The functional polymorphism in the matrix metalloproteinase-7 promoter increases susceptibility to esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma and non-small cell lung carcinoma

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An A to G transition at the 181 base pair upstream of the transcription initiation site of the matrix metalloproteinase-7 (MMP-7) gene (−181A/G) may modify the development and progression of some diseases via influencing the transcription activity of the promoter. To assess the effects of the functional single nucleotide polymorphism on cancer susceptibility and progression, the MMP-7 −181A/G genotypes were determined by polymerase chain reaction–restriction fragment length polymorphism analysis among 258 patients with esophageal squamous cell carcinoma (ESCC), 201 patients with gastric cardiac carcinoma (GCA), 243 patients with non-small cell lung carcinoma (NSCLC) and 350 healthy individuals without cancer. The result showed that the frequency of the −181G allele in ESCC, GCA and NSCLC patients was significantly higher than that in healthy controls (P = 0.019, 0.023 and 0.004, respectively). Compared with the A/A genotype, genotypes with the −181G allele (A/G + G/G) significantly increased susceptibility to all three tumors, with adjusted odds ratio = 1.83 (95% CI = 1.12–2.99) for ESCC, 1.96 (95% CI = 1.17–3.29) for GCA and 2.00 (95% CI = 1.23–3.24) for NSCLC. Stratification analysis showed that smoking did not significantly influence the association between the MMP-7 −181A/G and GCA or NSCLC, while the −181G allele only significantly increased susceptibility to ESCC among smokers. In addition, association between the −181G allele and susceptibility to ESCC and GCA showed significance only among individuals with family history of upper gastrointestinal cancer. The correlation of the MMP-7 −181A/G polymorphism with potential of lymphatic metastasis was not observed in all three tumors. The study suggested that, the MMP-7 −181A/G polymorphism might be a candidate marker for predicting individuals who are at higher risk to certain tumors but might not be used to predict potential of lymphatic metastasis in ESCC, GCA and NSCLC.

Abbreviations: ESCC, esophageal squamous cell carcinoma; GCA, gastric cardiac adenocarcinoma; MMP, matrix metalloproteinase; NSCLC, non-small cell lung carcinoma; PCR–RFLP, polymerase chain reaction–restriction fragment length polymorphism; SNP, single nucleotide polymorphism; UGIC, upper gastrointestinal cancers.
tumor (22). Although overexpression of MMP-7 has been reported in several cancers such as gastric cancer (23), esophageal cancer (24), ovarian cancer (25), lung cancer (26) and pancreatic cancer (27), the role of the functional polymorphisms in the MMP-7 promoter in the development and progression of these tumors has not been demonstrated so far.

Our group has been exploring molecular markers with potential to predict occurrence and prognosis of different tumors, based on the hypothesis that there might be a similar genetic background that makes some individuals more susceptible to certain tumors and liable to metastases in cancer progression. We are particularly focusing on DNA markers since they could be stably detected from peripheral blood mononuclear cells at any stage of cancer. We have previously reported that the functional SNP in the MMP-3 promoter may be associated with increased risk of non-small cell lung cancer (NSCLC) and esophageal squamous cell carcinoma (ESCC), while the MMP-1 promoter polymorphism may not modify susceptibility and progression in NSCLC, ESCC and gastric cardiac adenocarcinoma (GCA) (18,19,28). Since MMP-7 plays crucial roles in cancer development and progression, we suspected that the polymorphic allele inducing higher level of MMP-7 expression might promote occurrence and metastases of some tumor types. We therefore genotyped the MMP-7–181A/G polymorphism among healthy individuals and patients with ESCC, GCA and NSCLC in a population of north China, with the aim to assess association of this polymorphism with the risk of development and lymphatic metastases of these tumors.

Materials and methods

Subjects

This hospital-based case–control study included 702 incident cancer patients (258 esophageal carcinomas, 201 gastric cardiac carcinomas and 243 lung carcinomas) and 350 healthy controls. The cases were hospitalized for tumor resection in the Fourth Affiliated Hospital, Hebei Medical University, between 2001 and 2003. The patients who were diagnosed as esophageal carcinoma, gastric cardiac carcinoma and lung carcinoma, and expected to have the possibility of tumor resection were randomly distributed into three sections of the Department of Thoracic Surgery. Since one important aim of our study was to analyze the role of the MMP-7 polymorphism in lymphatic metastasis of tumors, only patients from the first section were recruited, to avoid bias induced by variation in operation approaches by different surgeon groups. All of the cancer patients did not accept chemotherapy or radiotherapy before recruitment. Histological tumor typing was determined on the basis of biopsies or resected specimens in the Department of Pathology of the same hospital. All esophageal carcinomas were squamous cell carcinomas. All gastric cardiac carcinomas were adenocarcinomas and diagnosed according to the criteria of Siewert and Stein (29). Among lung cancer patients, 126 were adenocarcinomas, 106 were squamous cell carcinomas and the rest were other histological types including 5 bronchioloalveolar carcinomas, 3 mucoepidermoid carcinomas and 3 pneumoblastomas. The healthy subjects, having no history or diagnosis of any cancer and genetic disease, were recruited from individuals who visited the same hospital for physical examination and volunteered to give their blood for the epidemiological study during the same period of time as the cancer patients. All of the cancer patients and control subjects were unrelated Han nationality and from Shijiazhuang city or its surrounding regions. Information on sex, age, smoking habit and family history of cancers was obtained from cancer patients and healthy controls by interview conducted by two professional researchers. For smoking habit, the former and present smoking status, the number of cigarettes smoked per day and the time of starting and quitting were ascertained. The participants were also asked for family history of cancers, including if there are/were cancer patients in their family, the relationship of the cancer patients to the participants and the type of cancer they have/had. Individuals who formerly or currently smoked five cigarettes per day for at least 2 years were defined as smokers. Individuals with at least one first-degree relative or at least two second-degree relatives having esophageal/cardiac/gastric cancer were defined as having family history of upper gastrointestinal cancers (UGIC). The study was approved by the Ethics Committee of Hebei Cancer Institute and informed consent was obtained from all recruited subjects.

DNA extraction

From each subject, 5 ml of venous blood was drawn in Vacutainer tubes containing EDTA and stored at 4°C. Genomic DNA was extracted within 1 week after sampling by using proteinase K (Merck, Darmstadt, Germany) digestion followed by a salting out procedure (30).

MMP-7 SNP genotyping

The MMP-7–181A/G genotypes were determined by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) assay. The primers for amplifying the MMP-7 fragment were 5’-TGGTACCA-TAATGTCCTGAATG-3’ (forward) and 5’-TGGTATTCAGCCAGGAAACA-CAACAATGATT-3’ (backward). The fourth nucleotide close to the 3’ end of the backward primer was mutated from T to A to create an EcoRI recognition site when the –181G allele exists. The PCR was performed in a 20 μl volume containing 100 ng DNA template, 2.0 μl of 10x PCR buffer, 1.5 mM MgCl2, 1 U Tag-DNA polymerase (Biotools-Techn., Beijing, China), 200 μM dNTPs and 200 nM each primer. The PCR cycling conditions were 5 min at 94°C followed by 35 cycles of 30 s at 94°C, 30 s at 65°C and 30 s at 72°C, and with a final step at 72°C for 5 min to allow for the complete extension of all PCR fragments. An 8-μl aliquot of PCR product was subjected to digestion at 37°C overnight in a 10-μl reaction containing 1 U EcoRI (TakaRa Biotechnology, Dalian, China) and 1× reaction buffer. After digestion, the products were separated on a 3% agarose gel stained with ethidium bromide. As a result, the –181G alleles were represented by DNA bands with size at 120 and 30 bp, the –181A alleles were represented by a DNA band with size at 150 bp, whereas the heterozygotes displayed a combination of both alleles (150, 120 and 30 bp). For a negative control, distilled water instead of DNA in the reaction system was used for each panel of PCR. For 10% of the samples, genotyping was repeated once for quality control.

Statistical analysis

Statistical analysis was performed using SPSS12.0 software package (SPSS Company, Chicago, IL). Hardy–Weinberg analysis was performed to compare the observed and expected genotype frequencies using χ²-test. Comparison of the MMP-7 genotype distribution in the study groups was performed by means of two-sided contingency tables using χ²-test. The odds ratio (OR) and 95% confidence interval (CI) were calculated using an unconditional logistic regression model and adjusted by age and sex accordingly. A probability level of 5% was considered significant for all statistical analyses.

Results

The demographic distribution of cancer patients and healthy controls are shown in Table I. The age distribution in each tumor type was not significantly different from that in healthy controls. The gender distribution in ESCC, GCA and NSCLC patients was also comparable to that in healthy controls. Information on smoking status from 70 healthy individuals, 44 ESCC, 24 GCA and 9 NSCLC patients was unavailable, and family history of UGIC from 221 healthy controls, 50 ESCC and 31 GCA patients was unclear or failed to be recorded. Since only a few NSCLC cases had family history of cancers, its influence on susceptibility to lung cancer was not analyzed in this study. Among individuals with available information, the proportion of smokers in ESCC, GCA patients was not significantly or slightly different from that in healthy controls (χ² = 2.18 and 4.09, P = 0.14 and 0.043, respectively), whereas smokers in NSCLC patients were more frequently seen than in controls (χ² = 16.2, P < 0.001). Therefore, smoking significantly increased the risk of developing NSCLC, the age and gender adjusted OR was 1.74 (95% CI = 1.16–2.60). In addition, the frequency of family history of UGIC in ESCC and GCA patients was significantly higher than that in healthy controls (χ² = 32.14 and 46.85, P < 0.001, respectively). Thus, family history of UGIC significantly increased the risk of developing ESCC and GCA (age and gender adjusted OR = 9.43 and 13.70, 95% CI = 3.92–22.73.
and 5.65–33.33, respectively). Among 155 ESCC, 109 GCA and 197 NSCLC patients with available clinical information, lymphatic metastases were reported in 68, 46 and 123 patients, respectively, the rest were diagnosed as lymph node negative.

All of the cancer patients and healthy controls were successfully genotyped for the MMP-7 polymorphism. The genotyped results were completely matched to the original ones. The distributions of the MMP-7 genotypes in healthy controls, ESCC, GCA, and NSCLC patients did not deviate from that expected by Hardy–Weinberg equilibrium (data not shown). Among healthy controls, the frequency of the 181G allele in the development of ESCC and GCA, age and sex adjusted odds ratio was 1.74 (1.16–2.60), and 1.83 (1.12–2.99) for GCA and 2.00 (1.23–3.24) for NSCLC, respectively. Since smoking may modify the risk of ESCC and GCA, age and sex adjusted odds ratio was 9.43 (3.92–22.73) and 13.70 (5.65–33.33).

## Table I. Selected characteristics of MMP-7 SNP in ESCC, GCA and NSCLC patients and healthy controls

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control n (%)</th>
<th>ESCC n (%)</th>
<th>GCA n (%)</th>
<th>NSCLC n (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>229 (65.4)</td>
<td>186 (72.1)</td>
<td>146 (72.6)</td>
<td>171 (70.4)</td>
<td>0.21</td>
</tr>
<tr>
<td>Female</td>
<td>121 (34.6)</td>
<td>72 (27.9)</td>
<td>55 (27.4)</td>
<td>72 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>51.7 (10.7)</td>
<td>54.6 (10.4)</td>
<td>55.6 (10.2)</td>
<td>57.2 (10.5)</td>
<td>0.089b</td>
</tr>
<tr>
<td>Smoking statusc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-/current smoker</td>
<td>120 (42.9)</td>
<td>106 (49.5)</td>
<td>93 (52.5)</td>
<td>142 (60.7)</td>
<td>&lt;0.001^d</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>160 (57.1)</td>
<td>108 (50.5)</td>
<td>84 (47.5)</td>
<td>92 (39.3)</td>
<td></td>
</tr>
<tr>
<td>Family history of UGIC^c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6 (4.7)</td>
<td>63 (30.3)</td>
<td>&lt;0.001^c</td>
<td>66 (38.8)</td>
<td>&lt;0.001^c</td>
</tr>
<tr>
<td>Negative</td>
<td>123 (95.3)</td>
<td>145 (69.7)</td>
<td>104 (61.2)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>MMP-7 SNP allele type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>665 (95.0)</td>
<td>473 (91.7)</td>
<td>368 (91.5)</td>
<td>440 (90.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>G</td>
<td>35 (5.0)</td>
<td>43 (8.3)</td>
<td>0.019</td>
<td>34 (8.5)</td>
<td></td>
</tr>
</tbody>
</table>

ESC, esophageal squamous cell carcinoma; GCA, gastric cardiac adenocarcinoma; NSCLC, non-small cell lung carcinoma; ND, not determined; UGIC, upper gastrointestinal cancer.

*P-value for χ²-test.

^P-value for t-test.

Information on smoking status and family history was available from a subset of study subjects.

## Table II. Association analysis of the MMP-7 SNP with risk of ESCC, GCA and NSCLC development

<table>
<thead>
<tr>
<th>Groups</th>
<th>A/A</th>
<th>A/G</th>
<th>G/G</th>
<th>aOR 95% CI^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>316 (90.3)</td>
<td>33 (9.4)</td>
<td>1 (0.3)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>ESCC</td>
<td>216 (83.7)</td>
<td>41 (15.9)</td>
<td>1 (0.4)</td>
<td>1.83 (1.12–2.99)</td>
</tr>
<tr>
<td>GCA</td>
<td>167 (83.1)</td>
<td>34 (16.9)</td>
<td>0</td>
<td>1.96 (1.17–3.29)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>200 (82.3)</td>
<td>40 (16.5)</td>
<td>3 (1.2)</td>
<td>2.00 (1.23–3.24)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>145 (90.6)</td>
<td>14 (8.8)</td>
<td>1 (0.6)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>ESCC</td>
<td>94 (87.0)</td>
<td>14 (13.0)</td>
<td>0</td>
<td>1.38 (0.61–3.10)</td>
</tr>
<tr>
<td>GCA</td>
<td>69 (82.1)</td>
<td>15 (17.9)</td>
<td>0</td>
<td>2.57 (1.14–5.81)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>74 (80.4)</td>
<td>17 (18.5)</td>
<td>1 (1.1)</td>
<td>2.53 (1.19–5.38)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>111 (92.5)</td>
<td>9 (7.5)</td>
<td>0</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>ESCC</td>
<td>86 (81.1)</td>
<td>19 (17.9)</td>
<td>1 (1.0)</td>
<td>2.89 (1.25–6.67)</td>
</tr>
<tr>
<td>GCA</td>
<td>77 (82.8)</td>
<td>16 (17.2)</td>
<td>0</td>
<td>2.60 (1.08–6.25)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>119 (83.8)</td>
<td>21 (14.8)</td>
<td>2 (1.4)</td>
<td>2.40 (1.07–5.42)</td>
</tr>
<tr>
<td>Negative family history^bc</td>
<td></td>
<td></td>
<td></td>
<td>1.44 (0.80–2.60)</td>
</tr>
<tr>
<td>ESCC</td>
<td>125 (86.2)</td>
<td>20 (13.8)</td>
<td>0</td>
<td>1.57 (0.82–3.03)</td>
</tr>
<tr>
<td>GCA</td>
<td>89 (85.6)</td>
<td>15 (14.4)</td>
<td>0</td>
<td>1.57 (0.82–3.03)</td>
</tr>
<tr>
<td>Positive family history^bc</td>
<td></td>
<td></td>
<td></td>
<td>2.70 (1.33–5.41)</td>
</tr>
</tbody>
</table>

^aAge and sex adjusted odds ratio of the A/G=G/G genotypes against the A/A genotype.

^bThe stratification analysis was performed by comparing frequency of the cancer patients with and without family history of UGIC with that of the overall healthy controls.

^cFamily history of UGIC.

Healthy subjects was used in the stratification analysis because the family history of UGIC was rarely seen in this group according to the definition in the study. Interestingly, the different role of the −181A/G polymorphism in the development of ESCC and GCA was found between individuals with and without family history of UGIC, thus, the −181G allele significantly increased susceptibility to ESCC and GCA among individuals with family history of UGIC, while the
association was not observed among individuals without the family history (Table II). Additionally, the gender effect on the association between the MMP-7 polymorphism and susceptibility to ESCC, GCA and NSCLC was also analyzed, the increased risk for susceptibility to the three tumors in both gender groups was observed (data not shown).

Lymphatic invasion is an important factor to influence prognosis of ESCC, GCA and NSCLC. We therefore analyzed the correlation of the −181A/G polymorphism with potential of lymphatic metastasis in these tumors. However, only a slight tendency of the A/G + G/G genotypes towards the risk of lymphatic metastasis was observed in GCA (age and sex adjusted OR = 2.20, 95% CI = 0.75–6.47), while the frequency of the A/G + G/G genotypes in ESCC and NSCLC patients with and without lymphatic metastasis was quite similar (Table III). Therefore, the association between the −181A/G polymorphism and the risk of lymphatic metastasis in these three tumors was not observed, at least at the time of diagnosis.

**Discussion**

The present study shows that the −181A/G polymorphism in the MMP-7 promoter may be associated with the risk of all detected tumor types, i.e. genotypes with the −181G allele may significantly increase susceptibility to ESCC, GCA and NSCLC. This result is consistent with the report on colorectal cancer, which demonstrates that the frequency of the −181G homozygote in cancer patients is 2-fold higher than that in healthy controls (22). This consistency suggests that genotyping of the MMP-7−181A/G polymorphism may be useful in stratification of individuals who are at higher risk to develop certain cancers. The underlying mechanism for this association may be related to the promoter activity variations of the −181 alleles. Functional analysis has shown that nuclear proteins derived from differentiated U937 cells bind with higher affinity to the −181G allele than to the −181A allele. This binding difference has been supposed to be related to a putative binding site (NGAAN) for a heat shock transcription factor (HSTF), which exists in the −181G allele but is absent in the −181A allele (21). Transient transfection study has found that promoter activity of the −181G allele is 2- to 3-fold higher than that of the −181A allele on the same sequence background of another polymorphism, the −153C/T substitution (21). Although *in vitro* study has suggested that the −153C/T may also modify promoter activity of the MMP-7 gene, we did not evaluate its role in cancer development since the rare frequency of the −153T allele in the study population. The higher promoter activity of the −181G allele may indicate elevation of the MMP-7 mRNA and subsequently increase protein expression. Individuals with excess MMP-7 activity by harboring the −181G allele may predispose to malignant transformation through the ″shedase″ activity of MMP-7 protein, via recently described substrates such as tumor necrosis factor α, E-cadherin and Fas ligand. These substrates have been known to play important roles in signal transduction, cell–cell adhesion and apoptosis (3,5,31–35). In addition, elevated expression of MMP-7 induced by the −181G allele may lead to increased activation of other members of the MMP family such as MMP-2 (36). The latter may therefore modulate tumor development via regulating cancer cell growth, angiogenesis and immune surveillance (37).

The result shows that the −181G allele increases the risk of ESCC development among ex- or current smokers, but the association between the MMP-7 polymorphism and ESCC does not reach significance. This phenomenon is similar to our previous observations, which showed that the MMP-3 −1171 5A/6A polymorphism might modify susceptibility to ESCC only among smokers (18). The influence of smoking on the association of MMP polymorphism with tumor development has also been reported by Yu *et al.* (20) in which an additive interaction between the MMP-2 promoter polymorphism and smoking on the risk of developing lung cancer has been demonstrated. Since MMPs expression can be induced by smoking (38), we hypothesize that MMP alleles with higher promoter activities may react more strongly to smoking than those with lower activities. If this is true, individuals who smoke and harbor alleles with higher MMP expression may be more susceptible to cancer development. However, the hypothesis has not been supported by the result of other tumors, thus, the influence of smoking on the association between the MMP-7 polymorphism and susceptibility to GCA and NSCLC has not been observed. Therefore, the lack of significance for ESCC among non-smokers is probably due to low statistical power. In addition, the influence of smoking amount on the association has not been analyzed in this study, because we have found there is a significant variation in the method of tobacco preparation among the smokers in our series. Some patients from the countryside still use self-prepared tobacco whose quantity and quality can hardly be compared with that in the market. So, it is not reliable to make stratification analysis according to smoking amount in studies with small sample size like the present one. Investigations with larger sample size are needed to analyze the influence of smoking and its dosage effects, alone or in combination with the MMP polymorphisms, on the risk of cancer development.

The stratification analysis reveals that the association between the −181A/G polymorphism and susceptibility to ESCC and GCA shows significance only among individuals with a family history of UGIC. The genetic difference of esophageal cancer between familial and sporadic cases has been supported by a recent study, which showed that the gene expression patterns in familial cases differed from those in sporadic ones (39). In our previous studies on methylene-tetrahydrofolate reductase and NAD(P)H:quinone oxidoreductase 1, association between the functional polymorphisms and susceptibility to ESCC and/or GCA has also been confined to individuals with a family history of UGIC (40,41).
Although the exact mechanism remains unclear, these accumulated data suggest that individuals in families aggregated with UGIC patients may have special genetic background that makes them more susceptible to ESCC and GCA cancer.

Since metastasis is an important factor to influence prognosis of gastrointestinal and lung cancers, the association of the MMP-7-181A/G polymorphism with potential of lymphatic metastasis in ESCC, GCA and NSCLC has been analyzed in this study. However, the correlation between the -181A/G polymorphism and the risk of lymphatic metastasis has not been observed in any cancer. This result does not support the observation that overexpression of MMP-7 mRNA is related to lymph node metastasis in esophageal (42) and gastric cancers (8). Ghilardi et al. (22) has addressed that the -181G homozygote significantly increases the risk of lymph node involvement in colorectal cancer at the time of diagnosis and at the end of follow-up. On the contrary, it has been reported that there is only a slight tendency towards higher MMP-7 mRNA expression in tumors with lymph node metastasis in lung cancer (43). Moreover, animal experiment has also demonstrated that MMP-7 expression by colon adenocarcinoma cells contributes to the tumorigenicity but does not affect tumor invasion and metastasis (12). Therefore, the significance of MMP-7 expression in predicting lymphatic metastasis warrants further investigation with a larger sample size, and the influence of the -181A/G polymorphism on MMP-7 expression in different cancers needs to be addressed by genotype-phenotype studies. In addition, since the status of lymph node involvement has been determined at the time of diagnosis, no firm conclusions regarding the significance of the -181A/G polymorphism in tumor metastasis can be drawn until follow-up has been completed.

This pilot study has provided evidence that the MMP-7 polymorphism might be associated with susceptibility to ESCC, GCA and NSCLC, but it might not be used in predicting the potential of lymphatic metastasis in these tumors. Since the sample size in the study is small and only patients undergoing surgery have been recruited, selection bias that introduce unbalanced confounding factors, especially in the stratification analyses, might affect the conclusions of current investigation. Further studies with a larger sample size including all representative cancer patients are needed to verify our present observation.

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References


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