Prognostic value of MMP-7-181 A/G single nucleotid polymorphism and helicobacter pylori infection in gastric cancer

Mide kanserinde MMP-7 geni -181 A/G tek nükleotid polimorfizminin ve H. Pylori enfeksiyonu' nun prognostik önemi

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ÖZET

GİRİŞ ve AMAÇ: Mide Kanseri halen yüksek morbidite ve mortaliteye neden olmaktadır. Bu sebepten araştırmacılar, prognozu etkileyen faktörleri araştırmaya yönelmişlerdir.
Çalışmamızda Mide Kanseri tanısı ile opere olan tümör ve normal doku örnekleri kullanılarak MMP-7 polimorfizminin ve H. Pylori enfeksiyonunun Mide Kanseri'nin prognozuna etkisi araştırılmıştır.
YÖNTEM ve GEREÇLER: Ekim 2008 - Ekim 2010 tarihleri arasında Ankara Üniversitesi Tıp Fakültesi hastanesi, Cerrahi Onkoloji Departmanı'ndan mide adenokarsinomu olan vakalar içinde 50 kişi rastgele seçildi ve sağlıklı kontrol grubu da 50 kişiden oluşturuldu. Çalışma grubu 31 erkek ve 19 kadın olmak üzere 50 kişiden oluşmaktadır. Mide Kanser'li 50 hastanın; 15'inin (%30) AA, 20'sinin (%40) AG, 15'inin (%30) GG genotipine sahip olduğu, sağlıklı gönüllülerde ise 25' i AG, 9' u GG and 16'sı AA genotipine sahip olduğu bulundu.
BULGULAR: G1+G2 ile G3 evreleri A/G polimorfizmine göre karşılaştırıldığında G3 evrede G Allel sıklığının %53.8 G1+G2 evrelerde %45.8 bulunmuştur. Bu sonuç da G Allel sıklığının fazla olmasının Grade'i arttırdığını düşündürmüştür. Hastalar H. Pylori taşımalarına göre Tümör Boyutu ile karşılaştırıldığında T1+T2 evreye sahip olanların %0 oranında H. Pylori (+) olduğu T3+T4 olanların %65.1 oranında H.Pylori(+) olduğu bulunmuştur (p=0.02). Bu durum, H. pylori'nin mide kanseri için negatif bir prognostik faktör olduğu yönündeki daha önce yapılmış çalışmaları desteklemiştir.
TARTIŞMA ve SONUÇ: Bu çalışma da, Türk toplumundaki sağlıklı gönüllülerin A alleli sıklığı =% 57, G alleli sıklığı =% 43 olarak saptandı. Bu durumun Avrupa'daki G allel frekansı ile paralellik gösterdiği bulundu. Ülkemizde ve Avrupa'da mide kanseri prognozu Japonya'dan daha kötüdür, çünkü G allel frekansı Japonya'dan daha fazladır.
Anahtar Kelimeler: Mide kanseri, Matrix metalloproteinase 7, prognoz, H. Pylori

ABSTRACT

INTRODUCTION: Gastric Cancer is still causes high morbidity and mortality. So the researchers directed to research the factors affecting prognosis.
In our present study, the effects of both MMP7 -181G>A promoter polymorphism and H. pylori infection on gastric cancer prognosis was investigated in gastric adenocarcinoma.
METHODS: All of the cases (n=50) and healthy controls (n=50) were unrelated individuals who were selected from the Ankara University School of Medicine, Department of Surgical Oncology between October 2008 and October 2010. The study group consisted of 50 patients, including 31 males and 19 females, including 15=AA, 20=AG, 15=GG genotype. In the control group; 25=AG, 9=GG and 16=AA genotype was found.

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RESULTS: G1+G2 and G3 phases were compared according to A/G polymorphism. G allele frequency of stage G3=53.8% of patients with G1+G2 phase was found 45.8%. According to this result; the frequency of G allele being considered to increase the G phase. Patients compared with H.Pylori and tumor size, in stage T1+T2 no patients had H pylori (+), in T3+T4, 65.1% of those with H pylori(+) was found (p= 0.02). This situation proved previously conducted studies that H. pylori is a negative prognostic factor for gastric cancer.
DISCUSSION AND CONCLUSION: In this study healthy volunteers population was found the frequency of A allele=%57, frequency of allele G=43%, this condition is found to be parallel with the European's G allele frequency. In our country and in Europe stomach cancer prognosis is worse than Japan because frequency of G allele is more than Japan.
Keywords: gastric cancer, MMP-7, prognosis, Helicobacter Pylori

INTRODUCTION

Gastric Cancer is widely seen all over the world, despite advances of surgery it is still a very serious health problem that causes high morbidity and mortality. Currently the main treatment method of this disease is surgery. 5-year disease-free survival of gastric cancer is very low so the researchers directed to research the factors affecting prognosis(1). Similar to all other solid tumors, genetic and environmental factors play an important role in gastric cancer development and progression. Previous studies have clearly demonstrated that multiple genetic alterations are responsible for the development and progression of gastric cancer.(2)

Matrix metalloproteinase 7 (MMP7), also known as matrilysin, is located on chromosome 11 and it is the MMP with smallest structure (3). Matrilysin found excessively in human cancer tissues and its production is associated with cancer progression.Tumor formation is a multi-step process that involves cell growth, invasion, metastasis and angiogenesis. It has been shown that matrilysin plays an important role in several biochemical processes like degradation and destruction of extracellular matrix (ECM) proteins as well as destruction, activation and modification of non-ECM proteins (3).

MMP7 is a member of the MMP family that expressed from polarized glandular epithelium for organization of the defense against microbial colonization in stomach and gastrointestinal system (4). Therewithal, MMP-7 overexpressed in gastric malignancy and affects cell proliferation and apoptosis (5-7). Epithelial cells of gastrointestinal system, urogenital system and respiratory system are frequently exposed to bacterias. Maintenance of constitution and function of normal epithelium is provided by proliferation, migration and apoptosis of epithelial cells, in relation with immune system (cytokine secretion, chemokine, antigen presentation)

It has been shown that *Helicobacter pylori* (*H. pylori*) infection also cause susceptibility to gastric cancer. This situation is known as tumorigenesis that facilitated by bacteria (8,9). The role of *H. pylori* and MMP7 in the progression of cancer is still not clear.

In our present study, the effects of both MMP7 -181G>A promoter polymorphism and *H. pylor*i infection on gastric cancer prognosis was investigated in gastric adenocarcinoma.

MATERIAL and METHODS

All of the cases (n=50) and healthy controls (n=50) were unrelated individuals who were selected from the Ankara University Hospital, Department of Surgical Oncology between October 2008 and October 2010. The case group comprised tumor resection inpatients who were histopathologically confirmed to have gastric adenocarcinoma. Tissue samples were obtained after receiving the patients' informed consent granting permission for anonymous use of their tissue samples in future studies. This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Ankara University Faculty of Medicine (approval# 17-372). The patients had no family history of cancer and were free of concurrent malignant conditions other than gastric cancer. None of the patients had received chemotherapy or radiotherapy prior to surgery. If the lesions were considered as early gastric cancer during surgical resection, the patients were excluded from the study. Patients who were diagnosed with diffuse type gastric adenocarcinoma during histopathological evaluation were excluded from the study and only patients with

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the intestinal type of gastric adenocarcinoma were enrolled. Tumoral and normal mucosa samples were obtained from all the subjects. Samples of normal mucosa were collected from areas near the surgical margins and far from the tumors that were macroscopically free of tumor invasion. Routine histopathological examinations and *H. pylori* infection status were performed at the Department of Pathology, Faculty of Medicine, Ankara University, Ankara, Turkey.

Peripheral blood samples obtained from 50 volunteers admitted to outpatient clinic of general surgery for reasons except malignancy were included in the study as control group.

DNA Isolation from Tissue and Peripheral Blood Samples

DNA samples were obtained from approximately 0.5 cm^3 freshly frozen tissue specimens stored at 80˚C. DNA extraction was performed DNA isolation from solid tissue specimen was performed by using BDtract Genomic DNA Isolation Kit (40001, Maxim Biotech, CA, USA) according to the manufacturer's instructions. NucleoSpin® Blood XL (Macherey Nagel, 740 950. 50) kit was used for DNA isolation from pheripheral blood samples.

Genotyping of MMP7 -181A>G polymorphism

MMP7 -181A>G genotyping was done by PCR-RFLP method. The PCR of G2677T/A polymorphism was performed in a total volume of 25 µl, using 100 ng of genomic DNA with 10pmol primers each (F: 5′-TGGTACCATAATGTCCTGAATG -3′, R: 5′-TCGTTATTGGCAGGAAGCACACAATGA ATT -3′(Sugimoto ve ark., 2008), 0.2 mM of each dNTP, 1× buffer with KCl, 3mM of MgCl2 and 1U Taq DNA polymerase (Fermantas, EP 0402). The cycling conditions performed in a Techne TC-4000 Thermal Cycler (Bibby Scientific Limited, Staffordshire, UK) were as follows: amplification consisted of a five-minute denaturation step at 95°C; 35 cycles, 30s at 95°C, 30s at 60°C and 30s at 72°C; and a seven-minute final extension at 72°C, followed by cooling to 4°C. Genotype analysis was conducted using RFLP. Restriction digestion was performed in a total volume of 25 µl reaction mixture containing 10 µl PCR product and 20 U EcoRI restriction endonuclease. Reaction mixtures were incubated at 37°C overnight and the digested PCR products were resolved by electrophoresis in 3% agarose gels containing 0.5µg/ml of ethidium bromide and visualized by KODAK Gel Logic 200 image analyzing system. A allele: 150 bp; G allele: 120bp + 30 bp.

Statistical Analysis In statistical analysis, allele frequencies were tested with chi-square test, and genotype frequencies were tested with Wilcoxon signed rank test. P values less than 0.05 were taken to indicate a statistically significant difference.

RESULTS

The demographic and clinicopathological characteristics of the patients are summarized in Table 1. Of the patients, 31 were men and 19 were women, with a mean age of 58,5 (± 3,46) years, respectively. 86% of the patients were diagnosed at late stages (T3 and T4) and 64% of the patients had lymph node metastasis. 8% of the patients patient had a distant metastasis. Well-differentiated tumors were detected in 40% of the patients, whereas 60% of the patients had poorly differentiated tumors. *H. pylori* infection was positive in 54% of our patients. It is shown that, 27 of 40 patients (67%) with T3 tumor were H.pylori (+), there were no H. pylori (+) patients in T1 and T2 tumors. Fourteen of 25 patients (56%) who were H.pylori (-), had N0, 11 had tumors with lymph node metastasis. Sixteen of 26 patients (61%) who were H.pylori (+) had G3, 10 (38%) had G1 and 3 (1%) had G2 tumors. It seems that H. pylori negativity was higher in T1 and T2 patients while H.pylori positivity is higher in T3 patients. H.pylori negativity was higher in G1 stage while H. Pylori positivity was higher in G2 and G3 stages.

The allele and genotype distributions of the MMP7 -181 A>G SNP in the patients and controls are summarized in Table 2. Of the patients, 15 (30%) have AA, 20 (40%) have AG and 15 (30%) have GG genotype. There was no genotypic difference acoording to MMP7 – 181 A/G between cancerous and non-cancerous tissues (p>0.05). The A and G allele frequencies were found 50% each. In the control group, 25 volunteers (50%) have AG, 9 volunteers (18%) have GG and 16 volunteers (32%) have AA genotype. . The frequency of the A allele was calculated as 57% and the

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frequency of the G allele was found as 43% in the control group. When T3 group evaluated in itself, 32.5% have AA, 42.5% have AG and 25% have GG genotype.

Table 1. distribution of gastric cancer patients according to tumor size (T) and lymph node status (N)

	Frequency	Percent	Current Percent	Cumulative Percent
T1	4	8,0	8,0	8,0
T2	3	6,0	6,0	14,0
T3	40	80,0	80,0	94,0
T4	3	6,0	6,0	
Total	50	100,0	100,0	100,0
N0	18	36,0	36,0	36,0
N1	13	26,0	26,0	62,0
N2	12	24,0	24,0	86,0
N3	7	14,0	14,0	
Total	50	100,0	100,0	100,0

It is seem that G allele frequency is higher in patients with gastric cancer. The high frequency of G allele in G2 and G3 stages suggests that G allele carriers have worser prognosis. G allele frequency was higher in T4 tumor size.

Table 2. Comparison of the tumor size, grade and lymph node Involvement in H. Pylori (+) and (-) patients

	***H. Pylori* (+)**	***H. Pylori* (-)**
T2	0	3
T3	27	13
T4	1	2
G1	7	12
G2	3	1
G3	16	11
N0	6	14
N1	8	4
N2	8	3
N3	3	4

(T: Tumor size, G:Grade, N: Lymph Node Status)

When T1 + T2 + T3 tumor size compared with patients with T4 tumor size, it was found that G allele frequency was 83.3% in T4 patients in comparison to 47.9% in T1 + T2 + T3 patients. However, the the difference did not reach the statistical significance (p=0,204). The G allele frequency value of 83.3%, suggests that this clinical significance could be statistically significant when number of subjects increased.

When G1+G2 and G3 stages compared according to MMP7 -181 A>G SNP, G allele frequency was 53.8% in G3 and 45.8% in G1+G2 stages. While this result suggests that high frequency of G allele increase G stage, p value was 0.423 after Chi-square test was performed. However, the the difference did not reach the statistical significance. .

When tumor size of patients compared with G genotype carriage, 100% of T4 patients were G carriers (AG + GG) while 68.1% of T1+T2+T3 patients were G carriers and it was thought that G genotype increase tumor size, clinically. However, the the difference did not reach the statistical significance (p=0.545)When M0 and M1+Mx metastasis status compared according to MMP7 -181 A>G genotype, G allele carrier frequency (AG + GG) were 66.7% in M0 patients while 78.6% in M1 + Mx patients. However, the the difference did not reach the statistical significance (p=0,507).

When H.Pylori status compared according to tumor size, 0% of patients with T1+T2 stage had H. Pylori (+) while 65.1% of patients with T3+T4 stage had H.Pylori (+) (Table 3).

DISCUSSION

MMPs are zinc-dependent proteinases which are capable of breaking down many ECM proteins (10While MMPs play role in biological processes like tissue remodeling, wound healing, and embryonic development,they also have role in tumor invasion and metastasis by destruction of connective tissue, basal membrane and stromal matrix. MMP-7 is called as matrilysin. Besides a large proteolytic activity it is also involved in the activation of other MMPs (10).

It is known that MMP-7 expression is elevated in many cancer types such as colorectal, gastric, esophageal, pancreas, prostate, head, neck, lung, liver and breast. Furthermore, MMP-7 levels increase in premalignant lesions of colon adenomas, pancreas, stomach, breast and prostate.

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MMPs are generally expressed from normal tissues but on the contrary MMP-7 expressed mainly from tumoral cells. It has been shown that MMP-7 leads cancer progression by destruction of ESM and additionally inhibiting apoptosis of cancer cells, decreasing cell adhesions and increasing angiogenesis (10).

Table 3. Clinicopathologic Evaluation of MMP-7 -181 A / G Polymorphism

SNP	Group	Number	Allele			N	Genotype			
-181 A/G			**A**	**G**	**p**		**AG**	**GG**	**AA**	**p**
	Contol group	100	57 57%	43 43%	-	50	25 50%	9 18%	16 32%	
	Gastric cancer patients	100	50 50%	50 50%	-	50	20 40%	15 30%	15 30%	
Tumor Size										
T1+T2+T3(n=94)			49 %52.1	45 %47.9	p>0.05					
T4(n=6)			1 %16.7	5 %83.3						
Grade										
G1+G2(n=44)			26 %54.2	22 %45.8	p>0.05					
G3(n=46)			24 %46.2	22 %53.8						
Lymph node invasion										
N0(n=36)			0.50	0.50			6 %33	6 %33	6 %33	
N1+N2+N3(n=64)			0.50	0.50			14 %43	9 %28	9 %29	
Metastasis					***AG+GG***		***AA***			
M0					24(%66.7)		12(%33.3)			p>0.05
M1+MX					11 (%78.6)		3%21.4			
H Pylori	**H Pylori (-)**				**H Pylori (+)**					
T1+T2(n=7)	7 %100				0 %0					p<0.05
T3+T4(n=43)	15 %34.9				28 %65.1					

SNP= Single Nucleotide Polymorphism

In a study investigating the prognostic significance of MMP-7 in gastric cancer, stomach tissues obtained from patients operated because of gastric cancer were stained immunohistochemically and MMP-7 signal intensity was compared with patients tumor size, lymph node metastasis and distant metastasis rates and as a result, more lymph node metastasis and distant metastasis rates were found in patients with higher MMP-7

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levels and this was adversely affecting survival (10). On the basis of this results, it has been shown that MMP-7 is an independent predictor of survival in gastric cancer.

In our study, when T1 + T2 + T3 tumor size compared with patients with T4 tumor size, it was found that G allele frequency was 83.3 % in T4 patients in comparison to 47.9% in T1 + T2 + T3 patients. Carrying G allele is thought to increase the size of the tumor. P value was 0.204 (p>0.05) when the results were evaluated by Chi-square test. The G allele frequency value of 83.3 %, suggests that this clinical significance could be statistically significant when number of subjects increased.

When tumor size of patients compared with G genotype carriage, 100% of T4 patients were G carriers (AG + GG) while 68.1 % of T1+T2+T3 patients were G carriers and it was thought that G genotype may be correlated with increase tumor size, clinically. Although p value is 0.545, it is expected that this relationship could be statistically significant when number of subjects increased.

The risk of gastric cancer increases in gastric epithelial cells exposed to H.pylori infection for a long time (11-12). When H.Pylori status compared according to tumor size, 0% of patients with T1+T2 stage had H. Pylori (+) while 65.1 % of patients with T3+T4 stage had H.Pylori (+) (Table 3). When this results evaluated with Chi-Square test p value was 0.02 and significant relationship found between H.Pylori positivity and tumor size and this results support the proposal in Chin Wu et al. study (13) that "H. pylori is a negative prognostic factor for gastric cancer".

It has recently shown that MMP-7-181 A/G polymorphism is associated with poor prognosis in gastric cancer (14). In a study that Sugimoto et al. performed about relation between MMP-7 polymorphism and susceptibility to gastric cancer with progression of gastric cancer, they found about MMP-7- 181 A/G polymorphism that; 83.1% of cases had AA, 16.9% had AG and 0% had GG genotype. They found that MMP-7-181 G allele carriers relatively have serious risk for development and poor prognosis of gastric cancer considering A allele carriers (15) (OR, 2.32; 95% CI, 1:24 to 4:35). When clinical stages of the patients evaluated, it has been shown that G allele carriers have significantly increased risk for Stage 3-4 cancer (OR, 3.66; 95% CI, 1.54-8.73). In our study, when G1+G2 and G3 stages compared according to A/G polymorphism, G allele frequency was 53.8 % in G3 and 45.8% in G1+G2 stages. While this result suggests that high frequency of G allele increase G stage, p value was 0.423 after Chi-square test was performed. No significant relationship considered because p value was >0.05. However, it is also expected that this relationship could be statistically significant when number of subjects increased.

A previously performed study revealed that A/A allele carriers have better prognosis and less distant metastasis rate than G/G allele carriers (16). In our study, when M0 and M1+Mx metastasis status compared according to G allele carriage, AG + GG rate were 66.7% in M0 patients while 78.6% in M1 + Mx patients. Carriage of G allele can lead to distant metastasis clinically but p value was 0.507. High rate of M1 + Mx patients suggests that this relationship could be statistically significant when number of subjects increased.

Another study showed differences in MMP-7-181 A/G polymorphism for different ethnic groups. MMP-7-181 G allele was found in 41.1 % of the Europeans and between 2.8% and 6% in the East Asians. Therefore the difference of MMP-7-181 A/G polymorphism in this groups has thought to be the reason of why gastric cancer has different development rates in different ethnic groups (17). In our study, A allele frequency was 57% and G allele frequency was 43% in healthy volunteers and results found to be similar to the G allele frequency detected in Europeans. The poor prognosis of gastric cancer in our counrty and Europe than Far East countries was thought to be due to higher rate of G allele frequency.

In a study conducted by M. Honda and his friends, cancerous and non-cancerous tissues of 48 gastric cancer patients were compared after operation and immunohistochemical expression of MMP-7 and mRNA measurement was performed. Study results revealed that, in 41 (87%) of 48 patients, MMP-7 expression and mRNA were higher in cancerous mucosa than normal mucosa. Additionally in patients with overexpression of MMP-7 in cancerous tissues; a significant relation was found in terms of excessive gastric wall invasion, more lymphatic spread and more vascular invasion.

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They suggest that these findings strongly support the hypothesis that MMP-7 expression increases tumor invasion. (18). Based on this study, we compared cancerous and non-cancerous tissues of 50 gastric cancer patients with RFLP in our study but we did not find any difference between cancerous and non-cancerous tissues that will generate MMP-7-181 A/G changes in DNA level.

In conclusion; the healthy volunteers population was found the frequency of A allele=%57, frequency of allele G=43%, this condition is found to be parallel with the European's G allele frequency. In our country and in Europe stomach cancer prognosis is worse than Japan because frequency of G allele is more than Japan.

We compared cancerous and non-cancerous tissues of 50 gastric cancer patients with RFLP in our study but we did not find any difference between cancerous and non-cancerous tissues that will generate MMP-7-181 A/G changes in DNA level.

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