Current Evidence on the Association between Mmp-7 (-181A>G) Polymorphism and Digestive System Cancer Risk

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Abstract

The matrix metalloproteinase (MMPs) family comprise of more than 20 enzymes that are capable of degrading extracellular matrix proteins [1-3]. MMPs not only play important roles in physiological ECM remodelling, such as wound repair, tissue regeneration and embryo development, but are also associated with pathological conditions, such as arthritis, atherosclerosis and autoimmune blistering disorders of the skin. There is also growing evidence suggesting that MMPs can degrade various components of the extracellular matrix and are involved in cancer development by modulating cell proliferation, apoptosis, angiogenesis, and so on [1,2] MMP7, localised on chromosome 11q21-q22, is one of the smallest members of the MMPs family, which can degrade elastin, proteoglycans, fibronectin and type IV collagen [3-23]. It also cleaves non-matrix substrates from the cell surface, such as E-cadherin, pro-tumour necrosis factor and Fas ligand. An A to G transition at -181 base pair position upstream of the transcription start site of MMP7 gene has been reported. The G allele has greater basal transcriptional activity than A allele in vitro [24]. Over-expression of MMP7 has been shown to occur in a wide variety of cancers, including tumours of the oesophagus, stomach, colorectal, kidney and breast [5,6], and this is correlated with tumour size, lymph node involvement and decreased survival. Recently, many studies indicating that the common MMP-7 (-181A>G) genetic polymorphism was correlated with cancer risk in many cancer types [7-22]. However, this relationship remains controversial in digestive system cancer, this meta-analysis was performed to evaluate the association between the MMP-7 (-181A>G) genetic polymorphism and digestive system cancer risk.

Search Strategy and Data Extraction

In this analysis, a literature research of the Pub Med database,
ISI Web of Knowledge, Medline, Embase and Google Scholar Search (up to date as of October, 2012) were conducted using the search terms including (“MMP7” or “matrix metalloproteinase 7”), “polymorphisms”, “cancer”, to obtain all genetic studies on the relationship of MMP-7 (-181A>G) polymorphism and cancer. We also used the combined phrases and a hand search of references of original studies on this topic. Figure 1 showed the flow diagram of study identification.

Data extraction was carried out independently by two investigators. We record the following information of each eligible study: the first author, year of publication, country of origin, genotyping methods, source of controls, number of cases and controls with different groups.

### Statistical Analysis

The strength of relationship between MMP-7 (-181A>G) polymorphism and cancer was assessed by using Crude OR with 95% CI. We examined the association between the MMP-7 (-181A>G) polymorphism and digestive cancer risk using homozygote comparison (GG vs. AA), heterozygote comparison (GA vs. AA), dominant genetic model (GG + GA vs. AA) and recessive genetic model (GG vs. GA + AA). Between-study heterogeneity was evaluated by Q-test. Fixed effects model was used to pool the data when the P-value of Q-test ≥ 0.05, otherwise, random-effects model was selected. Egger’s test was used to

### Table 1: Main characteristics of included studies in the meta-analysis.

| Author       | Year | Cancer type | Country     | Ethnicity | Genotype assay | Source of Control | Case/Control | P‡         |
|--------------|------|-------------|-------------|-----------|----------------|-------------------|--------------|------------|
| Zhang        | 2005 | Gastric     | China       | Asian     | PCR-RFLP       | Population        | 201/350      | Yes        |
| Kim          | 2011 | Gastric     | Korea       | Asian     | PCR-RFLP       | Hospital          | 153/326      | Yes        |
| Malik        | 2011 | Gastric     | India       | Asian     | PCR-RFLP       | Population        | 108/195      | Yes        |
| Sugimoto     | 2008 | Gastric     | Japan       | Asian     | PCR-RFLP       | Hospital          | 160/434      | Yes        |
| Kubben       | 2006 | Gastric     | Holland     | European  | PCR-RFLP       | Population        | 79/169       | Yes        |
| Li           | 2008 | Gastric     | China       | Asian     | PCR-RFLP       | Population        | 338/380      | Yes        |
| Zhang        | 2005 | ESCC        | China       | Asian     | PCR-RFLP       | Population        | 258/350      | Yes        |
| Malik        | 2011 | ESCC        | India       | Asian     | PCR-RFLP       | Population        | 135/195      | Yes        |
| Lievre       | 2006 | Colorectal  | France      | European  | Tagman         | Population        | 596/565      | Yes        |
| Dziki        | 2011 | Colorectal  | Poland      | European  | PCR-RFLP       | Hospital          | 184/205      | Yes        |
| Ohtani       | 2009 | Colorectal  | Japan       | Asian     | PCR-RFLP       | Hospital          | 119/67       | Yes        |
| Ghilardi     | 2003 | Colorectal  | Italy       | European  | Sequencing     | Population        | 58/111       | Yes        |
| Woo          | 2007 | Colorectal  | Korea       | Asian     | PCR-RFLP       | Population        | 185/304      | Yes        |
| Fang         | 2010 | Colorectal  | China       | Asian     | PCR-RFLP       | Population        | 252/237      | Yes        |
| de Lima      | 2009 | Colorectal  | Brazil      | South America | PCR-RFLP  | Hospital          | 108/113      | Yes        |
| Vairaktaris  | 2007 | Oral        | Germany, Greek | European | PCR-RFLP       | Population        | 159/120      | No         |
| Qiu          | 2008 | Hepatocellular | China     | Asian     | PCR-RFLP       | Population        | 425/475      | Yes        |

‡ P value of Hardy-Weinberg equilibrium in controls; ESCC: esophageal squamous cell carcinoma

### Table 2: Results of meta-analysis for MMP-7 (-181A>G) polymorphism and digestive cancer risks.

| Study groups        | OR (95% CI) | £ | OR (95% CI) | £ | OR (95% CI) | £ | OR (95% CI) | £ |
|---------------------|-------------|---|-------------|---|-------------|---|-------------|---|
| **Total**           | 1.21 (1.12-1.60)‡ | <0.001 | 1.06 (0.99-1.13) | 0.536 | 1.16 (1.03-1.36)‡ | <0.001 | 1.12 (0.95-1.31)‡ | <0.001 |
| **Cancer type**     |             |   |             |   |             |   |             |   |
| Hepatocellular      | 1.43 (1.10-1.87)‡ | 0.851 | 1.29 (0.99-1.68) | 0.771 | 1.36 (1.02-1.81) | 0.796 | 1.17 (0.96-1.93) | 0.215 |
| Gastric             | 1.22 (1.02-1.46)‡ | 0.523 | 1.82 (1.61-2.87) | 0.704 | 1.13 (1.01-1.28) | 0.711 | 1.25 (1.06-1.49) | 0.542 |
| Colorectal          | 1.13 (1.01-1.26)‡ | 0.020 | 0.805 (0.50-1.30)‡ | 0.006 | 0.86 (0.54-1.35)‡ | 0.006 | 1.08 (0.80-1.45) | 0.215 |
| Esophagus            | 1.00 (0.24-4.30)‡ | <0.001 | 1.45 (1.11-1.91)‡ | 0.146 | 1.19 (0.48-2.96)‡ | 0.002 | 0.81 (0.27-2.39)‡ | <0.001 |
| Oral                | 1.73 (0.38-1.39)‡ | 0.312 | 1.09 (0.26-4.55)‡ | 0.013 | 1.02 (0.30-4.35)‡ | 0.026 | 0.88 (0.56-1.36)‡ | 0.478 |
| **Ethnicity**       |             |   |             |   |             |   |             |   |
| Asian               | 1.40 (1.12-1.69)‡ | <0.001 | 1.26 (1.02-1.51)‡ | <0.001 | 1.18 (1.08-1.55)‡ | <0.001 | 1.14 (0.96-1.36)‡ | <0.001 |
| European            | 1.13 (0.60-1.97)‡ | 0.070 | 0.98 (0.49-1.77)‡ | 0.070 | 1.11 (0.76-1.52)‡ | 0.029 | 1.01 (0.73-1.51)‡ | 0.154 |
| **Source of Control** |             |   |             |   |             |   |             |   |
| Population-based    | 1.19 (0.91-1.90)‡ | <0.001 | 1.16 (0.98-1.37)‡ | 0.029 | 1.10 (1.01-1.72)‡ | <0.001 | 0.95 (0.68-1.37)‡ | <0.001 |
| Hospital-based      | 1.25 (1.01-1.74)‡ | <0.001 | 1.15 (0.88-1.50)‡ | <0.001 | 1.14 (0.84-1.54)‡ | <0.001 | 0.97 (0.82-1.39)‡ | 0.150 |

Abbreviations: CI, confidence interval; OR, odds ratio.

* Studies of comparison,$P$-value of Q-test for heterogeneity test, ‡ Random model was used.
assess the publication bias. (P<0.10 was considered representative of statistical significance). All statistical analyses were performed using STATA11.0 software and Review Manage (v.5; Oxford, England).

Results

Eligible studies

The main characteristics of these studies are shown in table 1. Genotype distribution of the MMP-7 (-181A>G) polymorphism among cancer cases and controls of the 16 studies are shown in table 2. The genotyping method contains the classic polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay, DNA sequencing, Affymetrix and Taqman. Among all the studies, seven colorectal cancer studies, six gastric cancer studies, two esophageal squamous cell carcinoma studies, one oral carcinoma and one hepatocellular carcinoma were included. Twelve studies were Asian descent, four studies were Caucasian descent and one study was South America descent. Hospital based controls were carried out in 5 studies, while population based controls were carried out in twelve studies.

Meta-analysis

Overall, as shown in table 2, we observed that the MMP-7 (-181A>G) polymorphism increased the digestive system cancer risk in homozygote comparison (GG vs. AA, OR=1.21, 95% CI=1.12-1.60) and dominant model (GG/GA vs. AA, OR=1.16, 95% CI=1.03-1.46) when all the eligible studies were pooled into the meta-analysis (Table 2). In the subgroup analysis, we found that the MMP-7 (-181A>G) polymorphism elevates gastric cancer risk in all the four models (GG vs. AA, OR=1.22, 95% CI=1.02-1.46; GA vs. AA, OR=1.82, 95% CI=1.16-2.87; GG/AG vs. AA, OR=1.13, 95% CI=1.01-1.26; GG/AG vs. AA, OR=1.25, 95% CI=1.06-2.39). Furthermore, we found significant association of MMP-7 (-181A>G) polymorphism with ESCC and colorectal cancer in homozygote comparison (GA vs. AA, OR=1.45, 95% CI=1.11-1.91) and homozygote comparison (GG vs. AA, OR=1.13, 95% CI=1.01-1.26) respectively. Compared with gastric cancer, ESCC and colorectal cancer, no significant associations were found in oral carcinoma and hepatocellular carcinoma.

We then evaluated the effects of the MMP-7 (-181A>G) polymorphism according to different ethnicities and different source of control. As shown in table 2, in the stratified analysis by ethnicity, a significantly increased risk was found among Asian populations in both ethnic subgroups. The results did not present any obvious evidence of publication bias in the subgroup analyses for GG vs. AA p=0.576, AA vs. AA P=0.872GG+GA vs. AA p=0.675, GG vs. GA+AA P=0.721.

Discussion

The result of this meta-analysis involving 3,518 cases and 4,596 controls suggested that the MMP-7 -181A/G polymorphism was overall significantly associated with digestive system cancer risk, especially in Asian population.

Recently, Malik MA conducted one study indicating that individuals who living in the Kashmir Valley carrying -181 GG genotype were related to high risk of gastric cancer [9]. Besides, Ghilardi et al. observed the -181A/G polymorphism was associated with increased risk of colorectal cancer development [17]. However, Peng et al. performed a meta-analysis and suggested the association between MMP7 -181 A G and increased cancer risk was found in the gastric cancer subgroup, no significant difference was found in the colorectal cancer subgroup [23].

In this meta-analysis, significant association was found between the MMP7 -181 A/G polymorphism and risk of gastric cancer. Besides, the association was more significant in the recessive model compared with the dominant model. Functional analysis in vitro has shown that nuclear proteins bind with higher affinity to the -181 G allele than to the -181A allele and promoter activity variation of the -181G allele may induce elevation of the protein expression, so individuals with GG genotype may have a higher risk of the gastric cancer than with GA genotype. For ESCC and colorectal cancer, the significant associations were just found in the dominant model and homozygote model respectively. We also found Asians with GG genotype had higher risk of cancer compared to Caucasians. Several factors such as environmental factors and different genetic backgrounds might contribute to the difference. Furthermore, inconsistent results were observed between hospital-based studies and population-based studies. Controls in population-based studies were more representative of general population than controls from hospital-based studies.

As in all research, our study has limitations. First, the controls were not uniformly defined. Second, studies involved in different ethnicities are warranted to estimate the effects of this functional polymorphism on digestive system cancer risk. Third, due to the original data of the eligible studies are not available. It is difficult to evaluate the roles of diet, alcohol consumption, and smoking status in digestive cancer development.

In conclusion, our meta-analysis suggested that the MMP7 -181
A/G polymorphism may be a risk factor in digestive system cancer development, especially among Asian population. Large well-designed studies are needed to validate our findings in the future.

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