Glutathione-S-transferase (GSTM1, GSTT1) and the risk of gastrointestinal cancer in a Korean population

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AIM: To evaluate the association of glutathione S-transferase mu (GSTM1) and glutathione S-transferase theta (GSTT1) null genotypes with the risk of gastric cancer (GC) and colorectal cancer (CRC) in a South Korean population.

METHODS: We conducted a population-based, large-scale case-control study including 2213 GCs, 1829 CRCs, and 1699 controls. Null and non-null genotypes of GSTM1 and GSTT1 were determined using real-time PCR.

RESULTS: The null genotypes of GSTM1 and GSTT1 were not significantly associated with elevated risk of gastric (OR = 1.070, 95% CI = 0.935-1.224; OR = 1.101, 95% CI = 0.963-1.259, respectively) or colorectal cancer (OR = 1.065, 95% CI = 0.923-1.228; OR = 1.041, 95% CI = 0.903-1.200, respectively). The frequency of the combined null GST genotype was not different between the two cancer groups and controls. Moreover, smoking, drinking, and age did not modify the association between these genotypes and the risk of gastric or colorectal cancer.

CONCLUSION: GSTM1 and GSTT1 null genotypes were not associated with increased risk of GC or CRC in Koreans.

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Key words: Glutathione S-transferase mu; Glutathione S-transferase theta; Gastric cancer; Colorectal cancer; South Korean population

Peer reviewer: Dr. Mark S Pearce, Paediatric and Lifecourse Epidemiology Research Group, School of Clinical Medical Sciences, University of Newcastle, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, United Kingdom

Piao JM, Shin MH, Kweon SS, Kim HN, Choi JS, Bae WK, Shim HJ, Kim HR, Park YK, Choi YD, Kim SH. Glutathione-S-transferase (GSTM1, GSTT1) and the risk of gastrointestinal cancer in a Korean population. World J Gastroenterol 2009; 15(45): 5716-5721 Available from: URL: http://www.wjgnet.com/1007-9327/15/5716.asp DOI: http://dx.doi.org/10.3748/wjg.15.5716

INTRODUCTION

Gastric cancer (GC) and colorectal cancer (CRC) are the most common malignancies in Korea. Environmental factors, such as diet, infection, and smoking, and genetic factors have been shown to play a role in the development of these malignancies[1-4].

The glutathione S-transferase (GST) enzymes

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are involved in detoxification of many potentially carcinogenic compounds. The enzymes are encoded by at least five distantly related gene families (the alpha, mu, pi, sigma, and theta GSTs). In humans, marked interindividual differences exist in the expression of mu (GSTM1), and theta (GSTT1) GSTs\(^3\). The GSTM1 and GSTT1 null genotypes have been linked to increased risk of developing lung, bladder, colon, and skin cancers\(^{6-7}\), and several studies have shown that GSTM1 and GSTT1 null genotypes were associated with increased risk of GC\(^{8,9}\) and CRC\(^{10}\). However, some data have suggested that no relationship exists between the GSTM1 or GSTT1 null genotype and the risk of GC or CRC may be due to limited sample sizes or differences in the ethnicities or differences in the genetic subtypes studied, or they may also be attributable to differences in exposure to environmental factors. However, the majority of the reports involved small sample sizes, so the association of the GSTM1/GSTT1 null genotype and the risk of GC and CRC need to be confirmed in studies with larger numbers of samples.

The present study aimed to evaluate the association of the GSTM1 and GSTT1 null genotypes with the risk of GC and CRC, and to determine whether smoking, alcohol consumption, and potential confounders modify the association between these polymorphisms and GC or CRC risk.

**MATERIALS AND METHODS**

**Ethics**

This study was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital in Hwasun, Korea, and all patients provided informed written consent.

**Subjects**

The study included 4042 newly diagnosed cancer cases (2213 GC and 1829 CRC) and 1699 controls. The cases were histologically confirmed at the Chonnam National University Hwasun Hospital (Jeollanam-do, Korea), between April 2004 and June 2008. Cases with secondary or recurrent tumors were excluded. The tumor stages were classified according to the TNM classification, including clinical or pathological TNM stages. GC was classified by anatomical site as cardia (C16.0) or non-cardia (C16.1-16.8) and by histological type as intestinal, diffuse, or mixed type. The control group (n = 1699) consisted of participants in the Thyroid Disease Prevalence Study conducted from July 2004 to January 2006 in Yeonggwang and Muan Counties of Jeollanam-do Province and in Namwon City of Jeollabuk-do, Korea\(^{13}\). At the time of peripheral blood collection, all case and control subjects provided their informed consent to participate in this study.

**Blood samples and DNA isolation**

Blood samples were collected in EDTA-containing tubes, and DNA was extracted from the buffy coat for genotyping. Genomic DNA was extracted using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA) according to the manufacturer’s protocol.

**Genotyping**

GSTM1 and GSTT1 genotyping was performed using a TaqMan allelic discrimination assay with previously described primers and modified probes\(^{10}\). Real-time PCR was performed using a Rotor-Gene 3000 multiplex system (Corbett Research, Sydney, Australia) in a 10-μL reaction volume containing 200 nmol/L PCR primer, 10 nmol/L CY5-labeled probe for GSTT1, 100 nmol/L FAM-labeled probe for GSTM1, 0.5 U of f-Taq polymerase (Solgent, Daejeon, Korea), and 40 ng of genomic DNA. The primer and probe are as follows: GSTM1, Forward, 5′-GGAGACAGAAGAGGAGAGATTC-3′, Reverse, 5′-GCCCAAGCTGCATATGTTGTTG-3′, Probe, FAM-CCATGGTCTGTTCTTCAAAATGTTCA-BHQ1; GSTT1, Forward, 5′-CTTCAGAGGGCCCATGAG-3′ Reverse, 5′-CAAGGCGATCAGCTTCTGCTT-3′, Probe, CY5-AAGGACTTCCACCTGCAGACCCC-BHQ3.

**Statistical analysis**

Statistical analysis was performed using SPSS for Windows version 17.0. The descriptive data for the major characteristics of study groups are expressed as mean (range) and percent. We used t-tests to determine statistical differences in the continuous variables and \(\chi^2\) tests for the categorical variables. Adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using logistic regression models with adjustments for age and sex to estimate the association between genotype and GC or CRC. Interactions of genotype with smoking, alcohol consumption, and age were estimated using the logistic regression model, which included an interaction term as well as variables for exposure (smoking and alcohol drinking), genotypes, and potential confounders (sex and age). Subjects with wild-type genotypes were considered to have baseline risk. The subjects for which there was missing data for smoking, drinking, anatomical site, and histological type TNM staging were excluded in interaction analysis related with these variables. All tests were conducted at the \(P = 0.05\) level of significance.

**RESULTS**

We included 2213 cases of GC, 1829 cases of CRC, and 1699 cancer-free controls in the present study. The demographic characteristics of subjects are shown in Table 1. The proportion of men in the cancer cases was higher than that in the controls, and cases in both cancer groups tended to be older than controls. The proportion of smoking in GC cases was higher than that in the controls, but in CRC cases was lower than that in the controls. The proportion of drinking in both cancer groups was lower than that in the controls.

The frequency distributions of the GSTM1 null genotype in the control, GC, and CRC groups were 54.3%, 55.4%, and 54.9%, respectively. The frequency distributions of the GSTT1 null genotype in the control, GC, and CRC groups were 50.5%, 53.0%, and 51.9%,
respectively. No significant differences were observed in the frequencies of the GSTT1 and GSTM1 genotypes between cancer patients and controls (Table 1).

The GSTM1 and GSTT1 null genotypes were not significantly associated with risk of GC (OR = 1.070, 95% CI = 0.935-1.224; OR = 1.101, 95% CI = 0.963-1.259, respectively) or CRC (OR = 1.065, 95% CI = 0.923-1.228; OR = 1.041, 95% CI = 0.903-1.200, respectively). The GSTM1 and GSTT1 null genotypes were not significantly associated with the risk of GC or CRC, classified according to TNM stage, tumor site or histology type (GC) (Tables 2 and 3).

Smoking, alcohol consumption and age did not modify the association between the GSTM1 and GSTT1 null genotypes and the risk of GC or CRC (Tables 2 and 3).

No difference in the frequency of the combined GSTM1 and GSTT1 null genotype was observed between the two cancer groups and controls (Table 4).

**DISCUSSION**

The present large-scale study investigated the association between GSTM1 and GSTT1 null genotypes and susceptibility to GC and CRC in a South Korean population. In this study, we observed no significant association between either type of cancer and the GSTM1 and GSTT1 null genotypes. Additionally, no difference was observed in the frequency of the combined GST (M1 and T1) null genotype between the two cancer groups and controls. Moreover, smoking did not modify the association between these polymorphisms and risk of GC or CRC.

The reports examining the GSTM1 and GSTT1 null genotypes and their association with gastric cancer are quite inconsistent. Two reports suggested that the GSTM1
null genotype increased GC risk\textsuperscript{[3,8,11,13,14,28]}, and three reported that the GSTT1 null genotype increased GC risk\textsuperscript{[9,11,18]}. However, our results suggest that no associations exist which is in line with the majority of reports\textsuperscript{[11,12,19-21]}. In studies of Korean populations, no significant associations were detected between the GSTM1 and GSTT1 null genotypes and GC risk. One study conducted in Iksan, Korea, reported that the GSTM1 and GSTT1 null genotypes had no association with the risk of GC (for GSTM1 null, OR \(= 0.86\) and 95% CI = 0.49-1.51; for GSTT1 null, OR \(= 0.97\) and 95% CI = 0.55-1.71)\textsuperscript{[12]}. Hong et al\textsuperscript{[11]} reported similar results. Another study suggested that the GSTM1 and GSTT1 null genotypes were not associated with the risk of GC, overall, but that in individuals who consumed kimchi, a spicy Korean food made with fermented cabbage, the GSTM1 and GSTT1 non-null genotype increased the risk of GC\textsuperscript{[9]}. Two meta-analyses, by La Torre et al\textsuperscript{[22]} and Boccia et al\textsuperscript{[23]} suggested that the GSTM1 and GSTT1 null genotypes have no effect on the risk of GC per se, but may modulate tobacco-related carcinogenesis of gastric cancer.

Two studies reported that the GSTT1 null genotype increased the risk of CRC\textsuperscript{[10,24]}, and three studies reported decreased CRC risk, one for the GSTM1 null\textsuperscript{[25]} and two for the GSTT1 null genotype\textsuperscript{[26,27]}. However, five studies suggested that the GSTM1 and GSTT1 null genotype are not related to CRC risk\textsuperscript{[10,11,13,14,28]}. One Korean study suggested that the genotypes of GSTM1 are associated with cancer occurrence in individuals carrying the hMLH1/hMSH2 mutation who were family members of patients with hereditary nonpolyposis colorectal cancer\textsuperscript{[29]}.

The conflicting results regarding the associations between GSTM1 and GSTT1 null genotypes and risks for GC and CRC may be due to limited sample size or differences in the ethnicities or genetic subtypes studied, and they may also be attributable to differences in exposure to environmental factors.

Polycyclic aromatic hydrocarbons (PAHs) are the main carcinogens in tobacco smoke. The ultimate carcinogen (PAH-DE) can be detoxified through conjugation with glutathione by GSTs, which are phase II enzymes\textsuperscript{[30]}. Individuals with the null genotype of GSTM1 or GSTT1 would have less capacity for detoxification of PAHs, which would potentially increase their risk of chemical carcinogenesis. However, our data suggested that smoking did not modify the association between the GSTM1 and GSTT1 null genotypes and the risk of GC or CRC.

Four studies examined the interaction between smoking, GSTM1 or GSTT1 polymorphisms, and the risk of GC\textsuperscript{[10,11,18,21]}. One study suggested that smoking modifies the association between the GSTM1 null genotype and the risk of GC\textsuperscript{[25]}. In contrast, three studies reported that smoking did not modify the association between the GSTM1 and/or GSTT1 null genotype and GC risk\textsuperscript{[11,18]} in line with our results. Additionally, six studies evaluated the interaction between smoking, the GSTM1 or GSTT1 null genotype, and the risk of CRC\textsuperscript{[13,25,31-34]}. Two studies reported that smoking modifies the association between the GSTM1 and/or GSTT1 null genotype and CRC risk\textsuperscript{[32,33]}. However, four studies reported no interaction between the GSTM1 and/or GSTT1 null genotype and smoking in CRC risk\textsuperscript{[33,32,34]}, in agreement with our results.

Our study suggests that alcohol consumption did not modify the association of GSTM1 and GSTT1 null genotypes with the risk of GC or CRC, which is consistent with previous studies regarding GC\textsuperscript{[9,11,18]}. However, no studies have been reported examining whether alcohol consumption modifies the association of the GSTM1 or GSTT1 null genotype with the risk of CRC.

The detoxification potential of the GSTs was observed to decrease with age\textsuperscript{[30]}. Yeh et al\textsuperscript{[28]} reported that men aged \(\leq 60\) years with the GSTT1 null genotype were at significantly increased risk of rectal cancer, and one study reported the GSTT1 null genotype was not associated with the risk of GC, classified according to age less than or greater than 60 years\textsuperscript{[37]}. However, the present study suggested that age does not modify the association between GSTM1 and GSTT1 null genotypes and the risk of GC or CRC.

In our data, the GSTM1 and GSTT1 null genotypes were not significantly associated with the risk of GC or CRC, classified according to TNM stage, tumor site, and histology type (GC). To the best of our knowledge, no reports have been published regarding the GSTM1 and GSTT1 null genotypes and GC or CRC risk classified according to TNM stage.

Two studies investigated the association between the GSTM1 and GSTT1 null genotypes and the risk of non-cardia or non-cardia GC, and both studies suggested that no significant association exists\textsuperscript{[11,36]}, in line with our result. Seow et al\textsuperscript{[37]} reported that the GSTM1 and GSTT1 null genotypes were not associated with the risk of CRC, classified according to location of the tumor in the colon or the rectum. Suzuki et al\textsuperscript{[30]} reported finding no association between the GSTM1 null genotype and the risk of intestinal type or diffuse type GC, and Agudo et al\textsuperscript{[30]} reported finding no association between the GSTT1 null genotype and the risk of intestinal type or diffuse type GC, consistent with our results.

In our data, smoking was associated with increased risk

| Combined genotypes | GC  | CRC  | Controls | OR\textsuperscript{a} (95% CI) | OR\textsuperscript{b} (95% CI) |
|--------------------|-----|------|----------|-------------------------------|-------------------------------|
| T1(+)/M1(+)        | 607 (22.1) | 478 (21.4) | 385 (22.7) | 1.04 (0.86-1.27) | 1.02 (0.84-1.23) |
| T1(+)/M1(-)        | 707 (25.7) | 583 (26.1) | 456 (26.8) | 1.02 (0.84-1.23) | 1.19 (0.97-1.47) |
| T1(-)/M1(+)        | 632 (23.0) | 523 (23.4) | 391 (23.0) | 1.04 (0.86-1.27) | 0.97 (0.79-1.19) |
| T1(-)/M1(-)        | 800 (29.1) | 648 (29.0) | 467 (27.5) | 1.17 (0.97-1.41) | 1.11 (0.91-1.36) |

Adjusted for age, sex; OR\textsuperscript{a} for gastric cancer; OR\textsuperscript{b} for colorectal cancer.
of GC, but with decreased risk of CRC. Previous studies reported that smoking increased the risk of GC\textsuperscript{[9]}, in line with our results. The association between smoking and CRC has been inconsistent among studies. A recent meta-analysis suggested that smoking is significantly associated with CRC incidence\textsuperscript{[8]}. In our data, drinking was associated with decreased risk of both cancer groups. Drinking probably does not affect overall risk of stomach cancer, but there is some evidence that drinking may increase the risk of GC\textsuperscript{[43]}. The relationship between drinking and CRC risk has been controversial, but a meta-analysis found that high consumers of alcohol had an elevated CRC risk\textsuperscript{[42]}. We could not rule out the possibility that differential misclassification bias may have occurred in our study, because we retrospectively gathered information about smoking and drinking from electronic medical records in both case groups, while cross-sectional surveys were used to gather information about smoking and alcohol in controls.

The major strength of our study was its large sample size. Ours was the first investigation of the risk of GC and CRC according to the GSTM1 and GSTT1 null genotypes in a large Korean population.

The limitations of our study must also be acknowledged. First, the study did not consider genetic polymorphisms of other cancer related genes. Second, the study considered a limited number of environmental factors (smoking and alcohol consumption), and other environmental factors such as dietary intake were not considered.

In conclusion, the results of the present population-based, large-scale case-control study suggest that in a Korean population, the GSTM1/GSTT1 null genotype does not modulate an individual’s susceptibility to GC or CRC, and that smoking, alcohol consumption, and age do not modify the association between these genotypes and the risk of GC or CRC.

**COMMENTS**

**Background**

Gastric cancer (GC) and colorectal cancer (CRC) are the most common malignancies in Korea. Environmental factors and genetic factors have been shown to play a role in the development of these malignancies.

**Research frontiers**

The glutathione S-transferase enzymes are involved in detoxification of many potentially carcinogenic compounds. Several studies have shown that glutathione S-transferase mu (GSTM1) and glutathione S-transferase theta (GSTT1) null genotypes were associated with increased risks for GC and CRC. But some data suggested no relationship between GSTM1/GSTT1 null genotypes and the risk of gastric and colorectal cancer in Korean population. It also determined whether smoking, alcohol consumption, and age modify the association between these polymorphisms and GC or CRC risk.

**Innovations and breakthroughs**

This is the first investigation of the risk of GC and CRC according to the GSTM1 and GSTT1 null genotypes in a large Korean population. It also aimed to determine whether smoking, alcohol consumption, and age modify the association between these polymorphisms and GC or CRC risk.

**Applications**

This study suggested that GSTM1 and GSTT1 null genotypes were not associated with increased risk of GC or CRC in Koreans. Smoking, drinking, and age did not modify the association between these genotypes and the risk of gastric or colorectal cancer. Future research should focus on other parts of the GST genotype to understand its role and risk of gastric and colorectal cancer in Korean population.

**Terminology**

GST: Glutathione-S-transferase is a Phase II detoxification enzyme. The enzymes are encoded by at least five distantly related gene families (the alpha, mu, pi, sigma, and theta GSTs). In humans, marked interindividual differences exist in the expression of mu (GSTM1), and theta (GSTT1) GSTs.

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S-Editor Tian L  L-Editor O'Neill M  E-Editor Ma WH