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ORIGINAL ARTICLE

# Prognostic significance of matrix metalloproteinase-2 in gynecological cancer: a systemic review of the literature and meta-analysis

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## Summary

***Purpose:*** Matrix metalloproteinases (MMPs) are considered as mediators of metastases which may be associated with gynecological cancer survival. However, such relationship remains inconclusive. We carried out the present metaanalysis to evaluate the prognostic value of MMP-2 and MMP-9 in gynecological cancers.

***Methods:*** We searched 2 medical databases (Medline and Embase) and located 13 studies with 1841 patients that evaluated the relationship between MMP-2 and MMP-9 and 5-year survival. Risk ratio (RR) with 95% confidence intervals (95% CI) synthesized by random effect model were used to assess the strength of the association. Publication bias was evaluated by Begg-Mazumdar test and Egger's regression test.

***Results:*** Mortality was 1.53-fold higher in patients whose tumor cells were positive for MMP-2 (RR 1.53; 95% CI 1.03-2.27; p=0.03).Funnel plot was symmetrical (p=0.721 for Begg-Mazumdar test, and p=0.718 for Egger's regression test). Between-study heterogeneity was significant (p<0.001). Mortality was 1.26-fold higher in MMP-9 positive than negative patients, but without statistical difference (RR 1.26; 95% CI 0.94-1.68; p=0.12). Funnel plot was asymmetrical (p=0.024 for Begg-Mazumdar test).

***Conclusion:*** MMP-2 positivity in tumor cells is associated with worse survival in patients with gynecological cancers. Standardization of MMP positivity is needed.

**Key words:** matrix metalloproteinase, meta-analysis, ovarian cancer, overall survival

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## Introduction

Gynecological cancers are the leading cause of death in women. Despite development in diagnosis and treatment of gynecological cancers, the survival rate remains largely unchanged, especially in ovarian cancer. There are several common prognosis related factors such as FIGO stage, histological grade, CA-125, CIP2A, VEGF-A, Ets transcription factor, survivin, but actually few of these factors are routinely used in clinical practice [1-4], raising the need to find better markers that can identify patients with poor prognosis.

Extracellular matrix (ECM) degradation plays a predominant role in extracellular microenvironment homeostasis. Irregular proteolysis of ECM leads invariably to unregulated tumor growth, tissue remodeling, inflammation, tissue invasion, and metastasis. MMPs are a family of zinc-dependent proteolytic enzymes that are constantly correlated with other cellular and extracellular proteins, assumed to play a key role in a variety of physiological and pathological conditions [5,6]. Thorough and persistent investigations have clearly recognized that MMPs not only control the ECM turnover and cancer cell migration, but also regulate signaling pathways of cell growth, morphogenesis, angiogenesis, tissue repair and metastasis [7,8]. Gelatinolytic activity of MMP-2, a 72 kDa type IV collagenase, has been associated with malignant phenotype of different solid neoplasms. Switch from the initial form of pro-MMP-2 (72 kDa) to enzymatic MMP-2 (62 kDa), which is mediated by intracellular furin-like proteinases, is essential to its proteolytic activity. Owing to its unique ability to degrade type IV collagen, the major component of ECM and basement membrane, tumor cells can easily penetrate the ECM and spread locally and/or distantly (metastasis) [9]. The level of MMP-2 was found to correlate with the metastatic potential of numerous cell types [10]. MMP-9 is a 92 kDa type IV collagenase, also called gelatinase B, which can degrade collagen type IV, like MMP-2 [11].

Recently, several studies reported association of MMPs with prognosis of gynecological cancers (Table 1). Therefore, it is necessary to explore whether MMP-2 or MMP-9 expressions are prognostic factors in gynecological cancers.

Due to differences in study populations and designs, the results of some studies are inconclusive. Our aim was to prove the hypothesis that MMP-2 or MMP-9 are connected with 5-year overall survival in gynecological cancers. Thus, we conducted a meta-analysis of all available studies relating MMP-2 or MMP-9 with the prognostic outcome in patients with such malignancies.

## Methods

*Publication search*

Initially, we performed an online search in PubMed and Embase to identify all related studies (between January 1990 and May 31, 2011), regardless of the MMP subtype and publication language in patients with gynecological cancers. The search was carried out using the following keywords: "MMP" or "metalloproteinase", "gynecological cancer", "ovarian cancer", "cervical cancer", "endometrial cancer", with no special limits except time. Then we used Endnote (version 4.1) to screen the literature including all of the identified studies to avoid duplication of data by checking authors and medical centers, examining for each one the names of all authors and the different medical centers involved. References, reviews and editorials were also screened [12]. Additional information was obtained by sending email to authors if necessary.

We didn't use strict inclusion criteria and quality score to evaluate studies, due to the lack of general agreement on the meta-analysis of observational studies [13]. All studies measuring MMPs with immunohistochemistry in patients with gynecological cancers were included.

*Definitions of markers*

All of the studies had their own standards in MMPs positivity. Cut-off was 10% or close to 10% in the majority of the enrolled studies. When data with this cut-off were impossible we contacted authors or calculated data based on primary information in the original article.

The main outcome of meta-analysis was MMPs–related survival (mainly focused on MMP-2 and MMP-9). There were several types of survival, such as disease free survival (DFS), cancer specific survival

(CSS), recurrence free survival (RFS), overall survival (OS) and cumulative survival (CS). We just evaluated OS which indicated the percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. All studies had at least 60 months follow-up and censoring was unusual before this time point. In most studies, there were results of MMPs in stromal cells and tumor cells.

*Methodological assessment*

Information was carefully extracted by two of the authors (HLP and MY). Collected elements were author, publication year and country, median follow-up, FIGO stage, tumor location (ovary, uterus or cervix), MMP subtype (MMP-2 and MMP-9), definition of MMP positivity, survival type (OS, DFS, CSS, RFS and CS), cell types (stromal cells and tumor cells) and MMP antibodies. The number of patients censored alive before 60 months were also recorded. Disagreements were resolved by discussion among us. If disagreement still existed, the final decision was made by Dr. L.L.

Sometimes studies were consisted of a cohort of consecutive patients. With no quality score receiving general agreement for use in a meta-analysis, especially of observational studies, we did not weigh the quality of each study, but decisions of exclusion were always taken without knowledge of the global result of each study.

*Statistics*

REVMAN, version 5.1, was used for meta-analysis. Stata/SE (version 11.0) was used for Begg's and Egger's test. Survival distribution between MMP negative and MMP positive cases was significantly different with $p<0.05$. All of the data were extracted from univariate analysis evaluating whether the results were changing gradually over time with the publication of more recent studies.

In order to evaluate the prognostic role of MMP-2 and MMP-9 in gynecological cancers, we checked the influence of MMP-2 and MMP-9 by calculating the RR and its 95% CI between negative and positive groups by a method depending on the data provided in the publication. We used Q statistics (significance for $p <0.10$) to assess heterogeneity between studies.

## Results

*Studies and characteristics*

Our search retrieved a total of 521 references made up by 166 "cervical cancer", 131 "endometrial cancer" and 224 "ovarian cancer". A total of 35 studies were included after screening title and abstract. Full texts were reviewed and 22 studies were excluded due to lack of survival analysis or survival data [14-16]. Finally 13 studies with 1841 patients were included in our analysis. Data on 5-year survival could be obtained from original data or survival curves (using Engauge if necessary in all of these studies). There were 4 studies for both MMP-2 and MMP-9 [17-20], 2 for MMP-9 [21,22], and 7 for MMP-2 [23-29]. Therefore, 11 studies (n=1465 patients) on MMP-2, and 6 (n=960 patients) on MMP-9 were analyzed. In insufficient studies and samples we didn't evaluate the association between MMP-2 or 9 overexpression in stromal cells and 5-year OS [18,22,24,26,27].

There were 9 studies (n=915 patients) reporting an inverse relationship between survival and MMP-2 overexpression in gynecological tumor cells, whereas 2 studies reported no such relation (n=255 patients), and one study showed favorable relation (n=295 patients). Characteristics of the 13 original studies are listed in Table 1. Cancer was located in the ovary in 1208 patients (65.6%), in the uterus in 473 patients (25.7%), and in the cervix in 160 patients (8.7%). Information on the positive cut-off ranged from 5 to 25%. FIGO stages III+IV in ovarian cancer were more frequent than in cervical and endometrial cancer.

*Meta-analysis: survival at 60 months*

MMP-2 overexpression in tumor cells was related to poor prognosis, leading to more deaths within 5 years. The between-study heterogeneity was significant ($p<0.001$), so the random model was used. Mortality was 1.53-fold higher in patients whose MMP-2 in tumor cells was positive (RR 1.53; 95% CI 1.03-2.27; $p=0.03$; Figure 1). Funnel plot was symmetrical and smaller studies (excepting no.18) gave negative results ($p=0.721$ for Begg-Mazumdar test, $p=0.718$ for Egger's regression test, Figure 2). MMP-9 overexpression in tumor cells was not significantly associated with survival (RR 1.26; 95% CI 0.94-1.68; $p=0.12$; Figure 3).

The between-study heterogeneity remained significant (p=0.008). Mortality was 1.26-fold higher in MMP-9 positive patients. Funnel plot was asymmetrical and showed that 2 large studies [25,29] indicated negative results and conclusions were opposite to each other (p=0.024 with Begg-Mazumdar test; Figure 4).

## Discussion

Our meta-analysis showed that MMP-2 in tumor cells, detected by immunohistochemistry, does indeed predict poor survival in gynecological cancer. However, results should be interpreted in several aspects. MMP-2 expression had a significant prognostic effect on gynecological cancers, with a RR of 1.53. Moreover, studies with larger samples showed a strong association with MMP-2 than smaller studies, but publication biases were non-significant (p=0.721 for Begg-Mazumdar test, p=0.718 for Egger's regression test, Figure 2). Although MMP-2 proved to be a potential prognostic marker, FIGO stage and histology grade may contribute to its prognostic effect too. As MMP-9 had a similar structure and function with MMP-2, we subsequently performed MMP-9 analysis. MMP-9 in tumor cells wasn't correlated with survival, yet there was a trend to increased mortality with a RR of 1.26. The negative result of MMP-9 might be caused by the limited samples and publication bias (p=0.024 for Begg-Mazumdar test).

In the 13 eligible studies, there was one study examining MMP-9 expression in gynecological cancers using Western blot rather than immunohistochemistry. Lengyel et al. found that high MMP-9 determined by Western blot in 92 patients had no relation with 5-year survival [21]. This finding is consistent with our meta-analysis, although a different method was undertaken. Two studies [22,25] from the same research center (Oulu University, Finland) looked for the effect of MMP-2 and MMP-9 on prognosis (disease-related survival), and suggested that MMP-2 and MMP-9 are associated with favorable prognosis. Two more studies [26,29] didn't give an explicit cut-off value of positivity; Yilmaz et al. [29] evaluated the staining of MMP-2 by scoring the intensity and distribution of positive cells which they divided into 0-4 grades. Torng et al. [26] considered stronger cytoplasmic staining of stromal cells compared to nearby tumor cells as MMP-2 positivity. However, both studies showed that MMP-2 positivity indicated poor prognosis, which is consistent with our results. MMP-2 contributes to gynecological cancers growth

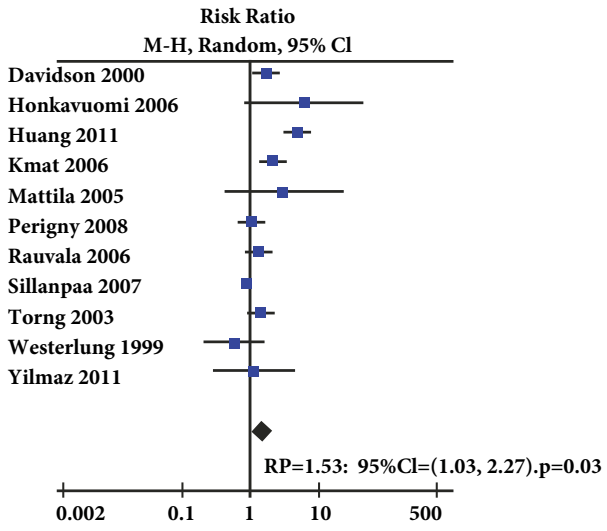


**Figure 1.** Meta-analysis of 11 studies evaluating the association between MMP-2 overexpression in tumor cells and the risk of death at 5 years. Each study is shown by the first author and year. CI: confidence interval.

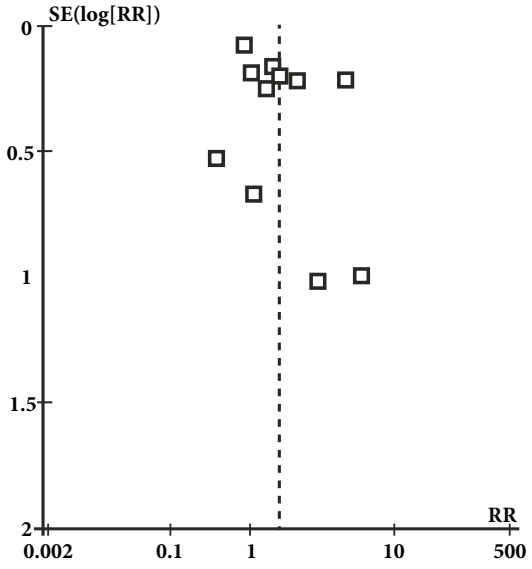


**Figure 2.** Funnel plot showing the relation between relative risk (RR) and standard error (log RR). The funnel plot is symmetrical.

and metastasis through several aspects. For the most, MMP-2 regulates the tumor microenvironment by directly degrading the ECM to promote cell growth and metastasis. Growing evidence demonstrates that MMP-2 proteolytically degrade the basement membrane which functions as a barrier to protect infiltration from tumor cells; this results to facilitating the tumor cells adhesion on the ECM and then invading into the peritoneal cavity, where they give rise to metastases [16,30-32].

Overexpression of MMP-2 along with surgical stage aroused our interest in the contribution of MMP-2 in metastasis [16,33,34]. The pattern of gynecological cancers' dissemination can be modeled as follows: during transformation, malignant cells are shed from the basement membrane and degrade ECM. This fact results in detachment of tumor cells, invasion into the peritoneal cavity, and development of metastases. In addition, activated MMP-2 proteolysis of the matrix including fibronectin, vitronectin and collagen I can contribute to the cancer cell adhesion and invasion [30,35-37]. These results were in line with former findings that expression of MMP-2 in metastatic locations was significantly higher than in primary cancer [38]. In conclusion, MMP-2 can regulate the gynecological cancers' growth and metastasis through distinct pathways, including promoting adhesion, invasion and angiogenesis; all these may provide an explanation for the observed modest association of MMP-2 and survival. On the other hand, the remaining members of MMP family, such as MMP-1, MMP-7, MMP-11, and MMP-13 are also considered to be associated with prognosis [39-43]. We believe that more studies are needed to evaluate the prognostic significance of these markers.

There are some clinical meanings in our meta-analysis.

*1: MMP-2 positivity is an indicator of advanced stage and disease outcome*

A series of studies proved that the expression of MMP-2 in gynecological tumor cells was stronger than in borderline and benign areas, and high expression of MMP-2 had close relationship with advanced tumor and metastasis [26,33,36]. Comparison of the expression and gelatinolytic activity of MMP-2 in cystadenomas , tumors of low malignant potential as well as

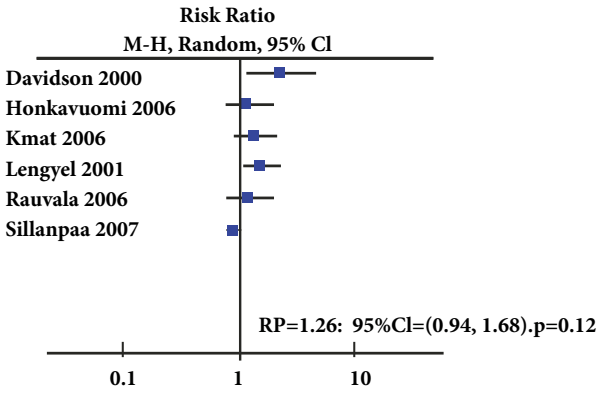


**Figure 3.** Meta-analysis of 6 studies evaluating the association between MMP-9 overexpression in tumor cells and the risk of death at 5 years. Each study is shown by the first author and year. CI: confidence interval.

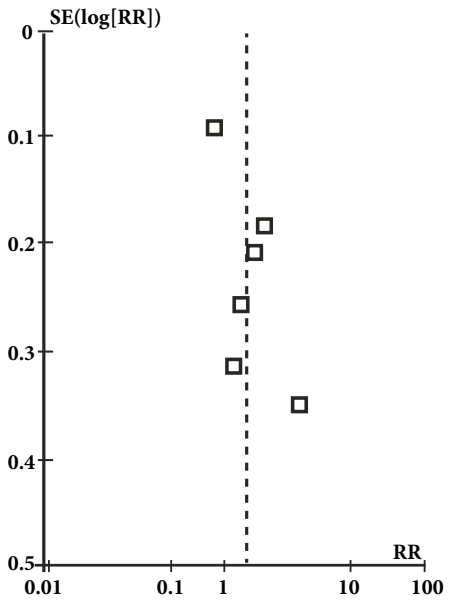


**Figure 4.** Funnel plot showing the relation between RR and SE (log RR) .The largest study (MMP-9) has negative result. The funnel plot is asymmetrical.

stage IIIc/IV ovarian cancer and their corresponding omental metastases indicated that MMP-2 expression was strongly associated with increasing surgical stage of malignant ovarian tumors [36]. This idea has been supported by Sakata et al., who proved that increased expression of MMP-2 was related to tumor stage, which indicated that the level of MMP-2 in patients with stage III and IV tumors is higher than in those with stage I and II tumors [17,35,45]. Tester et al. also demonstrated strong enzymatic activity of MMP-2 (62 kDa) in advanced ovarian cancer and its metastases but only seldom in benign tumors [44]. Based on this information, ovarian cancer stage and grade of malignancy can be efficiently and easily evaluated by

**Table 1.** Main characteristics of 13 included studies

| *Author (year-country) [Ref.no.]* | *No.of samples* | *Median follow-up (months)* | *Clinical stage (FIGO)* | *Tumor location* | *MMP subtype* | *Cutoff staining for MMP positivity(% cell population)* | *Survival analysis* | *Selected cells* |
|---|---|---|---|---|---|---|---|---|
| Davidson [ 17] (2000-Israel) | 68 | 70 | III-IV | ovary | MMP-2 MMP-9 | 25 | DFS OS | Tumor |
| Kmat [18 ] (2006-USA) | 90 | NR | I-II:24 III-IV:72 | ovary | MMP-2 MMP-9 | 5 | DFS | Tumor and stromal |
| Honkavuori [19 ] (2006-Finland) | 266 | NR | I+II:205 III+IV:43 | uterus | MMP-2 MMP-9 | 10 | RFS,CSS | Tumor |
| Rauvala [20 ] (2006-Sweden) | 160 | NR | I+II:125 III+IV:36 | cervix | MMP-2 MMP-9 | 20 | DSS | Tumor |
| Lengyel [ 21] (2001-USA) | 84 | 55 | III | ovary | MMP-9 | Negative: <6U/ug | OS | Tumor |
| Sillanpaa [22 ] (2007-Finland) | 292 | 28 | I+II:125 III+IV:36 | ovary | MMP-9 | 20 | CSS,DRS,RFS | Tumor and stromal |
| Huang [23 ] (2011-China) | 219 | 25.5 | NR | ovary | MMP-2 | 5 | OS | Tumor |
| Perigny [24 ] (2008-USA) | 92 | 19 | III | ovary | MMP-2 | 10 | OS | Tumor and stromal |
| Sillanppa [25 ] (2007-Finland) | 295 | NR | I-II:127 III-IV:168 | ovary | MMP-2 | 10 | OS,DRS,RFS | Tumor |
| Torng [ 26] (2003-China) | 35 | 39.9 | I-II:20 III-IV:15 | ovary | MMP-2 | NC | CSS,DFS | Tumor and stromal |
| Westerlund [27 ] (1999-Finland) | 33 | 35.5 | I+II:12 III+IV:21 | ovary | MMP-2 | 10 | OS | Tumor and stromal |
| Talvensaari [ 28] (2005-Finland) | 112 | 88 | I+II:96 III+IV:16 | uterus | MMP-2 | 10 | OS | Tumor |
| Yilmaz [29 ] (2011-Turkey) | 95 | 39 | I:73 II+III:22 | uterus | MMP-2 | NC | OS | Tumor |

NR: not reported, NC:not clear, CS: cumulative survival, OS: overall survival, DFS: disease free survival, RFS: recurrence free survival, CSS: cancer specific survival, DSS: disease specific survival, DRS: disease related survival

MMP-2 positive rate. A previous study of clinical and histomorphological data proved that positive staining for MMP-2 was associated with bad prognosis [38]. A large amount of research indicated that MMP-2 was significantly associated with advanced stage, higher grade, smaller tumor size at operation, and higher incidence of recurrence [21,23,25,26]. Taking these aforementioned results into account, it could be concluded that positive expression of MMP-2 plays a central role in determining disease outcome in gynecological cancers.

*2: MMP can be a marker to assess timing of surgery*

It is well known that histological grade is important for surgery. To further investigate the relationship between MMP-2 expression and histological grade in malignant gynecological tumors, Kamel et al. evaluated the MMP-2 expression and correlated clinical and pathological parameters, mainly surgical stage, histological grade, omental metastasis, and lymph node metastasis [16]. This study demonstrated that the expression of MMP-2 was significantly correlated with the histological grade. The authors also showed that overexpression of MMP-2 indicates poor timing of surgery. In view of these findings, histological grade can be assessed through expression of MMP-2, and then, according to the histological grade to determine the optimal operation time.

*3: The present meta-analysis promotes thought on biologic therapeutic target*

Signaling pathway dysfunction is a vital event in tumorigenesis that MMP-2 proteolytically activates TGF-β1 and then TGF-β signaling pathway, the fundamental signaling pathway, which plays an important role in tumor genesis and epithelial-mesenehymal transition [45]. Several studies [46,47] have reported different types of MMPs, including MMP-2, orchestrating distinct functions (such as promoting tumor angiogenesis) on the tumors' malignant progression. MMP-2 was further proved to stimulate angiogenesis directly by releasing VEGF [37]. Blocking experiments not only confirmed the former conclusion, but also implied that inhibition of MMP-2 attenuates both angiogenesis and lymphangiogensis, thus reducing lymph node metastasis [48,49]. Thus, designing molecules to directly antagonize MMP-2 and indirectly block TGF-β, VEGF which mediate MMP-2 signal pathway could lead to new targeting treatments.

There are some limitations in our meta-analysis. Firstly, we attempted to minimize publication bias by improving our searching strategy. Positive results are more likely to be published while negative data may go unpublished. Secondly, although there are many studies about MMP overexpression in gynecological cancers, they often lack survival information [50,51]. Thirdly, all studies are not strictly randomized controlled trials. Although we standardized factors such as age, menopausal status, histological grade and FIGO stage, some variability was unavoidable. Between-study heterogeneity was significant in this study, and elimination of the variability (experimental design, measurements, and definition of cut-off value) was not always possible [52].

In conclusion, this meta-analysis suggested that MMP-2 overexpression is associated with poor prognosis. Our results show that MMP-9 is not correlated with prognosis in gynecological cancers, maybe owing to inadequate studies and publication biases. Future investigations and randomized controlled trials with large number of samples are needed to confirm the prognostic significance of MMP-2 and MMP-9 in patients with gynecological cancers.

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