This abnormal phenomenon may be due to different methods: Bioinformatics analysis is based on cDNA arrays, while Lu's experiment is based on RT-PCR. As for the prognostic significance of maspin expression in breast cancer, more cases of breast cancer are crucial for future research.

In conclusion, at the protein and mRNA levels, maspin is lowly expressed in breast cancer tissue and is negatively associated with lymph node metastasis of breast cancer. High expression of maspin mRNA is positively associated with the overall survival rate of patients with breast cancer. Low expression of maspin may be a good potential marker for poor prognosis of patients with breast cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SS and ZGZ designed the study. SS and HYM prepared figures and tables, interpreted the data and wrote the main manuscript. JS and YZS participated in the research of the study and performed the statistical analysis. ZGZ and SS confirm the authenticity of the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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