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ORIGINAL RESEARCH

The prognostic significance of protein tyrosine phosphatase 4A2 in breast cancer

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Abstract: Although *PTP4A3* has been shown to be a very important factor in promoting cancer progression, the role of its close family member *PTP4A2* is still largely unknown. Recent reports have shown contradicting results on the role of *PTP4A2* in breast cancer progression. Considering this, we aimed to investigate the prognostic value of *PTP4A2* in five independent breast cancer data sets (minimum 198 patients per cohort, totaling 1,124 patients) in the Gene Expression Omnibus Database. We found that high expression of *PTP4A2* was a favorable prognostic marker in all five independent breast cancer data sets, as well as in the combined cohort, with a hazard ratio of 0.68 (95% confidence interval =0.56–0.83; $P<0.001$). Low *PTP4A2* expression was associated with estrogen receptor-negative tumors and tumors with higher histological grading; furthermore, low expression was inversely correlated with the expression of genes involved in proliferation, including *MKI67* and the *MCM* gene family encoding the minichromosome maintenance proteins. These findings suggest that *PTP4A2* may play a role in breast cancer progression by dysregulating cell proliferation. *PTP4A2* expression was positively correlated with *ESR*1, the gene encoding estrogen receptor-alpha, and inversely correlated with *EGFR* expression, suggesting that *PTP4A2* may be involved in these two important oncogenic pathways. Together, our results suggest that expression of *PTP4A2* is a favorable prognostic marker in breast cancer.

Keywords: breast cancer, PTP4A2, survival, prognostic marker, overexpression, minichromosome maintenance proteins

Introduction

The protein tyrosine phosphatase (PTP) family consists of PRL-1, PRL-2, and PRL-3, which are encoded by the *PTP4A1*, *PTP4A2*, and *PTP4A3* genes, respectively. Zeng et al[1] were the first to identify *PTP4A2* and *PTP4A3*, owing to their homology to *PTP4A1*; subsequently, the same group[2] showed that *PTP4A1* and *PTP4A3* could both promote cell migration, invasion, and metastasis. Recently, the molecular mechanisms for *PTP4A3*-mediated cancer progression have been studied and revealed,[3] with roles in the promotion of epithelial–mesenchymal transition,[4] angiogenesis,[5] cell cycle regulation,[6] and autophagy[7] having been discovered. Although overexpression of *PTP4A3* has been consistently shown to promote cancer progression in multiple types of cancer, there are very few reports on the role of *PTP4A2* in cancer progression.[8]

Overexpression of *PTP4A2* was shown to promote breast tumor formation in a mouse model.[9] However, two studies[10,11] have shown that *PTP4A2* was not differentially expressed between normal, benign, and cancerous tissues of the breast, while two other recent publications[12,13] demonstrated that increased expression of *PTP4A2* was correlated with a favorable overall and disease-free survival. These contradictory findings on the role of *PTP4A2* in breast cancer progression led us to investigate the prognostic significance of *PTP4A2* gene expression in five publicly

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available breast cancer data sets, each comprising at least 198 patients. We have assessed the association between *PTP4A2* expression and proliferation markers including *MKI67* and the *MCM* gene family encoding the minichromosome maintenance proteins, which were previously shown to confer prognostic significance in breast cancer patients.[14]

Materials and methods

Extraction of clinical and microarray gene expression data from breast cancer patient data sets

Five breast cancer patient data sets, GSE2034,[15] GSE3494,[16] GSE7390,[17] GSE11121,[18] and GSE12276[19] were identified in the Gene Expression Omnibus (GEO) database using the following inclusion criteria: data sets compiled using the HG-U133 microarray platform, comprising >180 patients, and for whom relapse or survival data were available. Microarray gene expression data were retrieved from the data matrices deposited in the GEO database by the original authors. R scripting was used to extract the expression values from probe sets of genes of interest, and the clinical data from the data matrices was downloaded from GEO as previously described.[20]

Correlations of gene expression levels and clinical data

All statistical analyses were performed using SPSS19.0. The associations between expression level of *PTP4A2* and clinical characteristics of the tumor, including estrogen receptor (ER) status and histological grade, and that between expression level of *PTP4A2* and expression of *MCM2-7* were tested by analysis of variance. The correlations between expression levels of *PTP4A2* and *MKI67*, *PTP4A2* and *ESR1* (the gene encoding ER-alpha), and *PTP4A2* and *EGFR* (gene encoding epidermal growth factor receptor) were tested by the Spearman's rank test. Expression levels of *PTP4A2* were divided into high and low levels using lower quartile expression level as the cutoff point for survival analysis. For Kaplan–Meier survival analysis, results were compared by the Wilcoxon–Gehan test.

Identification of genes coexpressed with *PTP4A2*

Patients were stratified into two groups based on their expression levels of *PTP4A2*. The gene expression patterns of patients in the *PTP4A2*-low subgroup and those in the *PTP4A2*-high subgroup were compared. Probe sets that were differentially expressed between these two subgroups were identified by the two-sample Welch's *t*-test. This test was used to avoid the type I error that can arise due to unequal variances of the values of probe sets between subgroups. Briefly, a Welch's *t*-test was applied to each probe set corresponding to a certain gene in the data matrix using our own Java application MyStats. *P*-values and the differential expression in fold changes for all the probe sets were generated as tab-delimited worksheets of Excel for further analysis. The genes were prioritized by ascending *P*-values.

Results

The association between *PTP4A2* expression level and survival in breast cancer patients

As shown in Figure 1, a low-level expression of *PTP4A2* was consistently (and in four of the five cohorts, significantly) associated with a shorter survival time in the breast cancer data sets tested. In cohort GSE2034, patients whose tumors expressed *PTP4A2* at a high level had a mean relapse-free survival time of 10.2 years, while those whose tumors expressed *PTP4A2* at a low level had a mean relapse-free survival time of 8.4 years (Wilcoxon–Gehan test, P=0.006; Figure 1A). In cohort GSE3494, patients whose tumors expressed *PTP4A2* at a high level had a mean disease-specific survival time of 10.7 years, while those whose tumors expressed *PTP4A2* at a low level had a mean disease-specific survival time of 9.5 years (P=0.191; Figure 1B). In cohort GSE7390, patients whose tumors expressed *PTP4A2* at a high level had a mean survival time of 19.7 years, while those whose tumors expressed *PTP4A2* at a low level had a mean survival time of 15.7 years (P=0.001; Figure 1C). In cohort GSE11121, patients whose tumors expressed *PTP4A2* at a high level had a mean distant metastasis-free survival time of 15.7 years, while those whose tumors expressed *PTP4A2* at a low level had a mean distant metastasis-free survival time of 11.9 years (P=0.006; Figure 1D). In cohort GSE12276, patients whose tumors expressed *PTP4A2* at a high level had a mean survival time of 2.4 years, while those whose tumors expressed *PTP4A2* at a low level had a mean survival time of 1.4 years (P<0.001; Figure 1E). Our results suggest that a low-level expression of *PTP4A2* is associated with a shorter survival time in breast cancer patients.

The association between the expression of *PTP4A2* and ER status

ER is a key biomarker in breast cancer, its status being associated with the efficacy of hormonal therapy. We analyzed

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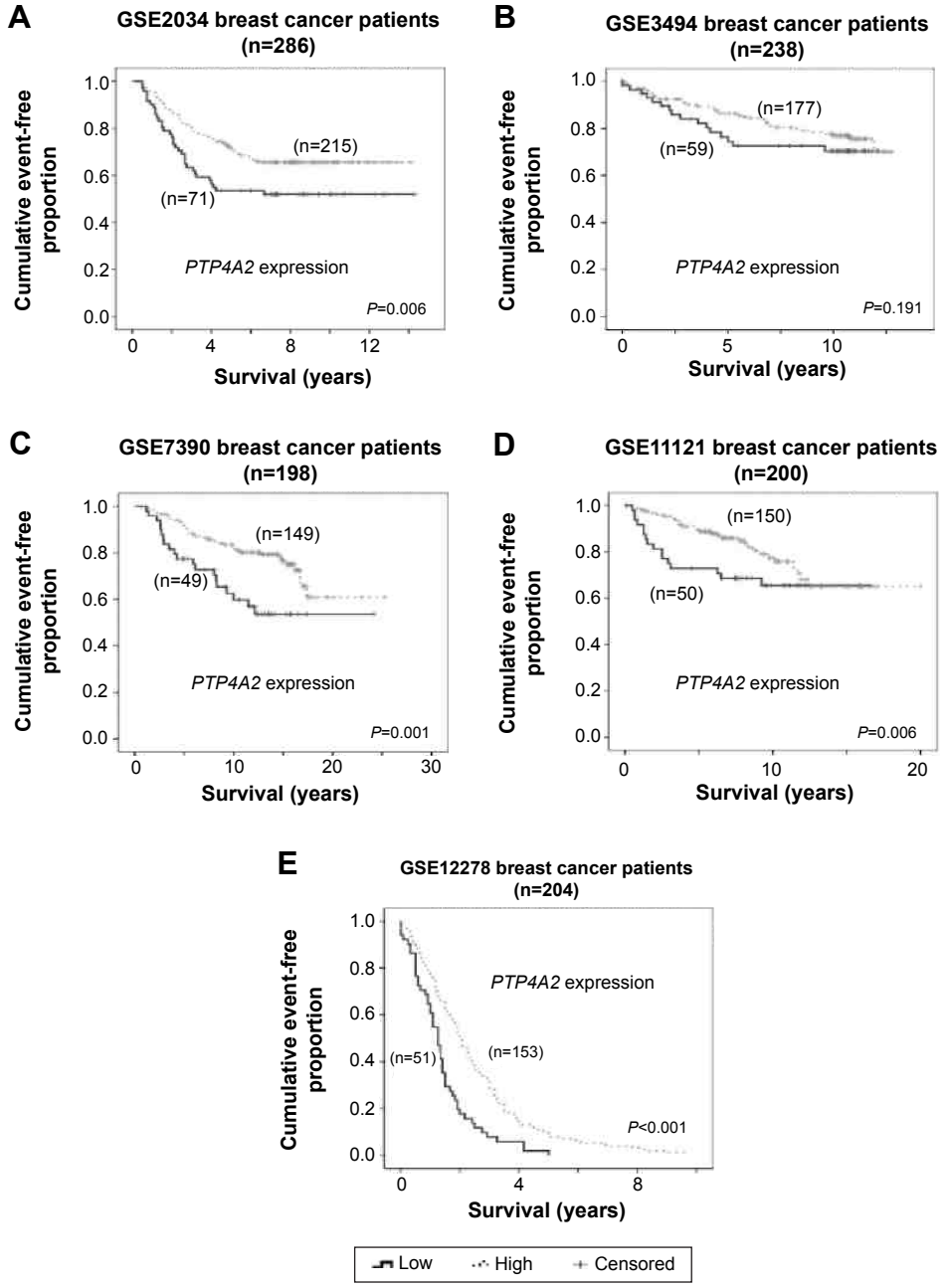

Figure 1 The association between *PTP4A2* expression and patient survival.
Notes: Kaplan–Meier curves for *PTP4A2* expression in (**A**) GSE2034, (**B**) GSE3494, (**C**) GSE7390, (**D**) GSE11121, and (**E**) GSE12276 breast cancer data sets.
Abbreviation: *PTP4A2*, protein tyrosine phosphatase 4A2.

all three cohorts for which patient ER status was known to investigate whether *PTP4A2* expression level varied between patients with ER-positive and those with ER-negative disease. In cohort GSE2034, the 77 ER-negative tumors had significantly lower level of expression of *PTP4A2* compared to the 209 ER-positive tumors ($P<0.001$; Figure 2A). In cohort GSE3494, the 31 ER-negative tumors had significantly lower level of expression of *PTP4A2* compared to the 201 ER-positive tumors ($P<0.001$; Figure 2B). In cohort GSE7390, the 64 ER-negative tumors had significantly lower level of expression of *PTP4A2* compared to the 134 ER-positive tumors ($P<0.001$; Figure 2C). Because ER-negative breast tumors are more aggressive and have a poorer prognosis,[21] and considering that we have observed high *PTP4A2* to be a favorable prognostic marker, it is unsurprising that low *PTP4A2* correlates with ER-negative status.

Interestingly, *ESR1* was identified as one of the genes being coexpressed with *PTP4A2* in all the five

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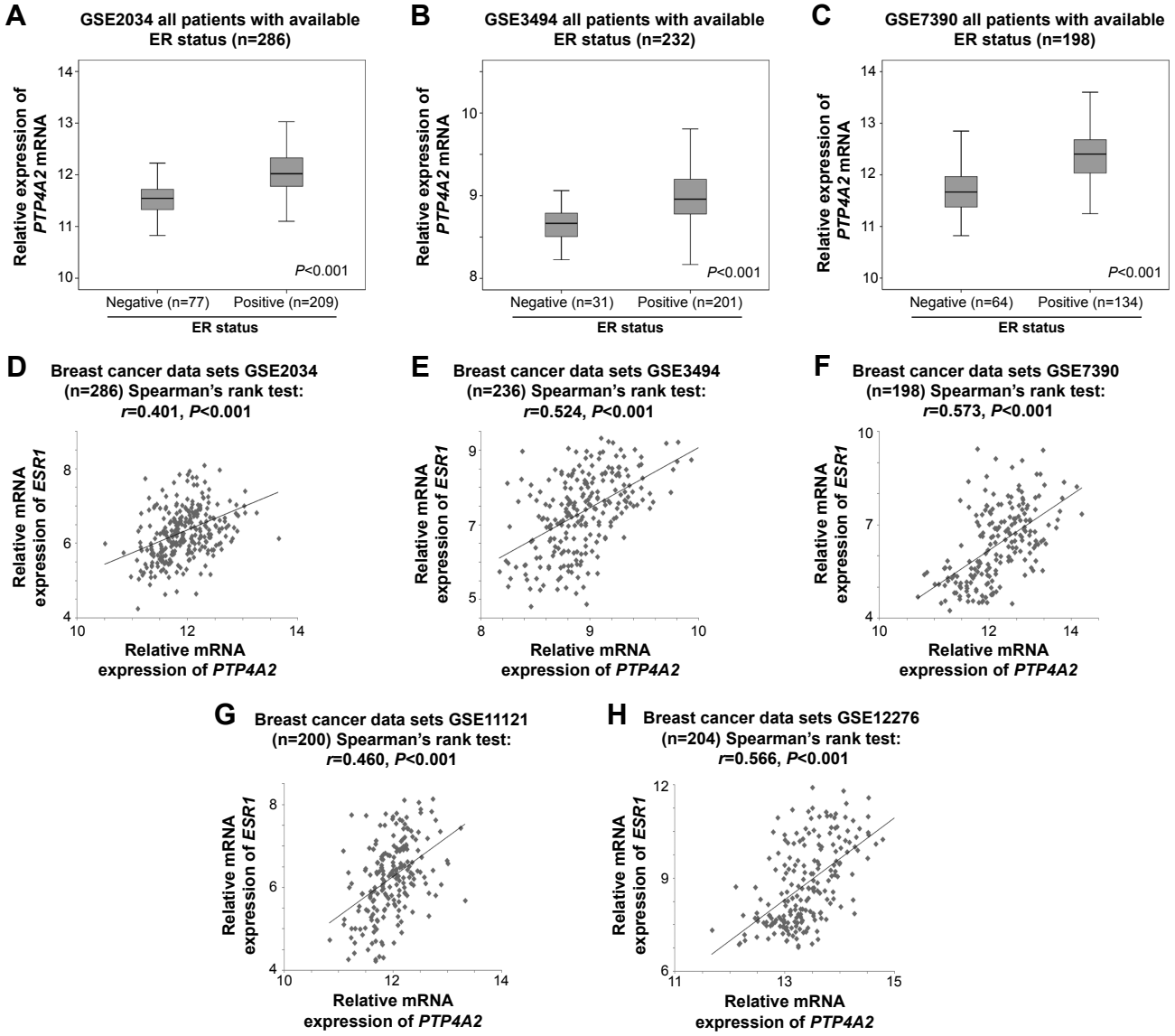

Figure 2 The association between *PTP4A2* expression and the ER status and expression.

Notes: Box plots of *PTP4A2* expression in tumors with different ER statuses in (**A**) GSE2034, (**B**) GSE3494, and (**C**) GSE7390 breast cancer data sets. Scatter plots for *PTP4A2* expression against *ESR1* expression in (**A**) GSE2034, (**B**) GSE3494, (**C**) GSE7390, (**D**) GSE2034, (**E**) GSE3494, (**F**) GSE7390, (**G**) GSE11121, and (**H**) GSE12276 breast cancer data sets.

Abbreviations: ER, estrogen receptor; *ESR1*, the gene encoding estrogen receptor-alpha; *PTP4A2*, protein tyrosine phosphatase 4A2.

breast cancer data sets. The expression levels of *PTP4A2* and *ESR1* were significantly correlated in GSE2034 (r=0.401, P<0.001; Figure 2D), GSE3494 (r=0.524, P<0.001; Figure 2E), GSE7390 (r=0.573, P<0.001; Figure 2F), GSE11121 (r=0.460, P<0.001; Figure 2G), and GSE12276 (r=0.566, P<0.001; Figure 2H) breast cancer data sets. Because ER-negative tumors had a lower expression of *PTP4A2*, while *ESR1* and *PTP4A2* expression was positively significantly correlated, our results suggest that *ESR1* and *PTP4A2* may be regulated in series or parallel in the same pathway.

The association between *PTP4A2* expression level and histological grade

Histological grade is another important prognostic factor in breast cancer.[22] Here, we also investigated the association between the expression level of *PTP4A2* and the histological grading of the tumors in the three cohorts for which tumor grade had been documented. As shown in Figure 3, *PTP4A2* expression was significantly lower in grade 3 tumors compared to those tumors with lower grading in GSE3494 (P=0.012; Figure 3A), GSE7390 (P<0.001; Figure 3B), and GSE11121 (P=0.009; Figure 3C), all the three breast cancer

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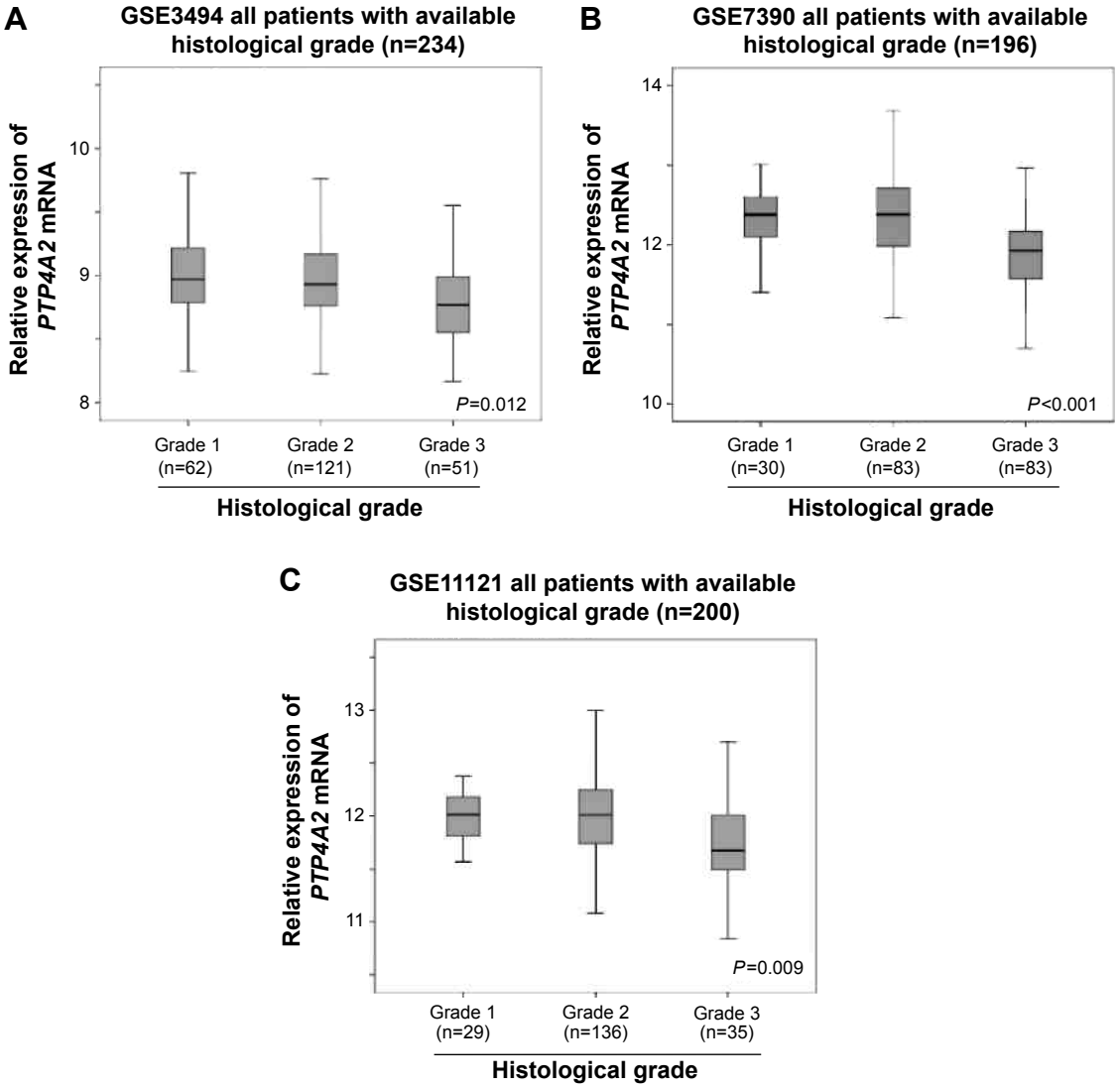

Figure 3 The association between *PTP4A2* expression and histological grading.
Notes: Box plots of *PTP4A2* expression in tumors with different histological grades in (**A**) GSE3494, (**B**) GSE7390, and (**C**) GSE11121 breast cancer data sets.
Abbreviation: *PTP4A2*, protein tyrosine phosphatase 4A2.

data sets with histological grading available in GEO database. The results suggest that *PTP4A2* expression is downregulated in breast tumor with increasing histological grading.

The association between *PTP4A2* expression and the expression of proliferation-related genes

Next, to further elucidate the role of *PTP4A2* in breast cancer progression, we investigated whether *PTP4A2* expression is correlated with the expression of proliferation-related genes. It has been previously shown that *MKI67* is an important prognostic and predictive biomarker in breast cancer.[23] In the present study, we investigated the correlation between the expression levels of *PTP4A2* and *MKI67*. As shown in Figure 4, the expression level of *PTP4A2* was inversely correlated with the expression level of *MKI67* in breast cancer specimens in GSE2034 (r=–0.354, P<0.001; Figure 4A), GSE3494 (r=–0.208, P=0.001; Figure 4B), GSE7390 (r=–0.434, P<0.001; Figure 4C), GSE11121 (r=–0.321, P<0.001; Figure 4D), and GSE12276 (r=–0.271, P<0.001; Figure 4E) breast cancer data sets.

The MCM proteins play an important role in the regulation of cell proliferation and the initiation of DNA synthesis,[24] and we have previously shown that members of the *MCM* gene family, when considered together, were a robust indicator of poor prognosis in breast cancer.[14] In the present study, we investigated the correlation between the expression level of *PTP4A2* and *MCM* gene family overexpression in the five breast cancer cohorts. As shown in Figure 5, the expression

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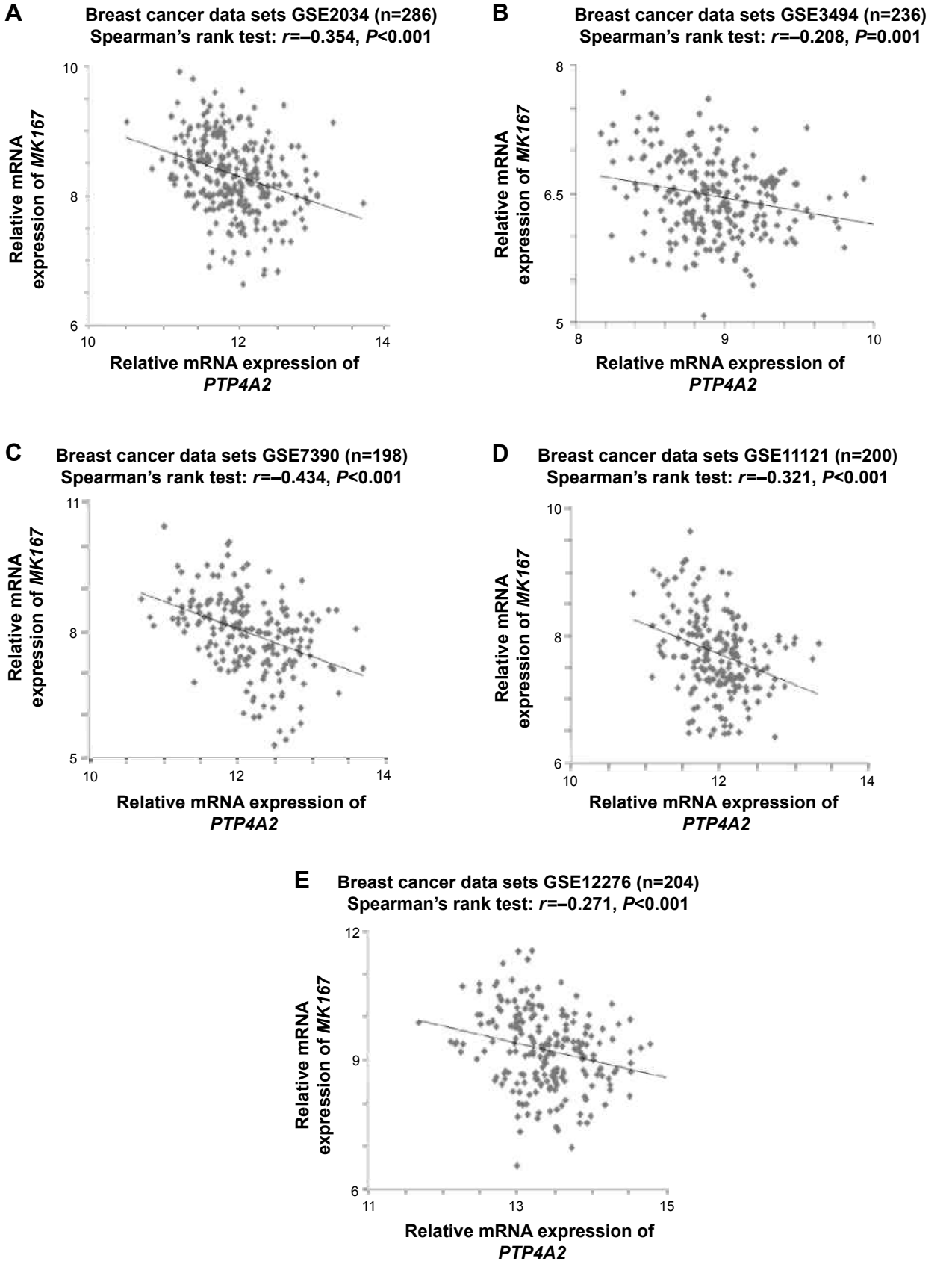

Figure 4 The correlations between *PTP4A2* expression and *MKI67* expression.
Notes: Scatter plots for *PTP4A2* expression against *MKI67* expression in (**A**) GSE2034, (**B**) GSE3494, (**C**) GSE7390, (**D**) GSE11121, and (**E**) GSE12276 breast cancer data sets.
Abbreviations: *MKI67*, marker of proliferation Ki-67; *PTP4A2*, protein tyrosine phosphatase 4A2.

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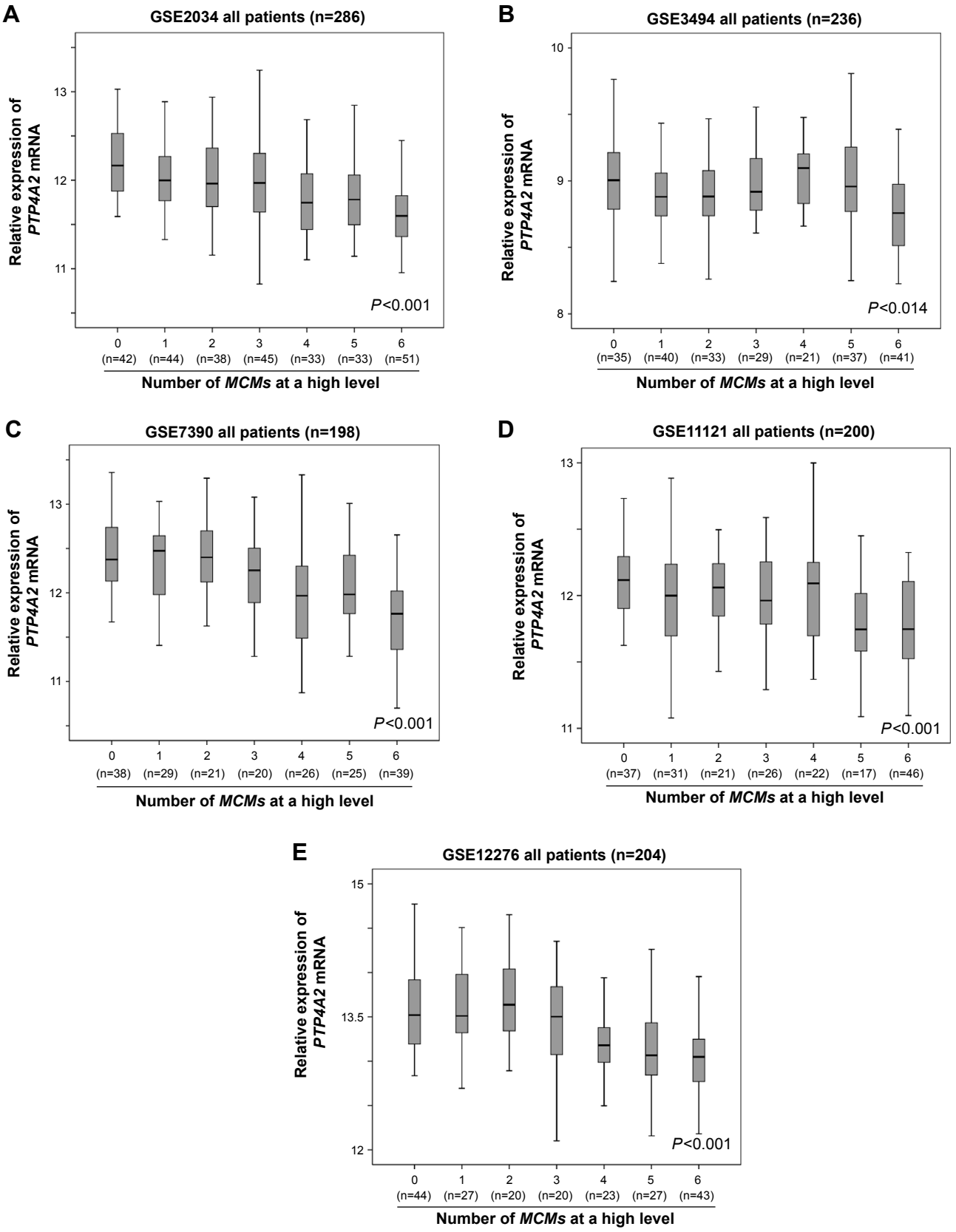

Figure 5 The association between *PTP4A2* expression and the number of overexpressed *MCM* genes.

Notes: Box plots of *PTP4A2* expression in tumors with increasing number of overexpressed *MCM* genes in (**A**) GSE2034, (**B**) GSE3494, (**C**) GSE7390, (**D**) GSE11121, and (**E**) GSE12276.

Abbreviations: *MCM*, minichromosome maintenance; *PTP4A2*, protein tyrosine phosphatase 4A2.

level of *PTP4A2* decreased as the number of *MCM* genes expressed at a high level increased in cohorts GSE2034 ($P<0.001$; Figure 5A), GSE3494 ($P=0.014$; Figure 5B), GSE7390 ($P<0.001$; Figure 5C), GSE11121 ($P<0.001$; Figure 5D), and GSE12276 ($P<0.001$; Figure 5E).

The prognostic significance of *PTP4A2* in patients with different ER statuses or histological grading

Because *PTP4A2* expression was shown to be associated with survival and ER status, we further investigated whether the prognostic value of *PTP4A2* is dependent on the ER status of the tumors. The five data sets were combined to increase the sample size and the statistical power to detect significant differences. In the combined data set, patients whose tumors expressed *PTP4A2* at a low level had a mean survival time of 12.9 years, which was significantly shorter than those patients whose tumors expressed *PTP4A2* at a high level, whose mean event-free survival time was 15.1 years ($P<0.001$; Figure 6A).

The prognostic significance of *PTP4A2* was further analyzed in the 716 (out of 1,124) patients for whom the

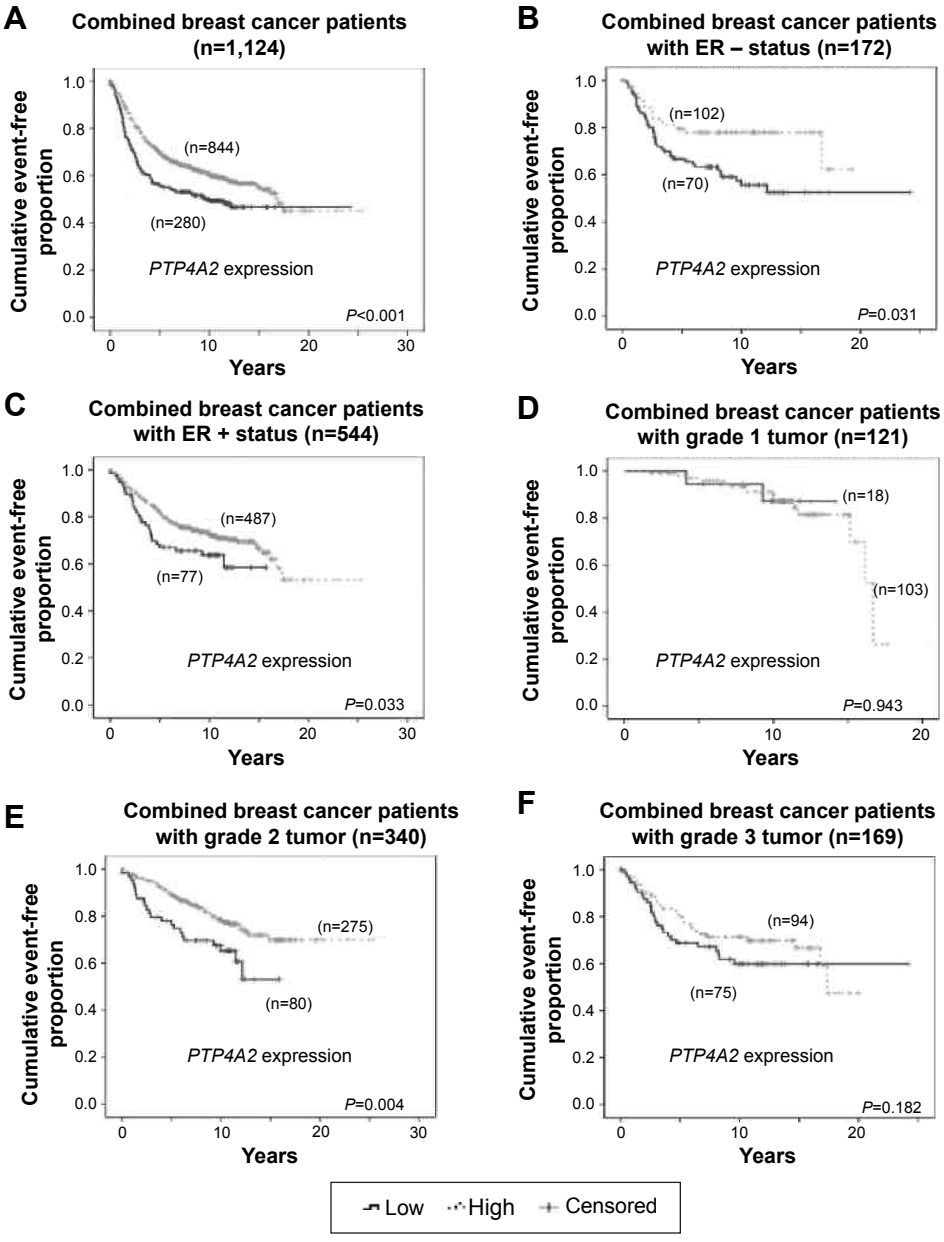

Figure 6 The association between *PTP4A2* expression and survival in patients stratified on clinicopathological parameters.
Notes: Kaplan–Meier curves for *PTP4A2* expression in the combined breast cancer data set for (**A**) the entire combined cohort, (**B**) patients with ER-negative tumors, (**C**) patients with ER-positive tumors, (**D**) patients with grade 1 tumors, (**E**) patients with grade 2 tumors, and (**F**) patients with grade 3 tumors.
Abbreviations: ER, estrogen receptor; *PTP4A2*, protein tyrosine phosphatase 4A2.

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ER status was known. In the 172 patients with ER-negative tumors, those patients whose tumors expressed *PTP4A2* at a low level had a significantly shorter event-free survival time than those whose tumors expressed *PTP4A2* at a high level (P=0.031; Figure 6B). Similarly, in the 544 patients with ER-positive status, those patients whose tumors expressed *PTP4A2* at a low level had a significantly shorter event-free survival time compared to those whose tumors expressed *PTP4A2* at a high level (P=0.033; Figure 6C).

The prognostic significance of *PTP4A2* was also analyzed in the 630 patients for whom tumor histological grade was known. In the 121 and 169 patients with grade 1 and 3 tumors, respectively, the event-free survival time was not significantly different between patients whose tumors expressed *PTP4A2* at a high level and those whose tumors expressed *PTP4A2* at a low level (Figure 6D and F). In the 340 patients with grade 2 tumors, those patients whose tumors expressed *PTP4A2* at a low level had a significantly shorter event-free survival time compared to those whose tumors expressed *PTP4A2* at a high level (P=0.004; Figure 6E).

The correlation between *PTP4A2* and *EGFR* expression

Considering that *EGFR* is known to regulate *PTP4A3*,[25] we aimed to determine whether *PTP4A2* and *EGFR* are coexpressed in breast cancer. As shown in Figure 7, the expression level of *PTP4A2* was inversely correlated with the expression level of *EGFR* in all five breast cancer data sets analyzed, including GSE2034 (r=–0.364, P<0.001; Figure 7A), GSE3494 (r=–0.475, P<0.001; Figure 7B), GSE7390 (r=–0.447, P<0.001; Figure 7C), GSE11121 (r=–0.468, P<0.001; Figure 7D), and GSE12276 (r=–0.394, P<0.001; Figure 7E).

Discussion

In the present study, we have demonstrated that *PTP4A2* expression is a favorable prognostic marker for breast cancer patients. A low-level expression of *PTP4A2* was associated with ER-negative tumor status, while *PTP4A2* expression level was positively correlated with *ESR1* expression level, suggesting that *PTP4A2* may be regulated by the ER pathway. However, the prognostic significance of *PTP4A2* was independent of tumor ER status. In addition, we found that *PTP4A2* expression level was significantly lower in breast cancers with high histological grade, and that *PTP4A2* expression was only significantly predictive of survival in patients with grade 2 tumors. On the other hand, *PTP4A2* expression was inversely correlated with that of proliferation-associated genes, including *MKI67* and *MCM2–7*. Finally, we have putatively identified *EGFR* as a gene coexpressed with *PTP4A2* in all five breast cancer data sets, suggesting that *PTP4A2* may be involved in the *EGFR* pathway.

The prognostic significance of *PTP4A2* is controversial because some reports suggest that *PTP4A2* promotes breast cancer progression,[9] while others suggest that *PTP4A2* plays an opposite role suppressing breast cancer progression.[12,13] Considering these contradicting reports, we tested the prognostic significance of *PTP4A2* in five large breast cancer data sets available in the GEO database. The results are highly consistent between these five breast cancer data sets, showing that a low-level expression of *PTP4A2* mRNA was associated with a shorter event-free survival time, therefore suggesting that *PTP4A2* expression is a favorable prognostic marker.

The regulation of *PTP4A2* during breast cancer progression is largely unknown. In the present study, we have revealed two pathways that could potentially regulate *PTP4A2*. The first one is the ER pathway, wherein *PTP4A2* expression was significantly higher in ER-positive tumors than in ER-negative tumors, and its expression was positively correlated with that of ER-alpha gene (*ESR1*). On the other hand, *PTP4A2* expression was inversely correlated with *EGFR*. Our results warrant further analysis to investigate in vitro whether *PTP4A2* is downstream of these two important pathways.

The observation of an association between increased expression of *PTP4A2* and decreased expression of proliferation genes provides further insight into the possible mechanism for the role of *PTP4A2* during cancer progression; alternatively, it is possible that *PTP4A2* is a driver that inhibits proliferation of breast cancer cells, while it is also possible that downregulation of *PTP4A2* is only a by-product of the dysregulated proliferation in breast cancer. Nonetheless, this result was consistent with the observation that *PTP4A2* expression is a favorable prognostic marker in breast cancer.

One limitation of our study is that, as protein expression data are not available in the tested cohorts, our study is limited to the analysis of mRNA levels of *PTP4A2*; investigation on PRL-2 protein expression in a breast cancer cohort is required to validate our results and confirm the prognostic significance of *PTP4A2*.

In conclusion, the prognostic significance of *PTP4A2* has been demonstrated with a high consistency. Because of the conflicting data presented previously, our study has provided convincing information that *PTP4A2* expression is a favorable prognostic marker. Nevertheless, further investigations on how *PTP4A2* is regulated and the molecular mechanisms driven by *PTP4A2* in breast cancer progression

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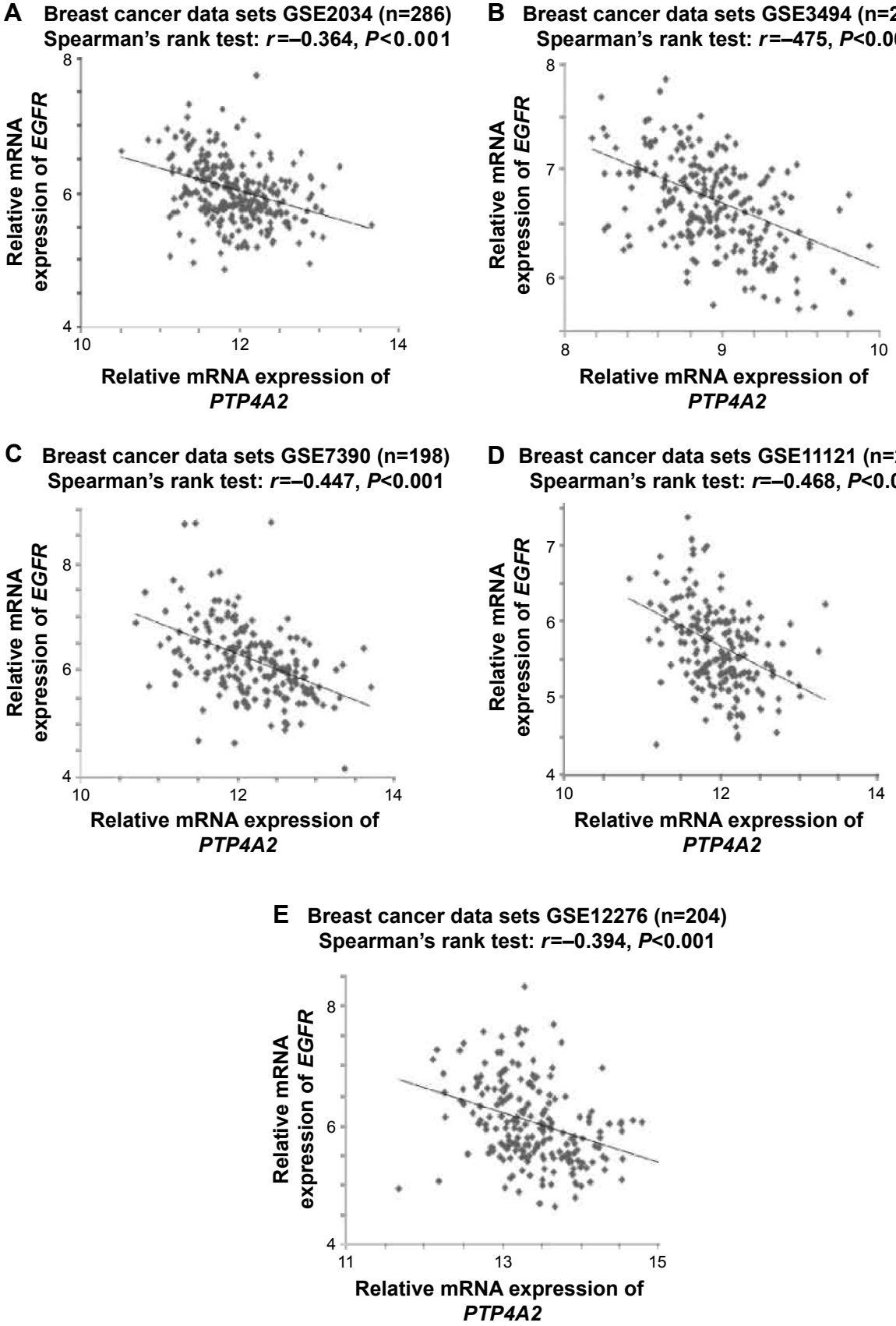

Figure 7 The correlations between *PTP4A2* expression and *EGFR* expression.
Notes: Scatter plots for *PTP4A2* expression against *EGFR* expression in (**A**) GSE2034, (**B**) GSE3494, (**C**) GSE7390, (**D**) GSE11121, and (**E**) GSE12276 breast cancer data sets.
Abbreviations: EGFR, epidermal growth factor receptor; *PTP4A2*, protein tyrosine phosphatase 4A2.

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are required to fully elucidate the role of *PTP4A2* in breast cancer progression.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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