Polymorphism of CYPIA1 and GSTM1 genes associated with susceptibility of gastric cancer in Shandong Province of China

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Abstract

AIM: To explore whether polymorphisms of the CYPIA1 and GSTM1 genes are associated with susceptibility of stomach cancer.

METHODS: A total of 102 stomach cancer cases and 62 healthy persons were diagnosed by pathology in 1998-2000 in the Qilu Hospital of Shandong University. Gene polymorphisms were detected by the PCR using sequence-specific primers. Data analysis of the case-control study was carried out using the unconditional logistic method.

RESULTS: After adjustment for age, sex, educational levels, and occupation, the risk factors for stomach cancer were shown to be smoking, Helicobacter pylori (H pylori), and presence of the CYPIA1 G/G and GSTM1 O/O genotypes. Interaction was observed between the combined genotypes of either CYPIA1 G/G and GSTM1 O/O genotypes or H pylori infection, or GSTM1 O/O and H pylori infection or smoking.

CONCLUSION: Polymorphisms of the CYPIA1 and GSTM1 genes, H pylori infection and smoking are related to susceptibility to stomach cancer.

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Key words: Stomach cancer; CYPIA1; GSTM1; Polymorphism

INTRODUCTION

It has been found that the progression of precancerous lesions to gastric cancer is associated with cigarette smoking, alcohol drinking, and Helicobacter pylori (H pylori) infection in high-incidence areas of China[1-3].

Individual susceptibility to cancer may be partly due to exposure to environmental risk factors, which can be partly explained by genetic variability in metabolic activities related to phases I and II detoxification enzyme pathways. Polymorphisms in these metabolic susceptible genes have been linked to increased risk of cancer in several case-control studies[4].

Cytochrome p450 enzymes, which represent a large multigene family with different substrate specificities, are important in phase I detoxification reactions. The CYPIA1 gene product, aromatic hydrocarbon hydroxylase, catalyzes the first oxidative step in the metabolism of polycyclic aromatic hydrocarbons, such as those found in tobacco smoke, to carcinogens. This gene is induced by exposure to agents such as dioxin, benzo [α] pyrene and other aromatic hydrocarbons[5].

Various CYPIA1 gene polymorphisms have been found to be differentially associated with increased risk of several cancers (including cancer of the lung, breast, and colon) in different specific ethnic groups[6-9].

Phase II enzymes, glutathione S-transferase (GSTs), also have activated metabolites of carcinogens to be subjected to metabolic conjugation and other kinds of detoxifications. Homozygous deletions or null genotypes of GSTT1 (theta class) and GSTM1 (mu class) genes may be associated with an increased risk of cancer[10,11].

The polymorphisms of these metabolic enzymes result from a difference of the genotypes. Some of these forms cannot metabolize carcinogens into non-cytotoxic agents as is observed in the wild-type proteins[10]. Otherwise some of them metabolize cytotoxic agents into compounds that have the potential to damage DNA associated with high susceptibility to many kinds of diseases or drug resistance[11].

Few studies have evaluated the relationship between CYPIA1, GSTM1, and the risk of gastric cancer, as well as the potential interactions between these genetic markers and other risk factors for gastric cancer in the Chinese population. The present study was to investigate the interaction between CYPIA1- and GST-susceptible genotypes of gastric cancer and H pylori infection or smoking.

MATERIALS AND METHODS

Patients with stomach cancer were recruited between January 1998 and January 2000 in the Affiliated Hospital of Shandong University. A biopsy was taken under gastroscope from all patients for their pathologic diagnosis. Of these patients, 102 (86 males and 16 females) had stomach cancer as the...
case group, and 62 (33 males and 29 females) had normal gastrointestinal mucous membrane and were used as the control group. All subjects were interviewed using a standardized questionnaire concerning their education, occupation, and cigarette smoking, etc. Blood samples (5 mL) were obtained from patients and controls, and 0.5 mL anti-clot solution of ACD was added. DNA was isolated from peripheral WBC by digestion with proteinase K, followed by phenol/ chloroform extraction, and ethanol precipitation prior to resuspension in buffer containing 0.05 mol/L Tris, 5 mol/L EDTA, pH 7.6.

CYPIA1 genetic polymorphisms were determined as described previously[10]. Two pair primer sets were used to detect the polymorphism within exon 7 of the CYPIA1 gene by PCR. One pair primers were sense primer 1A1A: 5’-GAAGTGATCTCGGTAGACCA-3’ and antisense primer c53: 5’-GTAGACAGAGTCTAGGCCTCA-3’; the other pair primers were sense primer 1A1G: 5’-GAAGTGATCTCGGTAGACCCG-3’ and antisense primer c53: 5’-GTAGACAGAGTCTAGGCCCTCA-3’ located about 190 bp downstream of the polymorphism site (Figure 1).

PCR was carried out in two tubes with a total volume of 30 μL containing 0.4 μg of genomic DNA, 1 μL of each of 1A1A and C53 primers 1A1G and C53 were added into the other tube, 2.5 μL of 10×PCR buffer, 2.5 μL of 25 mmol/L Mg2+, 1.5 μL of 10 mmol/L dNTP, 2 U Taq DNA polymerase. The program was initiated for 4 min of denaturation at 94 °C, followed by 30 cycles of amplification with denaturation for 30 s at 94 °C, annealing for 30 s at 72 °C, and an extension at 72 °C for 45 s, a final elongation at 72 °C for 5 min on a Perkin Elmer PCR amplifier. The PCR products were then subjected to electrophoresis on 1.8% agarose gels. If there were light intensity bands at 215 and 268 bp, the genotype was recorded as +/+ . If there was only a light band of 268 bp, the genotype was recorded as +/O . All subjects were tested with an antibody against H pylori for evidence of infection using an ELISA kit.

To examine the association between CYPIA1 and GSTM1 genotypes and stomach cancer, we calculated the odds ratio (OR) and 95% confidence interval (CI) by unconditional logistic regression. The ORs were adjusted for potential confounding factors, including age, sex, education, and occupation.

Possible modification of the association between genetic polymorphism and stomach cancer risk was also evaluated by stratifying cases and controls into tertiles based on a variety of parameters. As reported previously, both smoking and H pylori infection led to a significant increase in risk (Table 1).

RESULTS

We initially assessed the risk of stomach cancer using a variety of parameters. As reported previously, both smoking and H pylori infection led to a significant increase in risk (Table 1).
There was no evidence for an increased risk of gastric cancer associated with sauerkraut and mildew food consumption or imbibing white spirit in Chinese population. However, frequent consumption of raw garlic was associated with an apparently reduced risk. The most significant factor associated with increased risk of stomach cancer was a CYPIA1 G/G genotype where the OR was 4.84 compared to the A/A and A/G genotypes. The GSTM1 O/O genotype was also associated with an increased risk of gastric cancer (Table 2).

When the ORs were calculated for the combined CYPIA1 and GSTM1 genotypes, a combination of CYPIA1 A/A and GSTM1 +/+ or +/O gave a baseline of 1.0 as shown in Table 3. The OR for GSTM1 O/O genotype was 3.34 (95%CI: 1.13-9.87). The OR for CYPIA1 G/G was 4.16 (95%CI: 0.40-43.45). However, combined CYPIA1 G/G and GSTM1 O/O enhanced the risk of gastric cancer (OR = 16.48, 95%CI: 2.36-115.0). There was a significant interaction.

When the ORs were calculated for the combined CYPIA1 genotypes and H. pylori infection, a combination

### Table 1 Distribution of cases and controls by age, sex, education, and occupation

| Variable         | Value level | Gastric group | Control group | $\chi^2$ | P   |
|------------------|-------------|---------------|---------------|---------|-----|
| Age (yr)         | <35         | 4             | 18            |         |     |
|                  | 35-         | 13            | 21            |         |     |
|                  | 45-         | 85            | 23            | 38.945  | <0.001 |
| Sex              | Male        | 86            | 33            |         |     |
|                  | Female      | 16            | 29            |         |     |
| Education years  | <5          | 57            | 14            |         |     |
|                  | 6-          | 29            | 28            |         |     |
|                  | 13-         | 16            | 20            |         |     |
| Occupation       | Farmer      | 63            | 24            |         |     |
|                  | Worker      | 21            | 18            |         |     |
|                  | Card        | 18            | 20            | 8.573   | = 0.014 |

| Age (yr)         | 35-         | 13            | 21            | 83.95   | <0.001 |
|                  | 45-         | 85            | 23            |         |     |
| Sex              | Male        | 86            | 33            |         |     |
|                  | Female      | 16            | 29            |         |     |
| Education years  | <5          | 57            | 14            |         |     |
|                  | 6-          | 29            | 28            |         |     |
|                  | 13-         | 16            | 20            |         |     |
| Occupation       | Farmer      | 63            | 24            |         |     |
|                  | Worker      | 21            | 18            |         |     |
|                  | Card        | 18            | 20            | 8.573   | = 0.014 |

### Table 2 Relative risk of stomach cancer in relation to observed factors

| Factors                        | Controls | Cases | OR \(^1\) | 95%CI  | OR \(^2\) | 95%CI  |
|-------------------------------|----------|-------|-----------|-------|-----------|-------|
| Chinese sauerkraut            | 53       | 95    | 1.00      | 0.88  | 0.24      | 0.04  |
| Sometime                      | 6        | 4     | 0.37      | 0.09  | 0.39      | 0.41  |
| Often (2+/wk)                 | 3        | 3     | 0.56      | 0.17  | 0.39      | 0.41  |
| Mildew food                   | 59       | 94    | 1.00      | 0.87  | 0.27      | 0.77  |
| Sometime                      | 2        | 5     | 1.57      | 0.35  | 0.59      | 0.26  |
| Often (2+/mo)                 | 1        | 3     | 1.88      | 1.24  | 2.07      | 1.28  |
| Eat raw garlic/yr              | 20       | 77    | 1.00      | 0.95  | 1.11      | 0.41  |
| <1 000                         | 42       | 25    | 0.15      | 0.33  | 0.15      | 0.33  |
| >1 000                         | 35       | 53    | 1.00      | 0.33  | 0.15      | 0.33  |
| CYPIA1 genotype               | 24       | 27    | 0.74      | 0.59  | 0.26      | 1.34  |
| A/A                           | 3        | 22    | 4.84      | 5.91  | 1.28      | 27.24 |
| A/G                           | 3        | 22    | 4.84      | 5.91  | 1.28      | 27.24 |
| H. pylori infection            | 26       | 13    | 1.00      | 1.65  | 2.07      | 1.28  |
| +                             | 36       | 89    | 4.64      | 1.65  | 2.07      | 1.28  |
| Alcohol consumption           | 37       | 48    | 1.00      | 0.87  | 0.27      | 0.77  |
| 1-100                         | 8        | 9     | 0.87      | 1.03  | 0.26      | 0.40  |
| 100+                          | 17       | 45    | 2.04      | 4.39  | 1.11      | 0.41  |
| Smoking                       | 42       | 46    | 1.00      | 0.98  | 0.39      | 0.66  |
| <270                          | 14       | 15    | 0.98      | 2.46  | 0.66      | 1.94  |
| >270                          | 6        | 41    | 6.23      | 18.27 | 2.78      | 0.90  |
| History of cancer family      | 59       | 88    | 1.00      | 3.13  | 14.38     | 2.98  |
| Yes                           | 3        | 14    | 3.13      | 14.38 | 2.98      | 0.69  |
| GSTM1 genotype                | 36       | 33    | 1.00      | 5.71  | 2.72      | 1.32  |
| +/+ or +/O                    | 26       | 67    | 2.81      | 5.71  | 2.72      | 1.32  |
| O/O                           | 26       | 67    | 2.81      | 5.71  | 2.72      | 1.32  |

\(^1\)Non-adjusted OR, \(^2\)adjusted for age, sex, education, and occupation, \(^3\)drinking index = white alcohol/month×number of drinking years, \(^4\)smoking index = cigarette/day×number of smoking years.
of CYPIA1 A/A and no H pylori infection at a baseline of 1.0, the OR of H pylori infection alone was 7.19 (95%CI: 1.98-26.11), and the OR of CYPIA1 G/G genotype alone was 13.18 (95%CI: 0.42-414.9). The OR significantly enhanced for the combined CYPIA1 G/G genotype and H pylori infection compared to the baseline group (Table 4).

As shown in Table 4, when compared to the combined CYPIA1 A/A genotype and non-smoking at a baseline of 1.0, the OR of smoking alone was 1.53 (95%CI: 0.47-4.96), and the OR of CYPIA1 G/G genotype alone was 4.90 (95%CI: 0.90-26.73), both of them did not reach a significant level. However, the ORs were significantly higher for the combined CYPIA1 G/G genotype and smoking as compared to the baseline group (Table 5).

As shown in Table 5, when compared to the combined GSTM1 +/+ or +/O genotype with no H pylori infection at a baseline of 1.0, the OR of H pylori infection alone was 4.19 (95%CI: 1.16-15.13). In combined GSTM1 O/O genotype and H pylori infection group, the OR was 12-fold higher than that in the baseline group (Table 6).

As shown in Table 7, when compared to the combined GSTM1 +/+ or +/O genotype with no smoking at a baseline of 1.0, the OR of smoking alone was 1.22 (95%CI: 0.37-4.01), and the OR of GSTM1 O/O alone was 3.08 (95%CI: 1.11-8.54). An interaction between the GSTM1 O/O genotype and smoking was also observed with a fourfold increase compared to that in the baseline group.

**DISCUSSION**

In this study, since the biopsy from cases and controls was tested by gastroscopy, there was no bias caused by misclassification.

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**Table 3** Relative risk of stomach cancer for combined CYPIA1 and GSTM1 genotypes

| CYPIA1 | GSTM1 | Controls | Cases | OR  | 95%CI |
|--------|-------|----------|-------|-----|-------|
| A/A    | */+ or +/O | 22 17   | 1.00  |
| O/O    | 13 35   | 3.34 1.13 9.87 |
| A/G    | */+ or +/O | 13 10   | 0.65 0.20 2.14 |
| O/O    | 11 16   | 1.67 0.52 5.36 |
| G/G    | */+ or +/O | 1 6    | 4.16 0.40 43.45 |
| O/O    | 2 16    | 16.48 2.36 115.0 |

1Adjusted for age, sex, education, and occupation; CI: confidence interval.

**Table 4** Relative risk of stomach cancer for combined CYPIA1 genotype and H pylori infection

| CYPIA1 | H pylori | Controls | Cases | OR  | 95%CI |
|--------|----------|----------|-------|-----|-------|
| A/A    | -        | 18 5    | 1.00  |
| +      | 17 22   | 7.19 1.98 26.11 |
| A/G    | -        | 7 5    | 1.59 0.29 8.91 |
| +      | 17 48   | 2.94 0.78 11.13 |
| G/G    | -        | 1 3    | 13.18 0.42 414.9 |
| +      | 2 19    | 28.11 3.95 199.8 |

1Adjusted for age, sex, education, and occupation; CI: confidence interval.

**Table 5** Relative risk of stomach cancer for combined CYPIA1 genotype and smoking

| CYPIA1 | Smoking | Controls | Cases | OR  | 95%CI |
|--------|---------|----------|-------|-----|-------|
| A/A    | None    | 21 21   | 1.00  |
|       | Yes     | 14 32   | 1.53 0.47 4.96 |
| A/G    | None    | 18 12   | 0.62 0.20 1.89 |
|       | Yes     | 6 15    | 0.92 0.24 3.53 |
| G/G    | None    | 5 13    | 4.90 0.90 26.73 |
|       | Yes     | 0 9     | 19.072.77 54.06 |

1Adjusted for age, sex, education, and occupation; CI: confidence interval; 2weighted OR by adding to 0.5 for each cell number.

**Table 6** Relative risk of stomach cancer for GSTM1 genotype and H pylori infection

| GSTM1 | H p | Controls | Cases | OR  | 95%CI |
|-------|-----|----------|-------|-----|-------|
| */+ or +/O | - | 16 5    | 1.00  |
| +     | 20 28   | 4.19 1.16 15.13 |
| O/O  | -      | 10 7    | 3.53 0.70 17.81 |
| +     | 16 60   | 12.37 3.37 45.46 |

1Adjusted for age, sex, education, and occupation; CI: confidence interval; 2two cases missing.
The results of this study showed that smoking and *H pylori* infection had an association with stomach cancer after being adjusted for age, sex, education, and occupation. Jarebinski et al.[36], in 1992 first reported that there is a weak association between smoking and stomach cancer. Liu and Wang[31] in 2002 made a meta-analysis of the relationship between smoking and stomach cancer, and found that cigarette smoking is a risk factor for gastric cancer, especially for male smokers. Finding from most case-control and cohort studies support the causal relation between smoking and gastric cancer.[14-16]. Epidemiological evidence relating *H pylori* infection to the etiology of gastric cancer showed that at least 30% of gastric cancers in the developing world and 50% of gastric cancers in the developed world may be attributed to *H pylori* infection.[17-20]. Studies indicate that *H pylori* infection is a frequent finding in patients with gastric adenocarcinoma and benign peptic ulcer.[21-23]. With respect to carcinogenic mechanism, *H pylori* affects several aspects of gastric epithelial cell function.[24-26]. The result from the present study is in agreement with these reports.

There are a number of studies on cytochrome p450 and GSTs associated with cancers, such as breast, lung, liver, esophagus, and stomach cancer.[8,11]. It was reported that in the presence of p450, CYPIA, CYP2E1, and CYP3A in stomach cancer, the expression of CYPIA (51%) and CYP3A (28%) increases in stomach CYP2E1, and CYP3A in stomach cancer, the expression 2.83-23.67) [31].

null genotype increases significantly (OR = 8.06, 95%CI, 1.01-6.22); when gastric cancer cases are compared to CG patients, the adjusted OR for GSTT1 is 2.33 (95%CI, 0.75-7.25).

In conclusion, CYPIA1 G/G and GSTM1 O/O genotypes are associated with the increase of stomach cancer in Chinese people. When the CYPIA1 G/G genotype for patients is combined with GSTM1 O/O genotype, then the risk factors involved are *H pylori* infection or smoking. A study needs to be carried out in future.

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### Table 7 Relative risk of stomach cancer for combined GSTM1 genotype and smoking

| GSTM1   | Smoking | Controls | Cases | OR | 95%CI |
|---------|---------|----------|-------|----|-------|
| **+/+ or */O** | - | 23 | 16 | 1.00 |       |
|         | + | 13 | 17 | 1.22 | 0.37 | 4.01 |
| **O/O**  | - | 19 | 30 | 3.08 | 1.11 | 8.54 |
|         | + | 7  | 37 | 4.32 | 1.27 | 14.69 |

1Adjusted for age, sex, education, and occupation; CI: confidence interval; 2two cases missing.
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