Association among lifestyle, clinical examination, polymorphisms in CDH1 gene and Traditional Chinese Medicine syndrome differentiation of gastric cancer

Junfeng Zhang, Zhen Zhan, Juan Wu, Chunbing Zhang, Yaping Yang, Shujuan Tong, Ruiping Wang, Xuewen Yang, Wei Dong

OBJECTIVE: To explore the association among lifestyle, clinical examination, polymorphisms in CDH1 gene and Traditional Chinese Medicine (TCM) syndrome differentiation of gastric cancer (GC).

METHODS: A hospital-based population of 387 GC patients was investigated in Jiangsu province. Relevant information regarding lifestyle and clinical examination were collected by a standard questionnaire. Four known single nucleotide polymorphisms (SNPs) in CDH1 were investigated by polymerase chain reaction-ligation detection reaction methods. Statistical analysis was conducted by SPSS 16.0 software.

RESULTS: The results showed that meal duration and the status of glutamic pyruvic transaminase were significantly associated with TCM syndrome differentiation of GC (both $P<0.05$). None of the four SNPs in the E-cadherin (CDH1) gene achieved significant differences in their distributions among the nine syndrome types of GC (both $P>0.05$). However, significant differences were observed in rs13689 genotype distributions between several pairs of syndrome types of GC, suggesting that rs13689 is correlated with the syndrome differentiation of GC.

CONCLUSION: Integrated analysis of lifestyle, clinical examination and CDH1 gene polymorphisms can contribute to a better understanding of the GC syndrome types and may improve the efficacy of interventions by stratifying disease according to TCM criteria.

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INTRODUCTION

Gastric cancer (GC) is one of the most common cancers worldwide and the second leading cause of cancer death; although both the incidence and mortality of GC have declined in recent years. There is substantial geographic variation in the incidence of GC internationally, with higher rates in East Asian countries such as Korea, Japan, and China. GC, one of the most prevalent malignant tumors and the second leading cause of tumor death in China, has become a public health priority, and treatment of GC continues to be a clinical challenge. Although combination therapy for GC is generally advocated, its adverse effects on the body, especially on the patient’s quality of life, have aroused the concerns of many researchers. Traditional Chinese Medicine (TCM) therapy is characterized by "syndrome differentiation treatment" and traditional Chinese herbal medicines have been shown to be good at treating GC and improving the patients' quality of life. Correct TCM syndrome differentiation is the most important principle that guides the prescribing of Chinese herbal formulae. The major advantage of TCM is that the treatment is based on syndrome differentiation. The phrases "same disease different treatments" and "different diseases same treatment" express the theory of choosing the specific remedy that will be most effective for a particular subtype of a disease. Moreover, TCM categorizes the disease based upon various dynamic functional aspects. However, TCM clinicians often have controversial opinions about the syndrome types and their connotations based on their differing clinical experiences, which make it difficult to draw a consensual conclusion and summary about clinical therapeutic effects.

It is now generally accepted that the pathogenesis of GC involves a multi-factorial interaction between environmental triggers and genetic susceptibility. It has been shown that the development of GC is related to age, gender differences and a number of environmental factors, such as a salty diet, tobacco smoking, alcohol consumption and Helicobacter pylori infection. In addition, host factors and genetic alterations also play an important role in the development and progression of GC through gene-environment interactions.

It is possible to integrate TCM syndrome differentiation and biomedical diagnosis in modern clinical practice. Recently many articles have exhibited that TCM syndromes of GC were correlated with a number of tumor-related molecules, such as estrogen and progesterone receptors, cell adhesion molecule 44, carcinoembryonic antigen, cancer antigen CA72-4, E-cadherin, C-erbB-2, P53, nm23, anti-intracellular adhesion molecule-1, vascular endothelial growth factor, kinase domain receptor, matrix metalloproteinase-2, and tissue inhibitor of matrix metalloproteinase-2. It is necessary to explore the components of the TCM syndrome of GC and provide a useful reference for standardizing TCM syndrome differentiation and treatment. In this paper, the association among lifestyle factors, clinical examination indexes, polymorphisms in the E-cadherin (CDH1) gene and TCM syndrome differentiation of GC.

MATERIALS AND METHODS

Study subjects

This research protocol was approved by the institutional review board of Jiangsu Province Hospital of TCM. All subjects were genetically unrelated ethnic Han Chinese. A total of 387 incident GC patients were consecutively recruited from January 2008 to July 2010 in Nanjing city, Jiangsu province, East China. A standard questionnaire was administered by trained interviewers to obtain demographic data and information regarding GC-related lifestyle factors (eating duration, preference for salty food, smoking, drinking, etc.) at the time of clinical examination. A 3-5 mL venous blood sample was collected from each subject along with a signed consent form.

Including criteria

Patients included in the study (a) were males or females over 20 years old but under 80 years old, (b) were of Han Chinese ethnicity (self-reported), (c) were local residents of three regions of Jiangsu province for at least 5 years, (d) had newly histopathologically diagnosed primary GC, (e) did not have previous malignant tumors in other organs, (f) had not had antitumor therapy before recruitment, including chemotherapy and radiotherapy and (g) did not have complicating severe heart failure, pulmonary insufficiency and kidney diseases.

Diagnostic criteria

All the patients have been confirmed by pathology. The standards used for GC syndrome differentiation were described elsewhere. Nine criteria were used for GC syndrome differentiations: spleen-stomach weakness (SSW), Yin deficiency due to stomach heat (YDSH), deficiency of both Qi and Yin (DQY), deficiency of both Qi and blood (DQB), liver-stomach disharmony (DLS), dampness-heat-toxin accumulation (DHT), stagnation of phlegm-muddiness (SPM), obstruction of blood stasis (OBS) and others.

Genomic DNA isolation from peripheral blood cells and genotyping

A commercial blood DNA extraction kit (AxyPrep-96 kit, Axygen, CA, USA) was used to extract genomic DNA isolation from peripheral blood cells. The standards used for GC syndrome differentiation and genotyping were described elsewhere. Nine criteria were used for GC syndrome differentiations: spleen-stomach weakness (SSW), Yin deficiency due to stomach heat (YDSH), deficiency of both Qi and Yin (DQY), deficiency of both Qi and blood (DQB), liver-stomach disharmony (DLS), dampness-heat-toxin accumulation (DHT), stagnation of phlegm-muddiness (SPM), obstruction of blood stasis (OBS) and others.
DNA from the blood samples. The purified DNAs were stored at −20°C until they were used for genotyping tests. The quality of DNA was assessed by agarose gel electrophoresis. Polymerase chain reaction-ligation detection reaction (PCR-LDR) methods were used for genotyping the four single nucleotide polymorphisms (SNPs) (rs13689, rs1801552, rs16260 and rs17690554) in the CDH1 gene. The SNPs were genotyped by Shanghai Biowing Applied Biotechnology Co., Ltd. (Shanghai, China). The four genotyped SNPs were identical to our published paper.

Statistical analyses
All statistical analyses were conducted using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). The frequencies of the nine differentiated syndromes of GC were compared in terms of demographic characteristics, lifestyle factors, clinical examination indexes and the allele frequencies of each SNP using the χ² test. Patient age was analyzed by non-parametric test and t test. All P values were two-sided and a P<0.05 was considered statistically significant.

RESULTS

Characteristics of the study subjects
In this paper, a total of 387 GC patients were included in the current analyses. Gender, age, and syndrome differentiation distribution of subjects are shown in Table 1. The gender proportions among the nine syndrome types of GC were significantly different (χ²=22.342, P=0.004), and pair-wise comparisons of gender proportions among the syndrome types were also compared. The results showed that the gender proportions of six pairs of syndrome types were significantly different (P<0.05), i.e., SSW vs OBS (χ²=5.411, P=0.020), YDSH vs DLS (χ²=8.197, P=0.004), DQY vs DHT (χ²=4.342, P=0.037), DQY vs OBS (χ²=7.786, P=0.005), DQB vs OBS (χ²=6.764, P=0.009), DLS vs DHT (χ²=10.112, P=0.001), and DLS vs OBS (χ²=13.708, P<0.001). There were no significant differences among the average ages of the nine syndrome types by two-sided χ² test (P>0.05), but it was noted that the average age of males was prominently higher than that of the females in the population of SSW (t=2.828, P=0.006) and SPM (t=2.487, P=0.017).

Relationship between syndrome types and lifestyle factors
To examine the relationship between syndrome types and lifestyle factors, the distributions of seven select lifestyle variables were analyzed by two-sided χ²-test. The results showed that meal duration was significantly correlated with the syndrome types of GC (P<0.05) (Table 2).

We also looked for correlations among lifestyle status and the syndrome types. With respect to insomnia, the results showed that there were significant differences between two pairs of syndrome types, i.e., SSW vs DLS (χ²=8.219, P=0.004), and DLS vs SPM (χ²=4.533, P=0.033). A significant difference was observed in breakfast eating behavior between DQB and OBS (χ²=6.738, P=0.034). For meal duration, there was a significant difference between YDSH and DHT (χ²=7.697, P=0.021). There were significant differences in the percentage of participants who smoked between two pairs

<table>
<thead>
<tr>
<th>Syndrome types</th>
<th>n (%)</th>
<th>Gender [n (%)]</th>
<th>Age (bar ± s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>&lt;60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>SSW</td>
<td>61 (15.8)</td>
<td>30 (49.2)</td>
<td>31 (50.8)</td>
</tr>
<tr>
<td>YDSH</td>
<td>59 (15.2)</td>
<td>29 (49.2)</td>
<td>30 (50.8)</td>
</tr>
<tr>
<td>DQY</td>
<td>23 (5.9)</td>
<td>13 (56.5)</td>
<td>10 (43.5)</td>
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<td>DQB</td>
<td>49 (12.7)</td>
<td>26 (53.1)</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>DLS</td>
<td>43 (11.1)</td>
<td>23 (53.5)</td>
<td>20 (46.5)</td>
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<tr>
<td>DHT</td>
<td>54 (14.0)</td>
<td>24 (44.4)</td>
<td>30 (55.6)</td>
</tr>
<tr>
<td>SPM</td>
<td>41 (10.6)</td>
<td>29 (70.7)</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td>OBS</td>
<td>35 (9.0)</td>
<td>17 (48.6)</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td>Others</td>
<td>22 (5.7)</td>
<td>16 (72.7)</td>
<td>6 (27.3)</td>
</tr>
</tbody>
</table>

χ²
- 10.802 - 22.342 - 8.472 4.200 7.989

P
- 0.2134 a 0.004 b 0.389 c 0.839 c 0.435c

Notes: SSW: spleen-stomach weakness; YDSH: Yin deficiency due to stomach heat; DQY: deficiency of both Qi and Yin; DQB: deficiency of both Qi and blood; DLS: liver-stomach disharmony; DHT: dampness-heat-toxin accumulation; SPM: stagnation of phlegm-muddiness; OBS: obstruction of blood stasis. *non-parametric test; †two-sided χ²-test; ‡t-test; ‡P<0.05.
of syndrome types, i.e., DLS vs OBS ($\chi^2=4.898, P=0.027$), and YDSH vs DLS ($\chi^2=4.423, P=0.035$).

When looking at drinking, there were significant differences between two pairs of syndrome types, i.e., DQB vs OBS ($\chi^2=10.256, P=0.017$), and DQB vs SPM ($\chi^2=10.451, P=0.015$). In contrast, according to regularly taking meals and preference for salty food, there were no significant differences between any of the pairs of syndrome types (all $P>0.05$).

**Relationship between syndrome types and clinical examination indexes**

To examine the relationship between syndrome types and the results of common clinical examination, the distributions of nine select clinical examination indexes were analyzed by two-sided $\chi^2$ test. The results showed that the status of glutamic pyruvic transaminase was significantly correlated with the syndrome types of GC ($\chi^2=15.687, P=0.047$) (Table 3).

Parallel comparison of the results of clinical examination between each syndrome type and all remaining syndrome types were also analyzed. Aspartate aminotransferase levels were significantly different for three syndrome types, i.e., DHT vs others ($\chi^2=5.929, P=0.015$), SPM vs others ($\chi^2=5.393, P=0.020$), and OBS vs others ($\chi^2=4.800, P=0.028$). For glutamic pyruvic transaminase, there were significant differences for four syndrome types, i.e., DHT vs others ($\chi^2=5.532, P=0.011$), SPM vs others ($\chi^2=5.393, P=0.020$), SSW vs DHT ($\chi^2=7.329, P=0.007$), and SSW vs SPM ($\chi^2=4.923, P=0.027$). Total protein was significantly different between DLS and DHT ($\chi^2=3.946, P=0.047$). In
Table 3 The relationship between syndrome types and clinical examination indexes [n (%)]

<table>
<thead>
<tr>
<th>Clinical examination index</th>
<th>Syndrome type</th>
<th>SSW</th>
<th>YDSh</th>
<th>DQY</th>
<th>DQh</th>
<th>DLS</th>
<th>DHT</th>
<th>SPM</th>
<th>OBS</th>
<th>Others</th>
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<td>Aspartate aminotransferase[^c]</td>
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<td>34</td>
<td>36</td>
<td>39</td>
<td>32</td>
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<td>21</td>
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<tr>
<td></td>
<td>Abnormal</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>12</td>
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<td>Glutamic pyruvic transaminase[^e]</td>
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<td>35</td>
<td>37</td>
<td>38</td>
<td>32</td>
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<td>3</td>
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<td>5</td>
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<td>0</td>
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<tr>
<td>Total protein[^f]</td>
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<td>36</td>
<td>13</td>
<td>24</td>
<td>30</td>
<td>27</td>
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<td>19</td>
<td>15</td>
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<td>Glutamyl GGT[^g]</td>
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<td>48</td>
<td>20</td>
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<td>9</td>
<td>7</td>
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<td>4</td>
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<td>Lymphocyte percent[^h]</td>
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<td>18</td>
<td>9</td>
<td>13</td>
<td>9</td>
<td>14</td>
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<td>Haemoglobin[^i]</td>
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<td>Lymphocyte percent[^k]</td>
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<td>Glucose[^l]</td>
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<td>9</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>3</td>
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</table>

Notes: GGT: gamma glutamyl transpeptidase; SSW: spleen-stomach weakness; YDSh: Yin deficiency due to stomach heat; DQY: deficiency of both Qi and Yin; DQh: deficiency of both Qi and blood; DLS: liver-stomach disharmony; DHT: dampness-heat-toxin accumulation; SPM: stagnation of phlegm-muddiness; OBS: obstruction of blood stasis. χ²=8.578, P=0.037; χ²=15.687, P=0.047; χ²=7.014, P=0.535; χ²=4.714, P=0.788; χ²=4.026, P=0.855; χ²=8.074, P=0.426; χ²=6.360, P=0.607; χ²=12.798, P=0.011; χ²=5.614, P=0.690. With respect to neutrophil granulocyte percentage, there were significant differences between three pairs of syndrome types, i.e., DQY vs DLS (χ²=4.215, P=0.040), and DLS vs OBS (χ²=4.703, P=0.030). With respect to neutrophil granulocyte percentage, there were significant differences between three pairs of syndrome types, i.e., DQY vs DLS (χ²=4.742, P=0.029), DLS vs others (χ²=7.739, P=0.005), and SPM vs others (χ²=6.514, P=0.011). However, with regard to glutamyl GGT, white blood cell count and glucose, there were no significant differences between either pair of syndrome types (all P>0.05).

Genotyping distribution and syndrome types of GC

In the present study, no statistical significance was observed in terms of the genotype and allele distributions of rs13689, rs1801552, rs17690554, and rs16260 among the nine syndrome types of GC (P>0.05) (Table 4).

Parallel comparison of the genotype distributions of the four SNPs in each syndrome type was also analyzed. For SNP rs13689, there were no significant differences among the genotypes TT, TC and CC between any of the pairs of syndrome types (P>0.05), but there were significant differences on the basis of the genotypic TT and TC/CC between three pairs of syndrome types, i.e., DQY vs OBS (χ²=4.329, P=0.037), YDSh vs OBS (χ²=3.917, P=0.048), and SSW vs OBS (χ²=4.022, P=0.045). In light of the SNP rs1801552, there were no significant differences for the genotypes CC, TT and TC between any pair of syndrome types (P>0.05), but it was significantly different between DLS vs SPM (χ²=4.566, P=0.033) on the basis of the genotypic CC and TC/TT. For SNPs rs17690554 and rs16260, there were no significant differences between any pair of syndrome types (P>0.05).
there were significant differences on the basis of the allele C and G between the members of three pairs of syndrome types, i.e., OBS vs DQB (χ² = 5.253, P = 0.022), OBS vs DHT (χ² = 5.143, P = 0.023), and OBS vs YDSH (χ² = 4.808, P = 0.043). However, for the SNP rs1801552 and rs16260, there were no significant differences on the basis of the allele distribution for any pair of syndrome types (all P > 0.05).

**DISCUSSION**

Syndrome differentiation in TCM is the comprehensive analysis of clinical information gained by the four main diagnostic TCM procedures: observation, listening, questioning, and pulse analysis. TCM syndrome differentiation can be used for the further stratification of the patients’ conditions with certain diseases, identified by orthodox medical diagnosis, which could help improve the efficacy of the selected intervention. In modern TCM research, it is possible to integrate syndrome differentiation with orthodox medical diagnosis leading to new scientific findings in overall medical diagnosis and treatment. Therefore, this study aimed to provide qualitative and quantitative parameters to pre-
cisely and objectively reflect the essence of TCM syndrome differentiation and promote the development and globalization of TCM. In the present study, we were interested to test whether some lifestyle factors, clinical examination indexes, and CDH1 gene polymorphisms were related with the syndrome type of GC.

Similar to previous research in China, our results showed that men generally develop GC twice as frequently as women, and the male proportions of the syndrome types YDSH, DHT, SPM and OBS were more than 300% of the female proportions. Previous studies have shown that several lifestyle factors, including regularly taking meals, preference for salty food, meal duration, smoking status, drinking status, and eating breakfast, were identified to influence the risk of GC with gender differences in east China.

Our results showed that lifestyle status was closely correlated with the syndrome differentiation of GC, most significantly, meal duration of the nine syndrome types was distinctly different ($\chi^2=35.717$, $P=0.003$), which may be an important reason for higher incidence rates in males than those in females. Our findings suggest that fast eating may play an important role in the formation of DHT.

Conventional clinical examination is widely accepted as a valid diagnostic in China. To explore the correlation between the status of clinical examination indexes and the syndrome types of GC, ten kinds of clinical laboratory indicators were selected to be analyzed by two-sided $c$-test. The status of glutamic pyruvic transaminase was found to be distinctly different in the nine syndrome types of GC ($P<0.05$). DHT surprisingly accounted for the highest proportion of abnormal status (25.5%). It was recently reported that increased serum amylase was found to be distinctly different in the nine syndrome types of GC ($P<0.05$). DHT surprisingly accounted for the highest proportion of abnormal status (25.5%).

These results indicate that DHT may be the most malignant and sophisticated syndrome type of GC. The TCM theory considers the tongue to be an outer extension of the spleen and stomach, and holds that the tongue coating is produced by gastric Qi through fumigating so that the status of spleen and stomach can be exactly and immediately manifested by the appearance of the tongue, which may reliably direct the dialectical therapy.

Tongue appearance was closely related with the image of gastroscopy and is of great importance in guiding the syndrome differentiation of GC. Our previous study found that the differentially expressed tumor-related genes were one of the root causes of the change in tongue appearance, such as tongue fur. Among the identified differently expressed genes, the E-cadherin (CDH1) gene, an important tumor suppressor gene located on chromosome 16q22.1, was correlated with TCM syndromes of GC. CDH1-mediated cell-cell adhesion is lost when many tumors become more malignant. Somatic loss of CDH1 is considered to be a defining feature in invasive lobular breast cancer and GC. Down-regulation of E-cadherin function, due to mutation, deletion, CpG hypermethylation, or snail-mediated transcriptional repression of the CDH1 gene, have direct consequences for cell shape, polarity, migration and inva-

sion, which are closely related to the development of cancer. Since 1998, an increasing number of germline mutations have been proposed to cause hereditary GC. And there is currently increasing interest in SNP mutations in CDH1, given that they could affect the efficacy of gene transcription and expression. To evaluate the molecular genetics of TCM syndrome type, the association between four SNPs in the CDH1 gene and the nine syndrome types of GC were analyzed in this paper. However, none of the four polymorphisms achieved significant differences in their distributions among the nine syndrome types of GC. Of interest are the significant differences of genotype distributions between the members of several pairs of syndrome types of GC. The results suggested that rs13689 was the most likely to be correlated with the syndrome differentiation of GC. Our latest research found that CA genotype of rs16160 and CG genotype of rs17690554 were associated with the risk of diffuse gastric cancer compared with their wild genotypes, but rs17690554 was not correlated to the syndrome differentiation of GC in this paper. Of course, owing to the limited number of each syndrome type of GC, the results needed to be validated in later studies with larger sample sizes.

To sum up, GC is caused by many well-known factors, including environmental factors, dietary habits, Helicobacter pylori infection and host genetic factors. This paper first observed the association among lifestyle factors, clinical examination indexes, polymorphisms in CDH1 gene and TCM syndrome differentiation of GC. The results indicated that TCM syndrome differentiation may contain richer information than the single Western Medicine genetics can detect, which would further assist in stratification in order to improve the efficacy of the intervention based on the TCM syndrome differentiation related clinical trial strategy.

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