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Glutathione S-transferase P1 gene polymorphism associated with gastric cancer among Caucasians

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ABSTRACT

Studies investigating the association between glutathione S-transferase P1 (GSTP1) codon 105 polymorphism and gastric cancer risk report conflicting results. The objective of this study was to quantitatively summarise the evidence for such a relationship. Two investigators independently searched the Medline and Embase databases. This meta-analysis included 10 case-control studies, which included 1161 gastric cancer cases and 2847 controls. The combined results based on all studies showed that there was no significant difference in genotype distribution [AA odds ratio (OR) = 1.14, 95% confidence interval (CI) = 0.91, 1.44; AG (OR=0.82, 95% CI = 0.66, 1.03); GG (OR = 1.11, 95% CI = 0.55, 2.24)] between gastric cancer and non-cancer patients. When stratifying for race, results were similar except that patients with gastric cancer had a significantly higher frequency of AA (OR = 1.53, 95% CI = 1.14, 2.06) and lower frequency of AG (OR = 0.70, 95% CI = 0.55, 0.89) than non-cancer patients among Caucasians. When stratifying by the location and Lauren's classification of gastric cancer, we observed no statistically significant differences in genotype distribution. This meta-analysis suggests that the GSTP1 codon 105 polymorphism may be associated with gastric cancer among Caucasians.

1. Introduction

Gastric cancer, the second leading cause of death from cancer throughout the world, is an important health problem. A 2005 analysis of the worldwide incidence of and mortality from cancer showed that 934,000 cases of gastric cancer occurred in 2002 and that 700,000 patients die annually of this disease.[1] Despite the overall decline in gastric cancer rates in most of the Western World, gastric cancer remains a serious fatal disease throughout much of the rest of the world.[2–4] Thirty-eight percent of worldwide cases occur in China, where it remains the most common cancer in both sexes as it is elsewhere in Eastern Asia.[5] Conversely, the incidence rates of adenocarcinomas of the proximal stomach and distal oesophagus have been increasing, particularly in the Western World.[6] A major strategy for facing this health care problem is the identification of individuals at risk, contributing for prevention and early detection of the disease. The knowledge on molecular alterations, which are involved in the carcinogenic process of gastric cancer, may lead to new and hopefully more effective means for controlling this lethal disease. In this perspective, the role of genetic polymorphisms in gastric cancer risk has motivated increasing interest in recent years.[7]

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Glutathione-S-transferases (GSTs) are the most important phase II enzymes of the xenobiotic pathway. These enzymes catalyse the conjugation of potentially mutagenic electrophilic compounds, with nucleophilic glutathione yielding less toxic and more water-soluble compounds, which are readily excreted via urine or bile.[8] Thus, GSTs protect our body from the harmful effects of carcinogens and a reduction of their activity can render an individual more susceptible to various cancers.[9] GSTP1 exhibits a polymorphism within its coding region, which leads to reduced enzyme activity.[10]

Over the last two decades, a number of case-control studies were conducted to investigate the association between GSTP1 codon 105 polymorphism and gastric cancer risk in humans. But these studies have reported conflicting results. No quantitative summary of the evidence has ever been performed. The purpose of this meta-analysis was to quantitatively summarise the evidence for such a relationship.

2. Materials and methods

2.1. Literature search strategy

Search was applied to the following electronic databases: MEDLINE (1966 to June 2008), EMBASE (1980 to June 2008). The following key words were used: 'glutathione S-transferase' or 'GST', 'gastric' or 'stomach', 'carcinoma' or 'cancer' or 'tumour'. The search was done without restriction on language, and was conducted on human subject. The reference lists of reviews and retrieved articles were handsearched simultaneously. Abstracts or unpublished reports were not considered. If more than one article was published by the same author using the same case series, we selected the study with higher sample size.

2.1.1. Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. For inclusion in the meta-analysis, the identified articles had to provide information on (i) the number of gastric cancer cases and controls studied; (ii) the number of individuals genotype (AA, AG, GG) in cases and controls. Major reasons for exclusion of studies were (i) no control; (ii) duplicate; (iii) no usable data reported.

2.2. Data extraction

All data were extracted independently by two reviewers (Zhou and Li) according to the prespecified selection criteria. Disagreement was resolved by discussion. The following data were extracted: study design and period, statistical methods, population, number of gastric cancer cases and controls studied and study results.

2.3. Statistical analysis

The statistical analysis was conducted using STATA 8.2 (StataCorp, College Station, Tex), $P < 0.05$ was considered statistically significant. Dichotomous data were presented as odds ratio (OR) with 95% confidence interval (CI). Statistical heterogeneity was measured using the Q statistic ($P < 0.10$ was considered representative of statistically significant heterogeneity). Heterogeneity was also assessed through visual examination of L'Abbe plots. Fixed effects model was used when there was no heterogeneity of the results of the trials. Otherwise, the random effects model was used. For dichotomous outcomes, patients with incomplete or missing data were included in sensitivity analyses by counting them as treatment failures. To establish the effect of clinical heterogeneity between studies on meta-analysis' conclusions, subgroup analysis was conducted on the basis of race and the location, stage, Lauren's classification and histological differentiation of gastric cancer.

Several methods were used to assess the potential for publication bias. Visual inspection of asymmetry in funnel plots was conducted. The Begg rank correlation method and the Egger weighted regression method were also used to statistically assess publication bias ($P < 0.05$ was considered representative of statistically significant publication bias).[11,12]

3. Results

3.1. Study characteristics

There were 60 papers relevant to the searching words. Through the step of screening the title, 34 of these articles were excluded (24 were not polymorphisms, nine were not case-control studies, one was not conducted in humans). Abstracts from 26 articles were reviewed and an additional 13 trials were excluded (10 were not case-control studies, three were not conducted in humans), leaving 13 studies for full publication review. Of these, three were excluded (three did not report usable data);[13–15] thus, 10 papers,[16–25] which included 1161 gastric cancer cases and 2847 controls, were found to match our inclusion criteria. Ten studies, including eight population-based case–control studies and two hospital-based case–control studies, were included in this meta-analysis. The studies had been carried out in China, Japan, Korea, USA, Italy, India, Spain and Turkey. The characteristics of the studies included in this meta-analysis are presented in Table 1.

3.2. Quantitative data synthesis

The combined results based on all studies showed that there was no significant difference in genotype distribution [AA odds ratio (OR) = 1.14, 95% confidence interval (CI) = 0.91, 1.44; AG (OR = 0.82, 95% CI = 0.66, 1.03); GG (OR = 1.11, 95% CI = 0.55, 2.24)] between gastric cancer and non-cancer patients. When stratifying for race, results were similar except that patients with gastric cancer had a significantly higher frequency of AA (OR = 1.53, 95% CI = 1.14, 2.06) and lower frequency of AG (OR = 0.70, 95% CI = 0.55, 0.89) than non-cancer patients among Caucasians. When stratifying by the location and Lauren's classification of gastric cancer, we observed no statistically significant differences in genotype distribution. (Table 2).

Statistically significant heterogeneity was observed between trials in all analyses with the Q statistic (AA $P = 0.01$; AG $P = 0.04$; GG $P = 0.001$). In addition, L'Abbe plots did show evidence of heterogeneity. Review of funnel plots could not rule out the potential for publication bias for all analysis.

Table 1 – Characteristics of studies included in the meta-analysis.

Study (author, year)	Design	Study period	Population (country)	Genotyping method	No. of cases	No. of controls	AA of cases	AG of cases	GG of cases	AA of controls	AG of controls	GG of controls
Tripathi 2008	PCC	DNR	Caucasians (India)	PCR-RFLP	76	100	46	26	4	52	36	12
Zhang 2007	PCC	2002-2005	Asians (China)	TaqMan	200	823	119	46	35	513	283	27
Wideroff 2007	PCC	1993-1995	Caucasians (USA)	TaqMan	114	206	52	46	16	91	94	21
Ruzzo 2007	PCC	DNR	Caucasians (Italy)	PCR-RFLP	90	122	49	30	11	53	61	8
Martinez 2006	PCC	DNR	Caucasians (Spain)	PCR	86	220	61	23	2	107	90	23
Hong 2006	HCC	2000	Asians (Korea)	PCR-RFLP	108	238	66	38	4	158	74	6
Tamer 2005	HCC	2001–2003	Caucasians (Turkey)	PCR	70	204	38	23	9	90	74	40
Mu 2005	PCC	1995–2000	Asians (China)	PCR-RFLP	196	393	125	62	9	265	116	12
Setiawan 2001	PCC	1995	Asians (China)	PCR	81	419	61	19	1	296	115	8
Katoh 1999	PCC	1992–1997	Asians (Japan)	PCR-RFLP	140	122	99	36	5	93	24	5

Abbreviations: HCC, hospital-based case–control; PCC, population-based case–control; DNR, data not reported; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

Publication bias was not evident when the Begg rank correlation method (AA $P = 0.13$; AG $P = 0.33$; GG $P = 0.33$) and the Egger weighted regression method (AA $P = 0.08$; AG $P = 0.84$; GG $P = 0.05$) were used.

4. Discussion

The rapid growth of human genetics creates countless opportunities for studies of disease association. Given the number of potentially identifiable genetic markers and the multitude of clinical outcomes to which these may be linked, the testing and validation of statistical hypotheses in genetic epidemiology is a task of unprecedented scale. Meta-analysis provides a quantitative approach for combining the results of various studies on the same topic, and for estimating and explaining their diversity. A meta-analysis of 379 studies addressing 36 genetic associations with disease found that association studies of the same disease are often inconsistent in their findings, and that the first study to report an association often indicates a stronger effect than in subsequent studies. This can lead to a distorted impression of the genetic aetiology underlying a given disease. A systematic meta-analytic approach may assist in estimating population-wide effects of genetic risk factors in human disease.[26,27]

A genetic predisposition to gastric cancer has been suggested by both epidemiological studies and case reports of gastric cancer families.[6] Recent studies suggest that single nucleotide polymorphisms may be related to the tumourigenesis of gastric cancer.[28] Individual genetic susceptibility may be critical in a variety of processes relevant to gastric cancer tumourigenesis such as (i) mucosal protection in the face of *Helicobacter pylori* infection and other carcinogens, (ii) the inflammatory response, which conditions the maintenance, severity and outcome of the *H. pylori* infection, (iii) the functioning of carcinogen detoxification and antioxidant protection, (iv) cell proliferation ability, (v) the intrinsic variability of DNA repair processes; and (vi) the cell apoptotic pathway.[7] The mechanism of human gastric tumourigenesis is still relatively unknown, and single nucleotide polymorphisms can be used as a tool in searching for genetic variations of the disease gene and susceptibility, and to increase understanding of the disease mechanism.[29]

Statistically significant heterogeneity was observed between trials in all analyses with the Q statistic. The most important factor that contributed to the heterogeneity was whether or not the genotype frequencies were in Hardy–Weinberg equilibrium, because the equilibrium may not hold among a case group if the genotype is truly associated with disease. Observed departures from equilibrium therefore suggest possible issues with the control group, or the study population in general, that might have generated less than ideal circumstances for the investigation of the GSTP1 codon 105 polymorphism and gastric cancer. A departure from Hardy-Weinberg equilibrium can also imply possible ethnic admixture in the population, if the polymorphic site varies in genotype by race.[30,31] In fact, race-specific variation in the distribution of genotypes in the GSTP1 codon 105 polymorphism has been demonstrated.[32,33] Because race may be related to disease, either through common risk factors or

Table 2 – Meta-analysis of GSTP1 codon 105 polymorphism and gastric cancer.

Stratification of gastric cancer	No. of studies	OR (95% CI) of AA	P	OR (95% CI) of AG	P	OR (95% CI) of GG	P
Location: Cardia versus non-cardia	1	1.17 (0.54,2.54)	0.69	DNR		DNR	
Asians	1	1.17 (0.54,2.54)	0.69	DNR		DNR	
Caucasians	0						
Lauren's classification: diffuse versus intestinal	2	0.86 (0.44,1.67)	0.47	0.83(0.29,2.37)	0.72	1.58(0.21,12.00)	0.66
Asians	1	0.72 (0.29,1.76)	0.90	DNR		DNR	
Caucasians	1	1.07 (0.39,2.93)	0.95	0.83(0.29,2.37)	0.72	1.58(0.21,12.00)	0.66

Abbreviations: OR, odds ratio; CI, confidence interval; DNR, data not reported.

other genes in linkage-disequilibrium with GSTP1, confounding by race, or population stratification, may have biased results in studies conducted on ethnically diverse populations that did not account for possible confounding. In this meta-analysis, subgroup analysis was conducted on the basis of race. In fact, five studies were conducted among Asians, and five studies were conducted among Caucasians. When stratifying for race, results were similar except that patients with gastric cancer had a significantly higher frequency of AA and lower frequency of AG than non-cancer patients among Caucasians.

GSTP1 codon 105 polymorphism also had been extensively studied and reported to be associated with some other cancers. A case-control study, included 3035 cases and 3037 population controls, conducted by Lee and colleagues suggested that GSTP1 codon 105 polymorphism was significantly associated with greater breast cancer risk.[34] A case-control study conducted by Rybicki and colleagues showed that men who carried the GSTP1 codon 105 polymorphism and were exposed at high levels to occupational PAH had increased risk for prostate cancer.[35] The study conducted by Mittal and colleagues demonstrated that the GSTP1 gene polymorphism is a strong predisposing risk factor for bladder cancer in the North Indian population.[36] The study conducted by Lee and colleagues demonstrated that the presence of the GSTP1 codon 105 polymorphism was associated with a poorer prognosis of oesophageal cancer.[37] A case-control study conducted by Miller and colleagues showed that the GSTP1 GG genotype appears to enhance the magnitude of the association between environmental tobacco smoke exposure and lung cancer.[38] The study conducted by Soya and colleagues demonstrated that a significant interaction was observed among smokers and tobacco chewers carrying GSTP1 mutant genotypes.[39] It supported the results achieved by us.

There are some limitations to this meta-analysis. First, only published studies were included in the meta-analysis; therefore, publication bias may have occurred, even though the use of a statistical test did not show it. Second, we could not obtain information from most studies on the presence or absence of a history of infection with *H. pylori*, a strong risk factor for gastric cancer. Third, as in most meta-analyses, these results should be interpreted with caution because the population from eight countries and controls were not uniform. Fourth, our meta-analysis is based on unadjusted estimates, while a more precise analysis could be performed if individual data were available, which would allow for an adjustment estimate (by age and sex). For this to be made, however, this approach requires the authors of all the published studies to share their data. Finally, meta-analysis remains retrospective research that is subject to the methodological deficiencies of the included studies. We minimised the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search for published studies and by using explicit methods for study selection, data extraction and data analysis.

In conclusion, this meta-analysis suggests that the GSTP1 codon 105 polymorphism may be associated with gastric cancer among Caucasians. Since half of the included studies were based on a limited number of cases (<100), it is critical that larger and well-designed multicentric studies based on the same ethnic group confirm our results.

Conflict of interest statement

None declared.

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