RESEARCH ARTICLE

Prognostic Value of MMP-9 in Ovarian Cancer: A Meta-analysis

Li-Na Li, Xin Zhou*, Yang Gu, Jun Yan

Abstract

Objective: Matrix metalloproteinase-9(MMP-9) plays an important role in tumor cell invasion. Although it has been studied frequently in ovarian cancer, its prognostic impact is still equivocal. The aim of this study was to more precisely estimate its prognostic significance. Method:We searched Pubmed, Embase, OVID, Sciencedirect and CBM databases to identify eligible studies. Hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (95% CIs) were pooled across studies using fixed-effects or random-effects models. We also performed subgroup analysis. Results: 30 studies (n=2552 patients) focusing on prognosis or expression of MM-9 were included. Increased expression of MMP-9 was associated with poor prognosis in ovarian cancer patients (HR=1.68, 95%CI 1.09-2.59, *p*=0.02). Besides, MMP-9 expression in ovarian cancer was significantly higher than non-malignant tumors (OR=11.46, 95%CI 8.47-15.50, *P*<0.00001). Moreover, increased expression of MMP-9 was significantly associated with FIGO stage (OR=4.85, 95%CI 2.60-9.04, *P*<0.00001), grade of differentiation (OR=3.34, 95%CI 2.46-4.54, *P*<0.00001), lymph node metastasis (OR=5.75, 95%CI 3.71-8.92, *P*<0.00001) and there was no association with histological type of ovarian cancer. Conclusions: Increased expression of MMP-9 was associated with poor prognosis in ovarian cancer patients. Down-regulation of MMP-9 is an attractive therapeutic approach which might improve outcome of ovarian cancer.

Keywords: MMP-9 - prognosis - expression - ovarian cancer - meta-analysis

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Introduction

Ovarian cancer is the leading cause of mortality from gynecologic malignancies in the United States. An estimated 25,200 new cases and 14,500 deaths were noted in 1998. Due to a lack of clear and effective diagnostic methods in identifying early stage disease, the prognosis of ovarian cancer is usually poor. The majority of patients are diagnosed with advanced stage, and there are no effective therapies for these patients, the five-year survival for ovarian cancer is about 44% (Landis et al., 1999; Siegel et al., 2012).

Several independent prognostic factors including FIGO stage, grade of tumor, and volume of residual tumor have been recognized as classical prognostic factors (Clark et al., 2001; Berman et al., 2003). Although these parameters reflect biological features of the tumour and patient, they don't allow adequate prediction of outcome for the individual patient (Oldenhuis et al., 2008). So the discovery of new prognostic factors should aid in a more accurate prediction of clinical outcome and may also reveal novel predictive factors and therapeutic targets.

Invasion and metastasis are the most important characteristics of ovarian cancer and are thought to be a multistep process that is dependent on the activity of many mediators. Matrix metalloproteinases (MMPs) are a unique family of zinc-dependent proteinases which degrade various components of the extracellular matrix (ECM), also they play an important role in many physiological processes as well as tumor invasion and metastasis (Kessenbrock et al., 2010; Stallings-Mann et al., 2007). In the MMPs family, MMP-9 (gelatinase-B) plays an important role in tumor cell invasion, because it can degrade gelatin and type IV collagen (a major component of the basement membrane which constitutes an important barrier to tumor cell invasion) (Himelstein et al., 1995).

Up to now, a large amount of studies confirmed that increased expression of MMP-9 is correlated with invasive and metastatic potential and poor prognosis in brain cancer (Lampert et al., 1998), neuroblastoma (Sugiura et al., 1998), gastric cancer (Murray., 1998), colorectal cancer (Zeng et al., 1999), breast cancer (Remacle et al., 1998), squamous cell carcinoma of the uterine cervix (Davidson et al., 1999), and ovarian cancer (Naylor et al., 1994).

Although a large number of studies were performed on the prognostic role of MMP-9 in ovarian cancer, not all the related studies showed consistent conclusions. Some studies suggested increased expression of MMP-9 is significantly related with poor survival, some showed no relation between MMP-9 and survival rate, and the others showed that increased expression of MMP-9 is related

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with well survival in ovarian cancer. Besides, numerous studies published in this field include a small number of cases. So we performed this meta-analysis of all available studies to evaluate the prognostic significance of MMP-9 expression for patients with ovarian cancer.

Materials and Methods

Literature search strategy

We performed an electronic search in Pubmed, Embase, OVID, Sciencedirect and CBM databases to identify studies about MMP-9 and ovarian cancer by using the terms "ovarian cancer", "ovarian neoplasm", "ovarian tumor", "ovarian carcinoma", "epithelial ovarian cancer", "MMP-9", "matrix metalloproteinase-9", "prognosis", "prognostic", "survival". The search ended in December 31th, 2012, and no lower date limit was employed. Appropriate references cited by the retrieved studies were also identified. Conference abstracts were not in the scope of our analysis owing to the limited data reported in them.
Selection criteria

Studies meeting the following criteria were included: (1) Studies must be published as original articles; (2) All observed patients must be diagnosed as ovarian cancer by pathology; (3) Study population was divided into increased MMP-9 expression group and normal group for expression analysis; (4) Log-Hazard ratio (HR) and its 95%CI were reported, or standard error (s.e.) and HR were given, or logrank X^2, survival curve and *P* value (Numerical value) were given in prognostic studies.

Studies were considered ineligible for the following reasons: (1) Follow-up was less than 3 year; (2) Non-original articles; (3) Animal studies focused on subjects such as rabbit, mouse and pig; (4) The same author or the same medical center with duplicate data, the article with higher influence factor and complete data was chosen.

Two researchers (L. Li and X. Zhou) independently examined abstracts of articles (n=354) to decide whether full-text articles should be obtained. Full-text articles (n=124) were examined and excluded if a more detailed examination revealed that they did not meet the inclusion criteria. The cases of disagreement were resolved by discussion. Disagreement which could not be resolved through consensus was resolved by a third independent reviewer.

Data extraction

The two primary researchers independently extracted data from each study. Data extracted from those studies included author's name, publication year, study location, number of patients, time of follow-up, methods of detection, cut-off value, and methods of HR estimation, HR and its 95% confidence interval (CI), tumor characteristics, quality assessment (Table 1).

Quality assessment of included studies

Study quality was assessed independently by two investigators (L. Li and X. Zhou) and scored by using the scale reported previously (Steels et al., 2001). The scores provided by the two investigators were compared and a consensus value for each item was achieved. The scores came from several aspects of methodology, four major classifications: the scientific design, the description of detection methods, the generalizability of results and the analysis of the study data. Each aspect had a maximum score: 10 points, so the total maximum score was 40 points. The total score was presented as percentages (ranging from 0-100%). the higher points, the better methodological quality.

Statistical analysis

The expression of MMP-9 and its impact on survival was measured by odds ratio (OR) and hazard ratio (HR) respectively. The first goal of our meta-analysis was to obtain a log-hazard ratio and its standard error for each study according to methods previously described by Parmar et al (1998) (Parmar et al., 1998). The most accurate approach is to obtain the log-hazard and its standard error directly from the paper. Second way, the number of patients at risk in each group, number of events and the log-rank statistic or its p-value were used to calculate the HR estimate and its variance. Otherwise, if the study did not provide a HR but reported the survival curve, we need to obtain data from survival curves. Survival curve could be read by Engauge Digitizer (version 4.1).

Between studies heterogeneity was tested by using the I^2 statistic. The I^2 value >50% was considered to represent substantial heterogeneity between studies. In this case, a random-effects model was applied, when I^2 value ≤ 50%, fixed-effects was used. Subgroup analysis performed on study location, publication year, number of patients, methods of detection and cut-off value. To estimate the expression of MMP-9 in ovarian cancer and different clinicopathological features, we use ORs and their 95% CIs. All statistical analyses with $P<0.05$ were considered significant. Statistical analyses were performed using Review Manager (RevMan) Version 5.1. Publication bias was tested using the funnel plot. Sensitivity analysis was also conducted by omission of low quality studies (< 70%) to evaluate the stability of the results.

Results

Studies included and characteristics

A total of 354 articles were identified from a search of the above databases using the search strategy as described above (Figure 1). We read 354 titles and abstracts which 230 are irrelevant. Subsequently, 124 studies of full-text were read for detail. Upon further review, 33 were

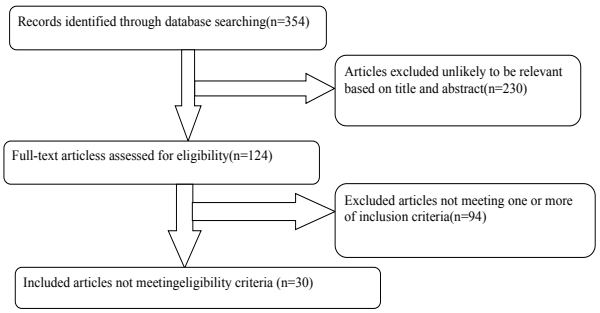

Figure 1. Flow Chart of Included Studies

Table 1. Characteristics of All Eligible Studies

Author's name	Year	Study location	Patients	Methods of detection	Cut-off value	Methods of HR estimation	HR	95% CI	MMP-9 expression ovarian cancer	MMP-9 expression non-ovarian cancer	Quality assessment
Alshenawy HA	2010	Egypt	120	IHC	25%	logrank X^2, P	2.55	[1.42,4.61]	88/120	none	88%
Anil K. Sood	2004	America	78	IHC	50%	none	none	none	48/78	none	93%
Aparna A. Kamat	2006	America	90	IHC	50%	HR	2.41	[1.31,4.43]	58/90	none	87%
Ben Davidson	2000	Norway	36	ISH	none	survival curve	3.51	[1.18,10.57]	none	none	92%
Ernst Lengyel	2001	America	103	zymography	none	survival curve	1.91	[1.03,3.48]	none	none	95%
Ge Lou	2005	China	65	IHC	5%	none	none	none	6/45	0/20	89%
Guo Bingqin	2011	China	100	IHC	10%	survival curve	3.44	[1.58, 7.57]	46/80	4/20	80%
Hu Jie	2011	China	100	IHC	25%	none	none	none	30/38	10/62	78%
Jean-Luc Brun	2011	France	69	IHC	none	logrank X^2,P	0.96	[0.48,1.91]	none	none	97%
Lee-Wen Huang	2000	Taipei	95	IHC	5%	none	none	none	43/47	38/48	90%
Li Daocheng	2008	China	119	IHC	50%	none	none	none	50/89	1/30	60%
Li Juanqing	2003	China	132	IHC	50%	none	none	none	67/67	55/65	75%
M.Maatta	2004	Finland	53	IHC	none	none	none	none	11/22	7/31	85%
Qin Mu	2011	China	94	IHC	20%	none	none	none	20/34	2/60	81%
S.Ozalp	2003	Turkey	45	IHC	50%	survival curve	0.76	[0.32,1.81]	17/30	2/15	92%
S.Sillanpää	2007	Finland	292	IHC	90%	survival curve	0.71	[0.52,0.97]	198/292	none	91%
Shen Yufei	2006	China	43	IHC	none	none	none	none	6/28	0/15	75%
Sun Shue	2008	China	76	IHC	25%	none	none	none	30/47	0/29	83%
Tian Liliang	2007	China	96	IHC	none	none	none	none	30/47	5/47	73%
Wang Fuling	2011	China	33	RT-PCR	none	survival curve	1.92	[0.48,7.70]	none	none	63%
Wang Xiaoyan	2004	China	47	IHC	5%	survival curve	3.38	[0.71,16.25]	30/47	none	88%
Wang Ximei	2005	China	94	IHC	none	none	none	none	44/60	12/34	84%
Wu Jingxian	2007	China	49	IHC	25%	none	none	none	25/40	0/9	76%
Xiaoxia Hu	2012	China	103	RT-PCR	none	survival curve	0.17	[0.01,2.22]	51/60	18/43	68%
Xing Lanying	2007	China	56	IHC	5%	none	none	none	27/32	none	65%
Yan Hui	2008	China	65	IHC	10%	none	none	none	30/40	5/25	77%
Zeng Xiaolin	2010	China	55	IHC	30%	none	none	none	36/45	0/10	82%
Zhang Danni	2011	China	139	IHC	30%	none	none	none	55/68	13/71	79%
Zhang Huijuan	2006	China	55	IHC	10%	logrank X^2, P	2.28	[1.01,5.22]	25/46	0/9	80%
Zhang Lijing	2007	China	50	IHC	25%	none	none	none	23/40	2/10	73%

excluded because only MMP-9 gene polymorphism was analyzed, 22 were excluded because the authors didn't give the useful data, 14 were excluded because it was not possible to allow for the calculation of HR stimulate owing to insufficient reported data, 11 were excluded because they have overlapped data with other studies, 8 were excluded because the evaluation was performed on animal studies, 6 were excluded because the follow-up was less than 3 years. At last, 30 studies (Davidson et al., 1999; Lee et al., 2000; Lengyel et al., 2001; Li et al., 2003; Ozalp et al., 2003; Määttä et al., 2004; Sood et al., 2004; Wang et al., 2004; Ge et al., 2005; Wang et al., 2005; Kamat et al., 2006; Shen et al., 2006; Zhang et al., 2006; Sillanpää et al., 2007; Tian et al., 2007; Wu et al., 2007; Xing et al., 2007; Zhang et al., 2007; Li et al., 2008; Sun et al., 2008; Yan et al., 2008; Alshenawy et al., 2010; Zeng et al., 2010; Guo et al., 2011; Hu et al., 2011; Qin et al., 2011; Wang et al., 2011; Zhang et al., 2011; Hu et al., 2012; Jean et al., 2012) were included in the meta-analysis.

The characteristics of these 30 included studies for the meta-analysis are summarized (Table 1). The total number of patients is 2552. 12 studies investigated the association of MMP-9 expression with survival (total number of patients is 1093), while 25 investigated the expression of MMP-9 with its clinical features (total number of patients is 2208). Immunohistochemistry (IHC) was widely employed in studies (26 studies), only two studies used RT-PCR, one used gelatin zymography and one used ISH.

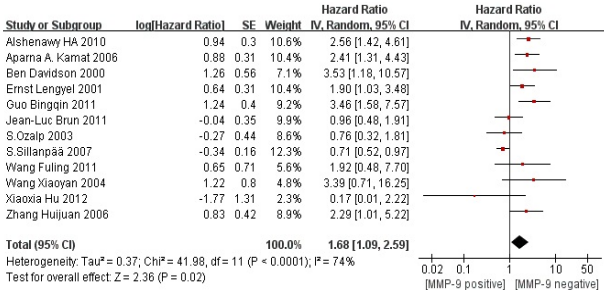

Figure 2. Forest Plot of HR with a Random-effects Model for Prognosis Between Increased Expression of MMP-9 Group and Normal Group in Ovarian Cancer

Study results report and meta-analysis

In the 12 studies associated with prognosis, eight (66.7%) reported that increased expression of MMP-9 was significantly related with poor survival, three (25%) showed no relation between MMP-9 and survival rate, one (8.3%) showed that increased expression of MMP-9 was related with well survival in ovarian cancer. Among these studies, one study reported the data from which the estimated HR can be directly retrieved, three were calculated by the number of events and the log-rank statistic or its p-values, the other 8 studies reported the data in the form of the survival curve. Among 25 studies associated with MMP-9 expression, twenty reported the difference between ovarian cancer and non-malignant tumor, 17 reported FIGO stage, 16 reported the grade of differentiation, 12 reported lymph node metastasis and 16

Table 2. Subgroup Analysis of MM-9 Increased Expression and Prognosis

Stratified analysis		Number of studies	Number of patients	Pooled HR (95%CI)	*P*-value	I^2 (%)	Heterogeneity *p*-value
Study location	China	5	338	HR=2.49, 95%CI 1.52-4.06	*p*=0.0003	23%	*p*=0.27
	Europe	3	397	HR=1.14, 95%CI 0.54-2.41	*p*=0.73	74%	*p*=0.02
	other countries	4	358	HR=1.96, 95%CI 1.42-2.70	*p*<0.0001	49%	*p*=0.12
Publication year	2000-2009	7	668	HR=1.66,95% CI 0.95-2.92	*p*=0.08	78%	*p*=0.0002
	2010-2012	5	425	HR=1.74, 95%CI 0.89-3.42	*p*=0.11	62%	*p*=0.03
Number of patients	<100	7	375	HR=1.71, 95%CI 1.23-2.37	*p*=0.001	41%	*p*=0.12
	≥100	5	718	HR=1.52, 95%CI 0.69-3.33	*p*=0.30	86%	*p*<0.0001
Cut-off value	<50%	4	322	HR=1.88, 95%CI 1.25-2.83	*p*=0.003	46%	*p*=0.13
	≥50%	3	427	HR=1.09, 95%CI 0.48-2.48	*p*=0.84	84%	*p*=0.002
Detection method	IHC	8	818	HR=1.65, 95%CI 0.97-2.78	*p*=0.06	80%	*p*<0.0001
	non-IHC	4	275	HR=1.97, 95%CI 1.21-3.20	*p*=0.007	35%	*p*=0.20

Table 3. Positive Expression of MMP-9 in Ovarian Cancer in Other Clinicopathological Characteristics

Clinical feature	Number of studies	Pooled OR (95%CI)	*P*-value	I^2(%)	Heterogeneity *p*-value
Ovarian cancer	20	OR=11.46,95%CI 8.47-15.50	*p*<0.00001	29%	*p*=0.11
FIGO stage	17	OR=4.85,95%CI 2.60-9.04	*p*<0.00001	74%	*p*<0.00001
Grade of differentiation	16	OR=3.34,95%CI 2.46-4.54	*p*<0.00001	24%	*p*=0.18
Lymph node metastasis	12	OR=5.75,95%CI 3.71-8.92	*p*<0.00001	0%	*p*=0.83
Histological type	16	OR=1.32,95%CI 0.93-1.87	*p*=0.12	0%	*p*=0.45

OR, odds ratio; CI, confidence interval

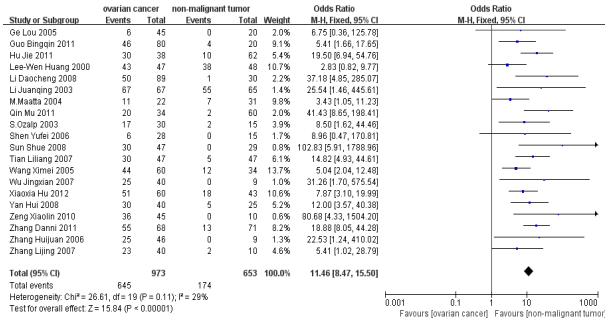

Figure 3. Forest Plot of OR with a Fixed-effects Model For Increased MMP-9 Expression in Ovarian Cancer and Non-malignant Tumor Group

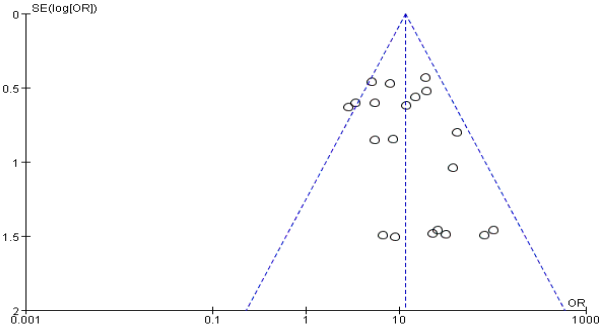

Figure 4. Funnel Plot of Publication Bias in Selection of Studies for Increased Expression of MMP-9 in Ovarian Cancer and Non-malignant Tumor Group

reported histological type of ovarian cancer. The quality of the included trials was evaluated according to the above aspects, and 4 trails were low quality according to the scores (< 70%).

We analyzed HR value of prognosis between increased MMP-9 expression group and normal group with the meta-analysis presented in Figure 2. Random model was chosen because of heterogeneity (p<0.0001 I^2=74%). There was significant difference between two groups (HR=1.68, 95%CI 1.09-2.59, p=0.02). Increased MMP-9 expression demonstrates a significant increase of mortality risk in ovarian cancer. As the heterogeneity is significant, we performed subgroup analysis by study location, publication year, number of patients, detection method and cut-off value. Subgroup analysis indicated a significant relation between increased MM-9 expression and prognosis in China (HR=2.49 95%CI 1.52-4.06, p=0.0003) (Table 2) and other countries (HR=1.96, 95%CI 1.42-2.70, p<0.0001), but not in Europe. Subgroup analysis also indicated a significant relation between increased MM-9 expression and prognosis in group of detection method with non-IHC (HR=1.97, 95%CI 1.21-3.20, p=0.007), cut-off value < 50% (HR=1.88, 95%CI 1.25-2.83, p=0.003) and studies with less than 100 patients (HR=1.71, 95%CI 1.23-2.37, p=0.001).

In addition, we analyzed OR value of increased MMP-9 expression in ovarian cancer and none-malignant tumor group presented in Figure 3. The OR values in subgroup of clinicopathological characteristics (FIGO stage, grade of differentiation, lymph node metastasis and histological type) were also analyzed (Table 3). Increased expression of MMP-9 was significantly associated with ovarian cancer(ovarian cancer versus non-malignant tumor OR=11.46, 95%CI 8.47-15.50, p<0.00001), FIGO stage (III-IV versus I-II OR=4.85, 95%CI 2.60-9.04, p<0.00001), grade of differentiation(poor versus well OR=3.34, 95%CI 2.46-4.54, p<0.00001), lymph node metastasis(positive versus negative OR=5.75, 95%CI 3.71-8.92, p<0.00001), but there was no association between increased expression of MMP-9 and histological type (serous versus mucinous OR=1.32, 95%CI 0.93-1.87, p=0.12). Besides FIGO stage use random model because of significant heterogeneity (p<0.00001, I^2=74%), the others use fixed model.

Sensitivity analysis was performed by omission of low quality studies and the results were the same (HR=1.77, 95%CI 1.12-2.78, p=0.01). In our meta-analysis, investigation of bias by a funnel plot showed substantial

funnel plot asymmetry for prognosis between increased MMP-9 expression group and normal group, suggesting the presence of publication or selection bias. For increased MMP-9 expression in ovarian cancer and non-malignant tumor group, no funnel plot asymmetry was found (Figure 4).

Discussion

The objective of our meta-analysis was to examine the association between increased MMP-9 expression and survival and clinicopathological characteristics of ovarian cancer. This meta-analysis combined the results from 30 studies of 2552 patients and revealed that increased MMP-9 expression significantly predicted poor prognosis of ovarian cancer patients (HR=1.68, 95%CI 1.09-2.59, p=0.02). However, significant heterogeneity exists among the these studies, subgroup analysis revealed that increased expression of MMP-9 was also significantly associated with poor prognosis subgroup with detection method of non-IHC(HR=1.97, 95%CI 1.21-3.20, p=0.007), cut-off value < 50% (HR=1.88, 95%CI 1.25-2.83, p=0.003) and studies with less than 100 patients (HR=1.71, 95%CI 1.23-2.37, p=0.001). However, due to the small number of studies in these subgroups, we recommend more prospective and high-quality studies to validate the prognostic value of MMP-9 studies. Moreover, significant correlations were observed between increased MM-9 expression and clinicopathological features including ovarian cancer and non-malignant tumor group (OR=11.46, 95%CI 8.47-15.5, p<0.00001), FIGO stage, grade of differentiation, lymph node metastasis.

Ovarian cancer is usually diagnosed in advanced stages. Invasion and metastasis are the most important characteristics of ovarian cancer and are thought to be a multistep process which is dependent on the activity of many mediators. Matrix metalloproteinases (MMPs) are a family of zinc-dependent metalloendopeptidases which are capable of degrading extracellular matrix and basement membrane components. Matrix metalloproteinases' activity is associated with multiple physiologic and pathologic processes, including morphogenesis, angiogenesis, wound repair, and tumor invasion and metastasis. MMP-9 (Gelatinase B, 92 kD type IV collagenase) is able to degrade type IV collagen, a component of all basement membranes, thereby facilitating stromal and vascular invasion by tumor cells (Aznavoorian et al., 1993).

According to our meta-analysis, there were several clinical significances. Firstly, increased MMP-9 expression significantly predicted poor prognosis of ovarian cancer patients. MMP-9 could be a therapeutic target and a tool for assessing treatment. Secondly, the result may indicate that increased MMP-9 expression significantly predicted poor prognosis of ovarian cancer patients in China, but no prognostic significance in Europe. Thus, the conclusion remains to be seen in further investigations. Thirdly, MMP-9 expression in ovarian cancer was significantly higher than non-malignant tumor. So MMP-9 might act as a potential marker for ovary cancer clinical diagnosis and a biomarker in discriminating benign and malignant tumors. At last, the increased expression of MMP-9 might serve as an indicator for identifying clinicopathological characteristics including ovarian cancer stage, metastatic potential and the grade of differentiation.

There are some limitations in this meta-analysis. Firstly, the heterogeneity of the included studies was significant. When subgroup analyses such as study location, publication year were performed, heterogeneity remained present. This indicates that not all sources of heterogeneity could be accounted for in this meta-analysis. Moreover, sensitivity analysis also did not help to clarify the source of heterogeneity in this analysis. Secondly, the method applied for evaluating MMP-9 expression were not the same, although, we performed a subgroup with only IHC detection, but the studies also did not use the same primary antibody, and the dilutions of the antibodies were also different, which leads to a potential bias because the sensitivity of the IHC may rely on the antibody concentration. Even if some groups of studies used the same antibody, subgroup analysis could not explore this technical problem, either. Moreover, cut-off values among included studies varied from 5% to 90%, which might produce heterogeneity. In addition, the heterogeneity in tissue samples can not be ignored.

In our analysis, published studies were all written in English, although we have not restricted our retrieval language, the bias may exist. Moreover, the bias caused by quality of included articles may be a factor which may influence the result of the study, even though we used a methodology assessing tumor-based biomarkers originally reported in a systematic review by Steels et al. (2001). In addition, approach of extrapolating the HRs might be associated with potential source of bias. In some trials, HR was not given directly, we obtained them from the survival curves, but this approach did not completely eliminate inaccuracy now. The estimated HR might be less reliable than the direct data. At last, Sensitivity analyses and funnel plot analyses concerning publication bias were also performed to confirm the reliability of our research results. The publication bias may be a problem for any meta-analysis. In our meta-analysis, the publication or selection bias in increased MMP-9 expression with prognosis exists, but no bias with MMP-9 increased expression in ovarian cancer and non-malignant tumor exists. So we need more trials to study for meta-analysis.

In conclusion, our meta-analysis revealed that increased MMP-9 expression was significantly associated with poor prognosis and clinicopahtological features in ovarian cancer. Increased expression of MMP-9 might be a predicative factor of poor prognosis in ovarian cancer patients. Down regulation of MMP-9 is an attractive therapeutic approach for ovarian cancer. In the future, higher quality studies, superior patient selection are awaited.

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