

## RESEARCH ARTICLE

# Prognostic Value of Matrix Metalloproteinase 9 Expression in Breast Cancer Patients: A Meta-analysis

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### Abstract

**Background:** Matrix metalloproteinase 9 (MMP-9) is related to tumor invasion and metastasis. However, the role of MMP-9 expression in breast cancer survival remains controversial. The purpose of this study was to accomplish a more accurate estimation of the association between MMP-9 expression and survival results in breast cancer patients through meta-analysis. **Methods:** A meta-analysis of published studies investigating the effects of positive MMP-9 expression on both relapse free survival (RFS) and overall survival (OS) was performed. Relevant literature was confirmed by searching electronic databases including PubMed, Ovid, EMBASE and China National Knowledge Infrastructure (CNKI) before November 1, 2012. Individual hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted and pooled HRs with 95% CIs were used to evaluate the strength of the association between positive MMP-9 expression and survival results of breast cancer patients. Funnel plot and Egger's regression tests were used to evaluate publication bias. Heterogeneity and sensitivity analysis was also conducted. All the work was completed using STATA. **Results:** A total of 2,344 patients from 15 evaluative studies were finally included. Pooled HRs and 95% CIs suggested that MMP-9 overexpression had an unfavorable impact on both OS (HR: 1.70, 95% CI: 1.41-2.04) and RFS (HR: 1.54, 95% CI: 1.17-2.01) in breast cancer patients. There was no significant heterogeneity observed in the studies reported for OS ( $P=0.360$ ,  $I^2=8.8\%$ ), but not RFS ( $P=0.002$ ,  $I^2=67\%$ ). Publication bias was absent among the studies both in OS and RFS cases ( $t=-0.54$ ,  $P=0.605$  and  $t=1.71$ ,  $P=0.131$ , respectively). Omission of any single study had little effect on the combined risk estimates on sensitivity analysis. **Conclusion:** The results of this meta-analysis suggest that positive MMP-9 expression confers a higher risk of relapse and a worse survival in patients with breast cancer. Larger prospective studies are now needed to evaluate the clinical utility of MMP-9 expression.

**Keywords:** MMP-9 - breast cancer - prognosis - overall survival - relapse free survival - meta-analysis

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### Introduction

Breast cancer is one of malignant tumors that jeopardize women's health seriously, accounting for 23% of all new cancer cases and 14% of all cancer deaths in women in 2008 worldwide (Jemal et al., 2011). In China, the incidence of breast cancer ranks first in female cancers and the mortality shows an upward trend during the past 30 years (Huang et al., 2012). How to make patients develop to the benign direction has become a serious problem, so it is urgent to study the prognostic factors of breast cancer patients for guiding therapy and improving the survival result. Up to now, the prognostic factors used extensively in clinical are tumor size, lymph node status, histological grade and type. However, they do not precisely forecast the clinical outcome in many patients with breast cancer (Donegan et al., 1997). Breast cancer is a multifactorial disease and biological factors involved in carcinogenesis should be deemed as potential prognostic factors. Recently, in order to help individual treatment and

enhance the prognosis in breast cancer patients, enormous endeavours have been made to identify various molecular markers as prognostic factors, such as bcl-2, cox2 and p27 (Callagy et al., 2008; Guan et al., 2010; Kim et al., 2012).

Matrix metalloproteinases (MMPs) are one of the most important metal enzyme involved in many physiological and pathological processes (Moore et al., 2012). There is growing evidence to suggest that MMPs are predominantly involved in extracellular matrix (ECM) cleavage and are closely related to the invasion and metastasis of tumor (Nagase et al., 1999). Over expression of MMPs can promote tumor cell detachments and metastasis (Zhang et al., 2012). Among all of the MMPs, MMP-9 has received increasing attention due to its broad substrates and copious expression of cells in recent years. As a kind of gelatinase, MMP-9 are also known as type IV collagenases that destroy type IV collagen in the vascular basal membrane (Beaudeau et al., 2004). In tumor, once MMP-9 is activated, it can degrade and destruct type IV collagen and gelatin in extracellular matrix near the surface of the tumor

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cells. Then, tumor cells invade to the surrounding tissues along the missing basement membrane and eventually lead to tumor invasion and metastasis (Duffy et al., 2000). Otherwise, MMP-9 also affect the adhesion ability of the tumor cells, playing an important role in tumor growth and angiogenesis (Rundhaug et al., 2005). An experiment with rat model suggested that MMP-9 may be involved in the process of metastasis of breast cancer to the brain (Mendes et al., 2005). Therefore, MMP-9 is regarded as a crucial role in tumor metastasis. Positive MMP-9 expression has been suggested to be associated with poor prognosis in non small lung cancer (Peng et al., 2012) and gastric cancer (Zhang et al., 2012) through meta-analysis.

There are several studies focused on the relationship between MMP-9 expression and breast cancer patients. Both tumor cell and stromal tissues in breast cancer tissue have been reported to have increased MMP-9 expression (Ranogajec et al., 2012). A considerable number of studies have proved that high MMP-9 expression is related to tumor stage and lymph node metastasis in breast cancer patients (Hanemaaijer et al., 2000; Hao et al., 2007; Gu et al., 2009). Furthermore, Oscar and Sullu have indicated a significant association between high MMP-9 expression and poor survival result in breast cancer patients (Sullu et al., 2011; Oscar et al., 2012). Whereas Wu and Rahko reported contrary results (Rahko et al., 2004; Wu et al., 2008). The discrepancies in findings may be due to some of the defects in individual study such as small sample size and low statistical power.

Meta-analysis has become a widespread, multifunctional, and effective tool which overcomes the drawback of small sample sizes by pooling results from a number of individual studies to generate the best assessment (Nordmann et al., 2000). The aim of this study is to obtain a more exact evaluation of the relationship between high MMP-9 expression and the survival results in breast cancer patients through meta-analysis.

## Materials and Methods

### *Search strategy and study selection*

Relevant literatures about MMP-9 expression and survival results in breast cancer patients were searched in PubMed, Ovid, EMBASE and China National Knowledge Infrastructure (CNKI) database update to November 1, 2012. Following keywords were combined in electronic searching: (“breast cancer” or “breast neoplasm” or “breast carcinoma”) and (prognostic or prognosis or survive) and (“MMP-9” or “matrix metalloproteinase-9” or “type IV collagenase” or “Gelatinase-B”). Papers written in English or Chinese were included. In order to minimize the deviation caused during the search process, references reported in all identified papers were screened too. The following inclusion criteria must be met in order to ensure the high quality of this article: (1) the patients were female primary breast cancer who underwent surgical resection; (2) MMP-9 expression was measured in tumor tissue(not serum or plasma); (3) it measured MMP-9 protein expression(not mRNA); (4) the method to evaluate MMP-9 expression was IHC; (5) it was a full paper that assessed the association between MMP-9 expression and

overall survival in breast cancer; (6) hazard ratio(HR) and 95% CI could be obtained from the article or calculated them based on the information in the paper; (7) follow-up time more than 5 years; (8) experiment, letter and article without sufficient data were excluded; (9) when the same author published articles repetitively, only the most complete and/or newest one was included.

### *Data extraction*

The confirmation of qualified literature was divided into two steps. First, two reviewers (Song and Guo) identified which articles need further review by reading the title and abstract independently. Second, the entire article was reviewed to ascertain whether to include in this meta-analysis. Data extracted from the literature included: name of first author, publication year, country, the number of patients, disease stage, cut-off value, location of MMP-9 expression in tissue, the percent of MMP-9 positive, HR and 95% CI. If the above information were not mentioned in the original study, the item was treated as “not reported (NR)”. Inconsistencies in the research process were resolved through debate and consultations.

### *Statistical analysis*

HR and 95% CI were used as the effective value to measure the impact of MMP-9 expression on survival of breast cancer patients in this meta-analysis. If the study provided both different and general estimates, we included only the general results. For example, the study which provided HR and 95% CI of tumor cell expression and stromal tissues and combined, only the combined data was included in our meta-analysis. In the individual study, some of them provided HR and 95% CI directly. For some other studies not given these data clearly, we calculated from available data or Kaplan-Meier survive cure by using the methods illustrated by Tierney et al. (2007) and Parmar et al. (1998). The available data refer to the total number of events, the number of patients in each group, the log-rank statistic and its P-value or the O-E statistic (difference between numbers of observed and expected events). If the only existing survival data were in the form of figures, the Kaplan-Meier survive cure was read by Engauge Digitizer version 4.1 (free software down-loaded from [http:// sourceforge.net](http://sourceforge.net)) to reconstruct the HR. Heterogeneity was assessed by Chi-squared test and Q-test. When heterogeneity was absent, fixed effect model was used. Otherwise, random effect model was used. If there existed heterogeneity, Galbraith plot was performed to find the main studies that may contribute to the heterogeneity. Publication bias was assessed by funnel plots and Egger’s linear regression test. Sensitivity analysis was performed to examine the stability of the pooled results. Furthermore, when univariate and multivariate analysis were both obtainable, the latter was chosen to be pooled because survival result in breast cancer is affected by multiple factors. By convention, an observed  $HR > 1$  implied a worse survival for the group with increased MMP-9 expression. This influence of MMP-9 expression on survival was considered as statistically significant if the corresponding 95% CI for the summary HR did not overlap 1.

**Table 1. Main Characteristics of the Eligible Studies in this Meta-analysis**

First author	Year	Country	Age(mean)	Stage	N	Location	Cut off(%)	Positive percentage measured	Outcomes	HR estimate	HR(95%CI)
Oscar	2012	Spain	NR	I-III	97	T+S	CS	49%	RFS	HR	2.00(1.10-3.60) T4.70 (1.40-15.20) S2.50 (1.40-4.60)
Sullu	2011	Turkey	52	I-III	117	T	CS	66%	OS	Curve	2.92(1.22-7.01)
Gonzalez(1)	2010	Spain	NR	I-III	124	T	CS	11%	RFS	HR	3.10 (1.80-5.30)
Gonzalez(2)	2010	Spain	NR	I-III	124	S	CS	23%	RFS	HR	1.44 (0.82-2.51)
Tian	2009	China	44	I-III	62	T+S	5	65%	OS	Curve	1.42(1.04-2.51)
Wu	2008	China	51	I to IV	60	T	50	77%	OS	A	1.36(0.662-81)
Feng	2008	China	NR	I-III	65	T	25	69%	RFS	Curve	1.13(0.51-2.50)
Zhao	2008	China	51	I-III	71	T	10	42%	OS	A	2.14(1.21-3.78)
Mylona	2007	Greece	57	I-III	175	S	10	30%	OS	HR	2.05(1.23-3.41)
Vizoso	2007	Spain	NR	NR	131	T+S	CS	NR	RFS	HR	2.44(1.27-4.67)
Li	2006	China	49	I-III	183	T+S	CS	66%	RFS	HR	2.60 (1.50- 4.50) T3.30 (1.50-7.40) S3.10 (1.8 0- 5.30)
Rahko	2004	Finland	64	I-III	168	T	50	55%	OS	Curve	2.14(1.21-3.78)
Li	2004	China	NR	I-III	270	T	1	60%	OS	HR	1.08( 0.50-2.00)
Pellikainen(1)	2004	Finland	59	I-III	421	T	85	52%	RFS	HR	1.13 (0.25-5.17)
Pellikainen(2)	2004	Finland	59	I-III	421	S	2 0	38%	RFS	HR	2.50 (0.80-7.84)
Fan	2003	China	53.5	I-III	66	T	CS	68%	RFS	A	1.26(1.02-1.57)
Scorilas	2001	Greece	56	I to IV	210	T+S	48	52%	OS	Curve	1.06(0.84-1.32)
									RFS	HR	1.67(1.04-2.78)
									RFS	HR	0.78 (0.35-1.75)
									RFS	HR	0.89 (0.49-1.61)

All *P* values were two sided and *P*<0.05 was considered as statistically significant. Statistical calculations were all performed using STATA version 11.0.

## Results

### Study characteristics

A total of 162 papers were confirmed by the initial search. After reading the abstract and title, 133 papers were not applicable to our aim. The remaining 29 papers were approved through scrutinizing the entire paper. Among the 29 papers, five literatures had no sufficient data to analyze (Remacle et al., 1998; Wang et al., 2002; Casar et al., 2010; Mohammad et al., 2012; Ranogajec et al., 2012). MMP-9 protein expression was measured in serum in five studies (Lepp et al., 2004; Lepp et al., 2005; Mattila et al., 2005; Quaranta et al., 2007; Sung et al., 2012) and one study measured MMP-9 expression in plasma (Ranuncolo et al., 2003). Two studies were excluded because duplicate cohorts of patients were used in other selected studies (Cheng et al., 2004; Casar et al., 2009). MMP-9 mRNA expression was evaluated in another study (Sieuwerts et al., 2005). Furthermore, two studies (Pellikainen 2004; Gonzalez et al., 2010) provided information about MMP-9 expression in tumor cells and stromal tissues respectively without general result, which we treated independently. Eventually, 15 studies met the inclusion criteria were included (Scorilas et al., 2001; Fan et al., 2003; Li et al., 2004; Pellikainen et al., 2004; Rahko et al., 2004; Li et al., 2006; Mylona et al., 2007; Vizoso et al., 2007; Feng et al., 2008; Wu et al., 2008; Zhao et al., 2008; Tian et al., 2009; Gonzalez et al., 2010; Sullu et al., 2011; Oscar et al., 2012).

The major characteristics of retained studies were listed in Table 1. There were 11 studies utilized overall

survival (OS) to assess the prognostic value of MMP-9 expression in breast cancer patients and 7 studies used relapse free survival (RFS) as the indicator. Three papers used both OS and RFS. The total number of patients in the included studies was 2344 ranged from 60 to 421 per study. The reported median age of patients ranged from 44 to 59 years across the eligible studies. Some of the studies defined the cut off value by complex score combining intensity and percentage of MMP-9 expression, while other studies only used the percentage of MMP-9 expression to define positive expression with the cut off value varied from 1% to 85%. MMP-9 positive expression rate was observed ranging from 11% to 77%. Among all of the included studies, HR and 95%CI were obtained from the original articles directly in seven studies, and data were calculated based on the available information in three individual studies. The remaining five papers, HR and 95% CI had to be extrapolated from Kaplan–Meier curves. There were also some differences in the testing location. Seven studies just defined the tumor cell positivity, while one study just defined stromal positivity. Oscar et al and Vizoso et al provided not only the results of the impact of MMP-9 expression in tumor cells and stromal tissues on RFS, but also the combined value.

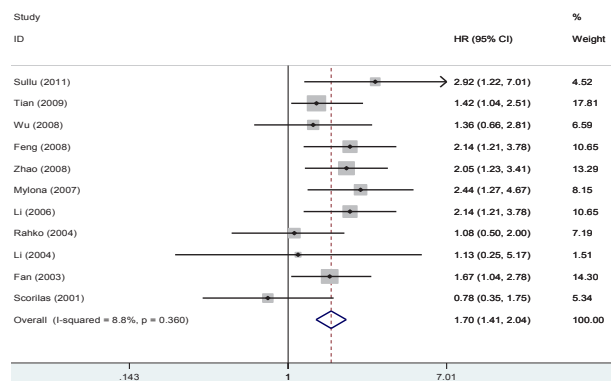
### Main results

The main results of the meta-analysis were summarized in Table 2. For the overall population, positive MMP-9 expression was associated with poorer OS (pooled HR: 1.70, 95% CI: 1.41-2.04, Figure 1) and RFS (pooled HR: 1.54, 95% CI: 1.17-2.01, Figure 2) in breast cancer patients. There was no significant heterogeneity among the studies that assessed the prognostic value of MMP-9 expression by OS (*P*=0.360, *I*<sup>2</sup>=8.8%), while heterogeneity was observed by RFS (*P*=0.002, *I*<sup>2</sup>=67.0%). Galbraith

**Table 2. Main Results of Eligible Studies Evaluating MMP-9 Expression and OS/RFS in Breast Cancer Patients**

	No. of studies	HR (95% CI)	Heterogeneity		
			$\chi^2$	<i>p</i>	<i>I</i> <sup>2</sup>
<b>Overall Survival(OS)</b>					
All	11	1.58(1.19-2.11)	10.96	0.360	8.8%
<b>Country</b>					
Asia	7	1.74(1.41-2.16)	3.01	0.870	0.0%
Non-Asia	4	1.57(1.08-2.27)	7.72	0.052	61.1%
<b>Location</b>					
T	7	1.83(1.45-2.30)	5.72	0.573	0.0%
S	1	2.44(1.27-4.67)	—	—	—
T+S	3	1.47(1.07-4.67)	4.08	0.130	50.9%
<b>Relapse free survival(RFS)</b>					
All		1.54(1.17-2.01)	24.26	0.002	67.0%
<b>Country</b>					
Asia	2	1.47(0.76-2.81)	1.25	0.263	20.2%
Non-Asia	7	1.32(1.16-1.51)	22.92	0.001	73.8%
<b>Location</b>					
T	6	1.63(1.36-1.94)	24.95	0.000	80.0%
S	4	1.35(1.12-1.63)	17.68	0.001	83.0%
T+S	3	1.71(1.22-2.38)	7.13	0.028	72.0%

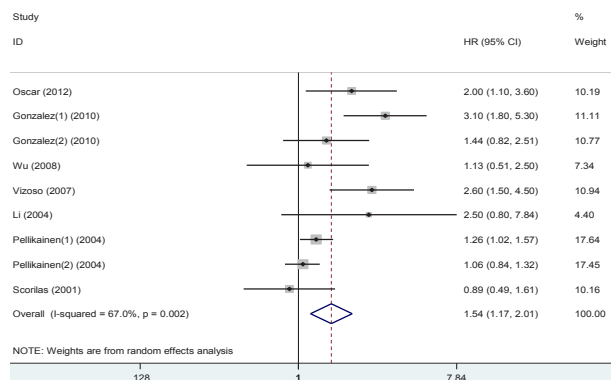
T, Tumor cells; S, stromal tissues



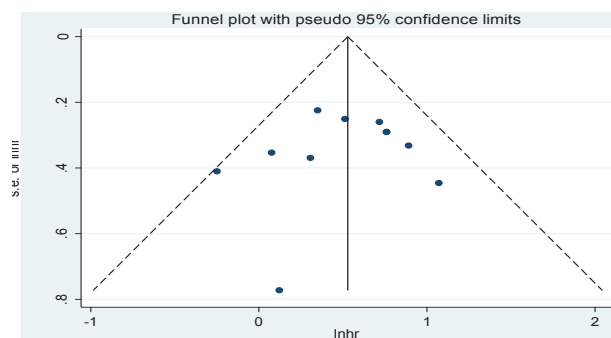
**Figure 1. Forest Plot Showing the Association Between Positive MMP-9 Expression and Overall Survival (OS) of Breast Cancer**

plot discovered that two studies (Vizoso et al., 2007; Gonzalez et al., 2010) may be the principal contributor to the heterogeneity .

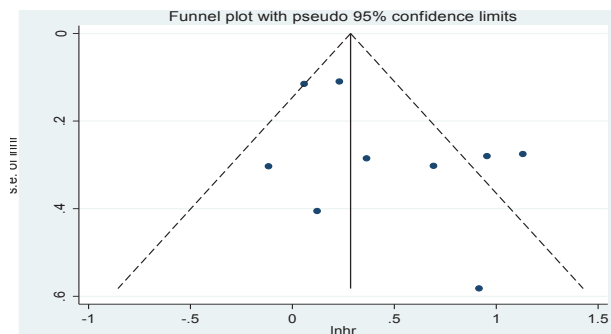
In the subgroup analysis on overall survival, the pooled results included 4 studies came from Non-Asia and 7 studies from Asia. Both of them showed significant association between positive MMP-9 expression and an unfavorable OS in breast cancer, with the HR and 95% CI of 1.57(1.08-2.27) and 1.74(1.41-2.16), respectively. No significant heterogeneity was detected among these studies. When the differences of location reported for detecting MMP-9 expression levels were taken into consideration, all pooled results of MMP-9 expression in tumor cell, stromal tissues and combined showed a significant relationship between positive MMP-9 expression and poor OS. In the subgroup analysis on relapse free survival, only two studies came from Asia and the pooled result showed no significant association between positive MMP-9 expression and RFS in breast cancer (HR 1.47, 95% CI: 0.76-2.81). While the combined results of non-Asia studies indicated that a significant



**Figure 2. Forest Plot Showing the Association Between Positive MMP-9 Expression and Relapse Free Survival (RFS) of Breast Cancer**



**Figure 3. Funnel Plot of the Meta-analysis Assessing MMP-9 Expression and OS in Breast Cancer**



**Figure 4. Funnel Plot of the Meta-analysis Assessing MMP-9 Expression and RFS in Breast Cancer**

relationship was found (HR 1.32, 95% CI: 1.16-1.51). When stratified by the location of MMP-9 expression, all the subgroup analysis proved a poor RFS with high MMP-9 expression in breast cancer.

*Publication bias analysis*

The funnel plots presented no proof of obvious publication bias for studies in either of the two outcomes. Further estimation using Egger’s linear regression test also failed to reveal any support for significant publication bias in OS ( $t=-0.54, P=0.605$ ) and RFS ( $t=1.71, P=0.131$ ). The funnel plot were shown in Figure 3 and Figure 4.

*Sensitivity analysis*

In order to gauge results stability, a sensitivity analysis, in which one study was deleted at a time, was performed. Both of the corresponding pooled HRs of OS and RFS were not significantly changed, suggesting the robustness of our results.

## Discussion

Breast cancer remains the most common cancer in woman. Despite tremendous progress in treatment, the survival result is still not optimistic (Jemal et al., 2011; Huang et al., 2012). For appropriate management of breast cancer patients in clinical, precise prognostic and predictive factors are urgent. The accumulating evidence showed that biological molecular play an essential role in the prognosis of breast cancer and seemed more specific than markers currently used in clinical such as TNM stage, weight loss and lymph node metastasis. Thus, a need for better prognostic markers based on tumor biology has arisen. Among them, MMP-9 positive expression was reported to be a poor prognostic factor for breast cancer patients and regarded as one of the most promising markers. Tumor metastasis is the leading cause of treatment failure and death in cancer patients. MMP-9, as a member of matrix metalloproteinases (MMPs), involved in extracellular matrix (ECM) cleavage, playing a critical role in tumor metastasis (Moore et al., 2012; Nagase et al., 1999). However, no unanimous results have obtained in existing literatures. So a meta-analysis of the literatures to analyze whether positive MMP-9 expression could be applied as clinically useful prognostic biomarker for breast cancer patients should be performed.

We achieved this meta-analysis by containing all available studies using a comprehensive search strategy in PubMed, Ovid, EMBASE and CNKI databases. The study was strictly set and performed the inclusion of literature and research standards. The use of a same cohort of patients in more than one published articles is existent. Through a strict review, two studies (Casar et al., 2009; Cheng et al., 2004) were excluded because identical cohorts of patients were used in other selected studies. This avoided the same patients being included in the meta-analysis repeatedly and diminished the potential bias. In this research, we choose HR as the indicator to compare time-to-event outcomes. Comparing with relative risk (RR), HR has its distinctive advantages including account for censoring and concerned about the time of death. It will be more accurate to describe the prognostic indicators by using HR.

In this meta-analysis, both overall survival (OS) and relapse free survival (RFS) were used to elucidate the prognostic value of positive MMP-9 expression in breast cancer. Our results utilizing summarized HR indicated that positive MMP-9 expression was associated with both worse OS (pooled HR of 1.58; 95% CI: 1.19-2.11) and RFS (pooled HR of 1.54; 95% CI: 1.17-2.01). MMP-9 expression was located in both tumor cells and stromal tissue. Subgroup analysis by location showed that a statistically significant impact of MMP-9 expression as a prognostic factor in both of tumor cells and stromal tissue. But we also noticed that some studies (Oscar et al., 2012; Tian et al., 2009; Vizoso et al., 2007; Li et al., 2006; Scorilas et al., 2001) combined the expression of tumor cells and stromal tissue to investigate the significance of MMP-9 expression, which made it difficult to explain which part of accumulation of MMP-9 played the most important influence on prognosis in breast cancer

patients. Therefore, the impact of different location of MMP-9 expression on prognosis seems still needed to be further confirmed by adequately designed studies with multivariate analysis. When taking account into the geographic area, as for the OS, we nevertheless found a statistically significant association between MMP-9 expression and OS in Asia and Non-Asia. As for the RFS, a significant relationship was observed in Non-Asia, but not Asia. Because of lacking of data in other breast cancer characteristics such as TNM and age, we could not draw definite conclusions of other subtypes.

Heterogeneity is the main factor affecting the quality of meta-analysis. There was no significant heterogeneity observed in the studies reported OS. However, when the studies reported the HR of RFS were pooled, a considerable degree of heterogeneity was noticed ( $I^2=70.1\%$ ). Stratified analysis did not make significant heterogeneity disappeared. Moreover, we applied to Galbraith plot to explore the heterogeneity between studies. After excluded the 2 studies (Gonzalez et al., 2010; Vizoso et al., 2007) that may contribute to the heterogeneity, pooled HR and 95% CI remain significant but the heterogeneity disappeared. However, because the information presented was limited, we cannot clearly clarify why these two studies were the main factors that cause heterogeneity. The strength of the conclusion about the association between MMP-9 expression and RFS in breast cancer seems weaker than OS when taking into account the heterogeneity. We must note this point when interpret the result. The heterogeneity was probably due to the difference in the baseline characteristics of patients (age and tumor stage), the duration of follow-up or others. IHC was used to assess the level of MMP-9 expression in breast cancer tissue. The primary antibody used had a significant influence on the sensitivity of IHC. However, the used of antibody in studies was also varied widely. Other factors such as storage time and revelation time may also cause potential bias. The treatments to the patients among the studies were not exactly the same, which may influence the results of survival time between the studies. However, no sufficient information was provided to explain it. All these sources of variability may cause bias.

For better interpreting the results, some inadequacies in this meta-analysis should be acknowledged. First, publication bias is a major concern in meta-analysis. Although no publication bias was observed among the eligible studies, something still need to be point out. Normally, literatures with positive results are often accepted by journals, while negative results studies tend to be more often rejected. We restricted our eligible studies published in English or Chinese, which probably provided additional bias. Second, there was no common cut off value in defining the positive MMP-9 expression in breast cancer patients. A standard threshold in the assessment of the degree of biomarkers expression such as MMP-9 is very important, which is beneficial to make more accurate evaluation of the biomarkers' real function. Third, most of studies included in the pooled analyses of breast cancer outcomes were analyzed by univariate analysis. Multivariate analysis is more credible than univariate analysis because confounding factors are taken into

account. Fourth, this analysis was performed at the study level. The attempt to perform subgroup analysis by other important clinical factors in breast patients such as TNM, hormone receptor status, differentiation and treatment were failed due to lack of sufficient data. Considering these limitations existing in this meta-analysis, our results should be rigorous exposition and the conclusions of this meta-analysis should also be drawn carefully.

The method of HR extrapolation requires stated. For the studies that HR and 95% CI were not reported directly, they were calculated from the available data mentioned in the publish articles. If even no available data was provided, we had to extrapolate the value from the survive curve based on the published method (Parmar et al., 1998; Tierney et al., 2007). This approach may have caused errors due to the inaccuracies in reading survive curve, so we try our best to minimize errors by reading the curve by two reviewers independently. It seems that the HR estimated from the curve may be less trustworthy than obtained directly. Consequently, we compared the HR and 95% CI with the published results to make sure of the accuracy of the estimated HR.

In conclusion, positive MMP-9 expression is a significant prognostic factor in patients with breast cancer who have been surgically treated. It is potentially a useful biomarker for predicting prognosis in breast cancer. As a prognostic factor for breast cancer patients, MMP-9 expression can help to make decisions for therapeutic of the breast cancer patients. Larger prospective studies with long-term follow-up are needed by multivariate analysis, which takes into account the well-known prognostic factors in breast cancer.

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The author(s) declare that they have no competing interests.

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