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The Role of Matrix Metalloproteinase-2 Expression in Gastric Cancer Susceptibility: A Systematic Review

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Abstract

Context: Gastric carcinoma (GC) is the most commonly diagnosed cancer that has been one of the main causes of cancer death worldwide. The matrix metalloproteinase-2 (MMP2) gene was expressed in the gastric cancer tissues compared to the matched normal tissues that are associated with the metastasis of gastric cancer cells.
Objectives: This systematic review was performed to investigate the role of *MMP-2* in gastric cancer among the different population.
Evidence Acquisition: We searched on electronic databases such as PubMed, Scopus, Science Direct and Cochrane Library Database without any language restriction for relevant publications which were published until April 2019.
Results: Thirty two original and relevant studies that evaluate the association between gastric cancer and *MMP-2* were included. This systematic review indicated that increased *MMP-2* expression has been seen in gastric cancer. *MMP-2* over-expression may play a crucial role in degrading extracellular matrix as well as stimulate angiogenesis.
Conclusions: MMP2 over-expression can play a critical role in tumor metastasis, tumor size, invasion, and lymph node invasion in GC.

Keywords: Gastric Cancer, Matrix Metalloproteinases-2, Systematic Review

1. Context

Gastric cancer (GC) is one of the most common malignancies (4th in men and 7th in women) with over one million new cases in 2018. In addition, GC includes about 10% of the new diagnoses of cancer cases and comprises 12% of the overall cancer-related deaths in the world (1). Based on reported data, GC is the 5th common carcinoma in men and women among developed countries and has the second rank for men individual in numerous countries of Asia and South America (2). However, due to the recognition of certain risk factors for susceptibility to GC, the worldwide morbidity and mortality rate has declined over the past few decades, but there is still a high prevalence of gastric cancer in some population in developing countries (3, 4). GC is a multi-factorial disease that its carcinogenesis mechanisms are still unknown. Based on previous epidemiological studies, the interplay of both genetic and environmental factors (such as age, sex, body mass index, infectious agents, diet, and lifestyle) play a major role in the gastric carcinogenesis that can be different among ethnic groups (5-7). Different genes are involved in variety of processes such as inflammatory response, DNA repair, cell proliferation, carcinogen detoxification, and antioxidant protection to development and susceptibility of gastric cancer and increase invasive progression and metastasis (8, 9).

Matrix metalloproteinases (MMPs), the main family of zinc-dependent enzymes, play an important role in the digestion of the extracellular matrix (ECM) (10). Furthermore, different studies have shown that MMPs affect cancer development processes such as apoptosis, cell proliferation, and immune system (11).

So far 24 different types of MMPs have been reported and 23 of them had been found in human (12). However, MMPs present in healthy individuals, but they are up-regulated in almost all types of cancer (13, 14). The high expression of different *MMP* genes has been correlated to metastasis, invasion, and survival of many human cancers (14). These MMPs are gelatinases, stromelysins, membrane-type MMPs, and other MMPs. Cells synthesize MMPs as an inactive zymogen and the N-terminal cleavage of propeptide leads to make them activated. Based on the re-

ported of previous studies, 4 members of this family are associated-MMPs with GC, MMP-1, -2, -7, and-9. The roles of MMP-2 (gelatinase A with 72 kDa) and MMP-9 (gelatinase B with 92 kDa) are more important than others in tumor invasion and metastasis, this importance is because of their substrates (11). MMP-2 and MMP-9 digest types IV and V of collagen, fibronectin and gelatin. The basement membrane is the first barrier for a metastatic epithelial tumor that consists of type IV collagen (15).

Among main *MMPs* genes related to cancer development, more attention has been focused on the Matrix metalloproteinase 2 which is over-expressed in the different human tumors. Expression level and activity of *MMP-2* are often associated with invasion, cell migration, and development of tumor cells (16). Known evidence indicates that MMPs, especially *MMP-2*, play a critical function in the degradation of ECM that are mediated by tumor cells. *MMP-2* gene with a total length of 27 kbs is located on chromosome 16q21 and contains 12 introns and 13 exons (17). Over-expression of *MMP-2* gene was reported to the GC tissues compared to the matched normal tissues that are correlated to the invasion and metastasis in GC cells (12).

2. Objectives

According to the evidence available on this issue, the present study aimed to conduct a review article of all original studies that have investigated the role of MMP-2 in gastric cancer among different population.

3. Methods

3.1. Search Strategy

We searched on electronic databases such as PubMed, Scopus, Science Direct, and Cochrane Library Database without any language restriction for relevant publications that were published until April 2019. In addition, following keywords and abbreviation terms were used in the search strategy to get relevant results: ["gastric cancer", "gastric carcinoma", "GC", "stomach carcinomas" or "stomach cancer"] and ["matrix metalloproteinase 2", "MMP-2", "MMP2", "72kDa Type IV Collagenase", "matrix metalloproteinase2" or "MMP2metalloproteinase"].

3.2. Selection Criteria

The criteria for the selection of relevant studies were: (1) the article type must be original research that focused on the association of *MMP2* expression in GC patients, (2) all studies must have used human specimens, (3) full-text article must be in English language, and (4) the study must give suitable data about the genetic, expression levels or activity of the MMP2.

3.3. Data Extraction

The required information from the included study was extracted using a standardized form. We documented the most relevant information such as the first author's name, publication year, publication Journal, geographical location, sample characteristics (size, sex, age, and type), subject or aim, used method, and main results that state the association between expression levels of *MMP-2* and gastric cancer.

4. Results and Discussion

This systematic review study indicated the role of *MMP-2* expression in gastric cancer susceptibility. Primarily, the highly sensitive search strategy recognized 152 articles. We reviewed all articles according to the inclusion and exclusion criteria (Figure 1). Finally, 32 original and relevant studies which had evaluated the association between gastric cancer and MMP-2 were selected. The articles were published between 1996 and 2019 (Table 1).

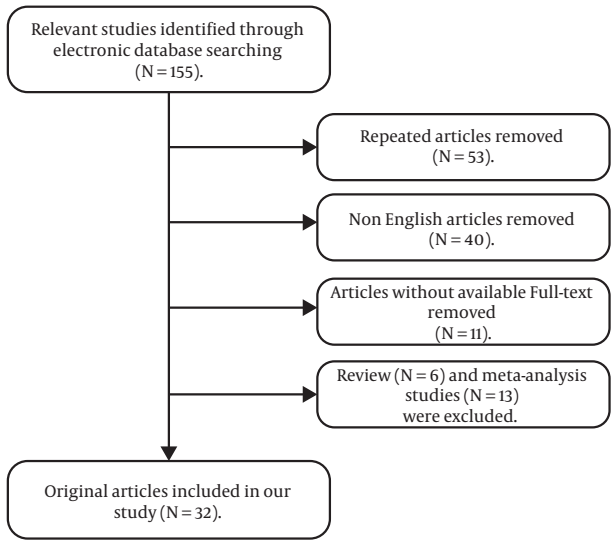

Figure 1. Flow chart for the selection procedure of the included studies

The total of 32 articles were included to be reviewed. The most of the population studied in these papers were from China (14 articles: 47%) and other studies were from Poland (5 articles), Germany (4 articles), Japan (3 articles), Netherlands (2 articles), Taiwan (2 articles), Finland (1 article), and Italy (1 article). Since the gastric cancer rate in the countries of East Asia and then in Eastern and Central Europe is higher than in other countries or parts of the world (47), therefore most of the studies have been reported from these countries.

Among 32 included articles, the total number of studied samples were 5661 individuals, among these cases, 3709 individuals were patients with gastric cancer and 2318 individuals were considered as controls. All available data such as mean age, sex status (male/female ratio), and sample types are presented in Table 1. Based on the obtained data from reported articles, study specimens were tissue (N: 24), blood (N: 5), tissue and blood (N: 2) and, lymph node (N:1).

These samples were used to study *MMP-2* expression (25 cases), *MMP-2* expression and immunoreactivity (2 cases), *MMP-2* expression and polymorphism (1 case), serum level analysis of MMP-2 (2 cases), and polymorphism (2 cases).

In each research, several methods have been used to reach the mentioned aims, and the IHC method has been used more than others. Accordingly, the most used method in the reviewed articles was the IHC method (19 cases) and then RT-PCR (9 cases), Gelatin Zymography (6 cases), ELISA (4 cases), PCR-RFLP (1 case), PCR-direct sequencing (1 case), RNA/DNA calculator with spectrophotometric (1 case), Tissue Microarray (TMA) (1 case), Immunostaining (1case), Sandwich enzyme immunoassay (1 case), PCR Based DHPLC analysis and DNA sequencing (1 case).

The analysis of the present study showed that the expression of *MMP-2* in the cancer subjects was mostly higher than control individuals. However, according to the study by Mroczko et al. 2011, the serum level of *MMP-2* gene was positively lower in GC patients than healthy individuals (29). Consistent with results of Mroczko et al. (29) 2011 and Lukaszewicz-Zajac et al. (26) 2013 that serum level of *MMP-2* was significantly lower in GC patients. In addition, according to Emara et al. 2009, *MMP-2* level was not significantly higher in GC patients than controls individuals (15).

Based on the findings of the present study, more than 50% of reported studies showed that abnormal changes in *MMP-2* expression play a critical role in tumor metastasis in GC. In addition, 8 studies examined the role of MMP-2 in the tumor invasion and resulted that *MMP-2* expression significantly correlated with tumor invasion (Table 1). Further, Bornschein et al. showed that *MMP-2* had a higher expression level in the invasive front compared to the center section of the tumor (23). These findings support the hypothesis that over-expression of *MMP-2* gene may play a crucial role in degrading type IV Collagen, gelatin, and laminin in basal membrane and other components of extracellular matrices, which is a vital step toward the development, invasion, and tumor metastasis. Additionally, the results of the other study by Zheng et al. showed that IL-1β could activate p38 and increase gastric adenocarcinoma (GA) cell migration and invasion (35). IL-1β- induced GA cell migration and invasion occur via activation of the 38 signaling pathway which leads to AP-1 activation and up-regulation of *MMP-2*.

Zheng et al. (35) and Partyka et al. (28) investigated the correlation between vascular endothelial growth factor (VEGF) and MMP-2 in cancerous tissue of metastatic patients. They found that MMP-2 and VEGF were positively associated with the tumor size, depth of invasion, lymphatic, and venous metastasis. Regarding their results, MMP-2 plays an important role in the "angiogenic switch" and tumor cells can synthesize and secrete high levels of MMP-2 paracrine and/or autocrine to stimulate angiogenesis and increase VEGF release (35).

In the other study, Chen et al., examined how JWA, a multifunctional microtubule-binding protein regulates GC angiogenesis via MMP-2 and the role of JWA and MMP-2 in the progression and prognosis of GC. JWA inhibits GC angiogenesis via Sp1-mediated *MMP-2* expression. Sp1 was the transcription factor of MMP-2; it has been reported that Sp1 up-regulates the MMP-2 gene in cancers and promotes angiogenesis in GC (24).

Ten studies surveyed the *MMP-2* expression and its effect on prognosis in GC patients. Among these, Donizy et al. (22), Lukaszewicz-Zajac et al. (26), Kubben et al. (37), Ji et al. (39), and Caenazzo et al (43) suggested the high expression of MMP-2 as an independent and molecular prognostic factor for gastric cancer. However, the other authors had a different idea, they declared that MMP-2 alone was not enough and suggested other molecules to accompany MMP-2 as a prognostic factor. According to the findings of other research by Yao et al. (21) and Ji et al. (39) MMP-9 was as a helpful factor along with MMP2. Also, Allgayer et al. suggested that consideration of interrelated tumor-associated proteases like uPA receptor in combination with MMP-2 may improve its prognostic power (42). The results of Wang et al. showed the evaluation of both telomerase activity (TA) and MMP2 protein can more effectively detect patients who are susceptible to disease recurrence and prognosis (27). As mentioned above, Chen et al. findings pointed out that JWA and MMP-2 may serve as prognostic biomarkers in GC (24).

Survey of *MMP-2*-1306 C/T polymorphism which reported by Miao et al. (13), Zhang et al. (17), and Wu et al. (33) proved that this SNP correlated with GC susceptibility, lymphatic or venous invasion, and progression of gastric cancer but not associated with the tumor diameter, the depth of tissue infiltration, lymphatic metastasis, survival rate, age, sex, *H. pylori* infection, Lauren's classification, tumor status, depth of invasion or lymph node metastasis, and metastasis of GCA (Gastric Cardia Adenocarcinoma). Miao et al. indicated that *MMP-2*-1306 C/T polymorphism is associated with the risk of gastric cancer development (13), but this result is not consistent with Wu et al. (33). In the study carried out by Zhang et al. showed that susceptibility of GC for patients with CC+CT genotype in *MMP-2*-1306 C/T

SNP was 1.803 times more than the individuals who have TT genotype (17), and Miao et al. proved it in their study too (13). However, Wu et al. reported that the C/T allele frequencies of *MMP-2*-1306 in GC patients did not differ from those of controls. In addition in the other study conducted by Wu et al. the cases with *MMP-2* 1306 C/C genotype were significantly more susceptible for lymphatic and venous invasion than cases with C/T or T/T genotype, but they did not differ in the survival rate (33).

Eventually, Wang et al. examined the effect of glutamine-enriched nutritional support on intestinal mucosal barrier function, MMP-2, MMP-9, and immune function in patients with advanced gastric cancer during the perioperative chemotherapy. The results showed that after three cycles of treatment by adding glutamine, MMP-2 level was positively decreased (20).

Jiang et.al surveyed the effect of CDH17 on MMP-2 expression by NF-κB pathway. Its results showed a positive relation; decreased or increased levels of MMP-2 was significantly regulated by CDH17 knockdown or overexpression, respectively. This effect was mediated by the NF-κB pathway in GC cells. In the present study, GC tissues had a considerably higher level of CDH17 mRNA than the matched para-carcinoma tissues in the same patient. CDH17 expression was associated with clinical lymph node metastasis. CDH17 induce these activities through the NF-κB/MMP-2 pathway (18).

Based on Deng et al. RAGE/ERK/Sp1/MMP2 pathway induced by glucose-derived AGEs (Advanced glycation end products) may result in GC progression and stimulating the invasion and metastasis of it. They found the accumulation of glucose-derived AGEs in cancer tissues and blood of GC patients and it's resulting in over-expression of RAGE, Sp1, and MMP2. This study revealed the following sequence: glucose-derived AGEs binding to RAGE, activating MEK1/2/ERK pathway, overexpression of Sp1, up-regulating MMP2 expression, and GC cells invasion, respectively (19).

5. Conclusions

In summary, our review indicated that increased *MMP-2* expression had been seen in gastric cancer. *MMP-2* overexpression may play a crucial role in degrading ECM as well as stimulate angiogenesis and increase VEGF releasing. Therefore, *MMP2* overexpression can play an important role in tumor metastasis, tumor size, invasion, and lymph node invasion in the GC. Furthermore, high-level expression of *MMP-2* may be strongly associated with poor prognosis in GC patients. Thus, the detection of *MMP-2* expression may serve as an independent prognostic factor for GC. In addition, *MMP-2* polymorphism such as -1306C/T can be correlated with GC susceptibility. However, further studies with larger sample sizes and more comprehensive and meta-analysis data are still required for the achievement to conclusive results.

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It is not declared by the authors.

Footnotes

Authors' Contribution: Kheirollah Yari designed the study, Fereshte Bibak and Samane Ahmadi had equal role and collected the data and wrote the first draft of the manuscript. Kheirollah Yari, Fereshte Bibak, Samane Ahmadi, Zeynab Khateri and Amirhossein Ahmadi read and approved the final manuscript.

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Table 1. Description of the Main Characteristics, the Properties of Samples and Studies, and the Main Results of All Eligible Articles

Reference	Publication Year	Population Nationality	Sample				Study			Main Results
			Size				Type	Subject	Methods	
			Total	GC, M/F	Control, M/F	Age, y				
(18)	2018	China	160	160 (103/57)	160 (103/57)	112 > 60, 48 ≤ 60	Tissue	*MMP-2* expression	IHC and qRT-PCR	CDH17 increased the level of MMP-2 via the canonical NF-κB pathway.
(19)	2018	China	160	160 (107/53)	160 (107/53)	95 > 60, 65 ≤ 60	Tissue	*MMP-2* expression	Gelatin zymographic	AGEs induced the migration and invasion of GC cells by increasing transcription of RAGE, Sp1, and MMP2.
(20)	2017	China	94	47 (29/18)	47 (30/17)	58.36 (40 - 70), 59.85 (40 - 75)	Blood	*MMP-2* expression	ELISA	The level of MMP-2 was declined after 3 cycles of treatment by adding glutamine.
(21)	2017	China	204	204 (140/64)	-	-	Tissue	*MMP-2* expression	IHC	Over-expression of *MMP-2* with *MMP-9* associated with metastasis and poor prognosis in early GC.
(22)	2015	Poland	60	60 (44/16)	-	63 (37 - 84)	Tissue	*MMP-2* Expression	IHC	Low expression of *MMP-2* in tumor and stromal compartments were correlated to poor prognosis.
(17)	2015	China	504	254 (162/92)	250	53.35 (26 - 75), 53.35 ± 3	Blood and Tissue	Polymorphism, *MMP-2* expression	Genotyping and IHC	*MMP-2*-1306C/T was statistically associated with the MMP-2 expression.
(23)	2015	Germany	128	28, 85/43	-	78 (70 - 78)	Tissue	*MMP-2* expression	IHC, RT-PCR	MMP-2 and MMP-7 at the invasive front of GC were not correlated with mTOR expression.
(24)	2013	China	439	81	358	-	Tissue	*MMP-2* expression	IHC and Real Time PCR	JWA and MMP-2 can play role as promising prognostic biomarkers in resectable GC.
(25)	2014	China	105	105	-	58 (32 - 84)	Tissue	*MMP-2* expression	IHC, RT-PCR	Activation of p38 induced metastasis in GC with up-regulation of AP-1/c-fos, *MMP-2*, and *MMP-9*.
(26)	2013	Poland	108	40 (30/10)	68 (14/54)	GC: 28 - 82, Control: 21 - 64	Tissue and Blood	*MMP-2* expression	IHC and ELISA	The positive reaction of MMP-2 was higher in GC compared to normal tissue.
(27)	2013	China	40	40 (32/8)	-	57.9 (18 - 77)	Tissue	*MMP-2* expression	IHC	Combined detections for the activity of telomerase and MMP-2 can identify patients at high risk in disease recurrence.
(28)	2012	Poland	24	24 (18/6)	-	63.7 (43 - 81)	Tissue	*MMP-2* expression	Spectrophotometric	The highly significant association between VEGF and MMP-2 in GC was reported.
(29)	2011	Poland	191	100 (73/27)	91 (60/31)	GC: 27 - 83, Control: 21 - 65	Blood	*MMP-2* expression in serum	ELISA	MMP-2 and TIMP-2 expression at serum level was positively lower in GC patients than in control subjects.
(30)	2010	Taiwan	189	189 (110/79)	-	62	Tissue	*MMP-2* expression	IHC	The Claudin-4 expression was positively associated with *MMP-2* expression.
(15)	2009	Poland	53	34 (24/10)	19 (11/8)	60.4	Serum	*MMP-2* expression in serum	zymographic	MMP-2 expression at serum level in GC individuals was not significantly higher than that in healthy group.
(31)	2008	China	44	44	-	-	Tissue	*MMP-2* expression	IHC	Metastatic GC presents higher MMP-2 immunoreactivity than primary GC.
(32)	2008	Germany	116	116 (69/47)	-	64 (33 - 85)	Tissue	*MMP-2* expression	IHC	MMP-2 plays a critical role in the invasion of GC
(33)	2007	Taiwan	523	240 (143/97)	283 (170/113)	59.95 (22 - 88)	Blood	polymorphism	PCR-direct sequencing, PCR-RFLP	1306 C/T polymorphism of MMP2 is correlated with invasion and progression of GC
(34)	2006	Finland	329	329 (171/158)	-	66	Tissue	*MMP-2* expression	IHC	Epithelial *MMP-2* expression in GC correlated with aggressive forms OF COX-2
(35)	2006	Japan	229	229 (166/63)	-	65.5 (38 - 88)	Tissue	*MMP-2* expression	Tissue microarray and Immunostaining	MMP-2, MMP-9 and VEGF play role in the angiogenesis and progression of GC.
(36)	2006	China	30	30 (17/13)	-	56.8 (26 - 82)	Lymph node	*MMP-2* expression	IHC, RT-PCR	Expression of *MMP-2* has a positive association with tumor invasion, tumor differentiation, and lymph node metastasis of GC.
(37)	2006	Netherlands	81	81 (60/21)	-	65.9 (35 - 91)	Tissue	*MMP-2* expression	gelatin zymography and ELISA	MMP-2 is positively correlated to the prognosis of GC than other MMPs or TIMPs.
(38)	2005	China	97	65 (50/15)	32	60.08 (31 - 81)	Tissue	*MMP-2* expression	IHC	MMP-2 gene plays the main role in metastasis, invasion, and prognosis of GC.

(39)	2005	China	77	67 (43/24)	10	62.2 (23 - 78)	Tissue	*MMP-2* expression	RT-PCR analysis of MMP-2mRNA	Expression of *MMP-2* in tumor tissues didn't correlate with depth of invasion. MMP-2 may play a critical function in the development, invasion, and metastasis of GC.
(13)	2003	China	1145	356 (308/48)	789 (672/117)	GC:58.4 (41 - 72), Control: 57.6 (45 - 76)	Blood	*MMP-2* Polymorphism	PCR based DHPLC, DNA sequencing	1306 C/T polymorphism in MMP2 is correlated with development risk but not metastasis of GC.
(40)	2001	Germany	114	114 (66/48)	-	64 (33 - 85)	Tissue	*MMP-2* expression	IHC	*MMP-2* expression is positively associated with lymph node metastasis and tumor progression in GC
(41)	1999	China	25	20 (13/7)	5benign ulcer patients	61.8 (38 - 74)	Tissue	*MMP-2* expression	RT-PCR	MMP-2 can play the main role in GC invasion and metastatic progression.
(42)	1998	Germany	203	203 (108/95)	-	63.8 (22 - 87)	Tissue	*MMP-2* expression	IHC	Immunohistochemical detection of MMP-2 was associated with the prognosis of GC.
(43)	1998	Italy	25	25 (11/14)	-	-	Tissue	*MMP-2* expression	RT-PCR, zymography	MMP-2 suggested as a new molecular-level prognostic factor.
(44)	1997	Japan	68	68 (42/26)	-	65.6	Tissue	*MMP-2* expression	RT-PCR, IHC, zymography	Activation of MMP-2 can be clinically relevant with GC susceptibility.
(45)	1996	Netherlands	50	50 (38/12)	-	66.3	Tissue	*MMP-2* expression	quantitative zymography	The mean level of MMP-2 was positively increased in carcinomas than in tumor-free adjacent mucosa of the stomach.
(46)	1996	Japan	46	46	46	-	Tissue	*MMP-2* expression	IHC, immunoassays, zymography	Activation of pro-MMP2 can be the main step for spreading of GC cells.

Abbreviations: AGEs, advanced glycation end products; ELISA, enzyme-linked immunosorbent assay; GC, gastric carcinoma; IHC, immunohistochemistry; mTOR, mammalian target of rapamycin; qRT-PCR, Quantitative real-time polymerase chain reaction; VEGF, vascular endothelial growth factor.