RESEARCH COMMUNICATION

Lack of Association Between the 8-oxoguanine DNA Glycosylase Gene Ser326Cys Polymorphism and Gastric Cancer: Evidence from a Meta-Analysis

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Abstract

Objective: To evaluate the association of 8-oxoguanine DNA glycosylase gene (OGG1) Ser326Cys polymorphism with gastric cancer via a comprehensive meta-analysis. Methods: A total of 12 publications were identified before January 20, 2011 including 1,390 cases and 3,299 controls. A random-effects model was applied irrespective of between-study heterogeneity. Data and study quality were assessed in duplicate. Results: No significant association was found for either allele or genotype with gastric cancer (odds ratio [OR]=0.96; 95% confidence interval [95% CI]: 0.82–1.13; P=0.66), and this was also the case after combining 326Ser/Cys and 326Ser/Ser genotypes together (OR=0.87; 95% CI: 0.63–1.20; P=0.40), or 326Cys/Cys and 326Ser/Cys together (OR=1.03; 95% CI: 0.87–1.22; P=0.72). Subgroup analysis by ethnicity indicated that comparison of allele 326Ser versus 326Cys generated a weakly and non-significantl protective effect on gastric cancer in Asians (OR=0.90; 95% CI: 0.75–1.09; P=0.29) and Turks (OR=0.65; 95% CI: 0.37–1.14; P=0.13), but a non-significant risk effect in Europeans (OR=1.10; 95% CI: 0.78–1.54; P=0.60) and Brazilians (OR=1.13; 95% CI: 0.81–1.58; P=0.48). No publication bias was observed. Conclusions: Our results collectively suggest that the OGG1 Ser326Cys polymorphism might not be a potential candidate risk factor for the development of gastric cancer.

Keywords: Gastric cancer - OGG1 gene - meta-analysis - polymorphism - association

Introduction

According to a recent survey, gastric cancer (GC) is one of the most frequent malignancies in Asian countries (Long et al., 2010). It is generally believed that GC is a multifactorial disorder influenced by multiple genes and environmental factors such as diet, smoking, drinking, and *Helicobacter pylori* infection (Crew and Neugut, 2004). Since some people are more susceptible to GC than others, it is essential to explain this inter-individual difference in susceptibility or resistance to this cancer. However, although great hope was expressed in genome-wide association studies to unlock the genetic underpinnings of GC, the results from such research have told us little (Yoshida et al., 2010). Therefore, evaluation candidate genes or loci still attracts widespread research interest.

The human 8-oxoguanine glycosylase 1 (OGG1) gene (chromosome 3p26), as a member of the base-excision repair pathway, is regarded as a logical candidate for involvement in the underlying cause of cancer (Collins and Gaivão, 2007), with its expressed protein actively removing the directly 8-hydroy-2-deoxyguanine (8-OHdG) from DNA. In particular, an exonic polymorphism,

1245 C>G (Ser326Cys), in OGG1 gene has been widely evaluated. Functional studies suggested that the OGG1 protein encoded by 326Cys allele exhibits lower DNA repair activity compared with its wild-type Ser326 allele (Kohno et al., 1998). In addition, substitution of OGG1 gene allele 326Ser by 326Cys might result in high cancer susceptibility (Sugimura et al., 1999; Xing et al., 2001; Elahi et al., 2002; Chen et al., 2003). These findings therefore encourage the identification of genetic polymorphisms that affect the OGG1 functionality.

The relationship between OGG1 gene Ser326Cys polymorphism and GC risk has been conducted across different ethnic populations, but the results are often irreproducible (Shinmura et al., 1998; Hanaoka et al., 2001; Takezaki et al., 2002; Tsukino et al., 2004; Poplawski et al., 2006; Capellá et al., 2008; Farinati et al., 2008; Canbay et al., 2010; Malik et al., 2010; Palli et al., 2010; Sun et al., 2010). As meta-analysis can provide a reliable estimate in genetic association studies, we thus decided to explore the influence of OGG1 gene Ser326Cys polymorphism with GC from the current literature, while addressing between-study heterogeneity and publication bias.

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Materials and Methods

Literature Search

Publications were identified through MEDLINE and EMBASE databases as of January 20, 2011. As a prerequisite, all reports were written in English and performed in humans. Subject terms used for searching were ('OGG1' OR '8-oxoguanine DNA glycosylase' OR 'hOGG1') AND ('gastric' OR 'stomach') AND ('gene' OR 'variant' OR 'polymorphism' OR 'allele' OR 'genotype'). The full text of the retrieved publications was scrutinized to decide whether information on the topic of interest was included. Reference lists of these retrieved publications and systematic reviews were also checked to determine whether citations of articles that were not initially identified. For these publications involving more than one geographic or ethnic heterogeneous group, each was treated separately. Where there were multiple publications from the same study population, the most complete and recent results were extracted.

Inclusion and Exclusion Criteria

Studies were qualified if they satisfied the following criteria: (i) evaluation of OGG1 gene Ser326Cys polymorphism and GC risk; (ii) case-control or nested case-control or cross-sectional studies using either hospital-based or population-based design; (iii) sufficient information upon genotype counts for estimating the odds ratio (OR) and its corresponding 95% confidence interval (95% CI). Meanwhile, we only focused on GC other than other second neoplasms.

Extracted Information

Two authors (ZW and WC) independently summarized the following information from all eligible studies: first author's last name, year of publication, ethnicity of the population studied, study design, number of subjects in each category, baseline characteristics of the study population, and the counts of persons with different Ser326Cys genotypes in GC patients and controls. Besides, information on Hardy-Weinberg equilibrium test was also tracked or calculated manually if missing. In the entire course, any discrepancies were adjudicated by a discussion and a consensus was reached.

Statistical Analysis

Since no available evidence favored any genetic models of inheritance for the polymorphism under investigation, we carried out the allelic (326Cys versus 326Ser), homozygous (Cys/Cys versus Ser/Ser), dominant (Cys/Cys plus Ser/Cys versus Ser/Ser) and recessive model (Cys/Cys versus Ser/Ser plus Ser/Cys), respectively. The Hardy-Weinberg equilibrium was assessed by the χ^2 test (R software version 2.9).

Between-study heterogeneity was assessed by the inconsistency index I2 statistic (ranging from 0 to 100%) with higher values suggesting the existence of heterogeneity (Higgins JP et al., 2003). In this meta-analysis, we implemented the random-effects model only to bring the individual effect-size estimates together. This is mainly because within a fixed-effects model, only sampling error contributes to the differences between the observed effect-size estimates across individual studies (Cohn LD and Becker BJ, 2003). In contrast, there are two sources of variance coexisted in a random-effects model including the sample error and between-study heterogeneity. Given the ubiquitous nature of heterogeneity between studies, it is appropriate to utilize a random-effects model (Borenstein M et al., 2009).

In addition, to look at more narrowly drawn subsets of the studies such as different study designs and ethnicities, subgroup analyses were undertaken. Furthermore, to estimate the extent to which one or more covariates explain heterogeneity, meta-regression, as an extension to random-effects meta-analysis, was employed.

Finally, the funnel plots and Egger regression asymmetry test were applied to examine publication bias. Egger's test can detect funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision.

Probability less than 0.05 was judged significant with the exception of the I2 statistic and publication test, where a significance level of less than 0.1 was chosen. Data management and statistical analyses were performed using STATA version 11.0 for Windows.

Results

Study Characteristics

Via an extensive search, there were 11 original articles (Shinmura et al. 1998; Hanaoka et al., 2001; Takezaki et al. 2002 ;Tsukino et al., 2004; Poplawski et al., 2006; Capellá et al., 2008; Farinati et al., 2008; Canbay et al., 2010; Malik et al., 2010; Palli et al., 2010; Sun et al., 2010) with 12 study populations that satisfied our inclusion/exclusion criteria totaling 1,390 GC patients and 3, 299 controls. Of these 12 populations, two were conducted in a population-based study design (Malik et al., 2010; Palli et al., 2010), and the remaining in a hospital-based study design (In addition, three of them were from Japan (including one from Japanese-Brazilian) (Shinmura et al. 1998; Hanaoka et al. 2001; Tsukino et al., 2004), two from China (Takezaki et al., 2002; Sun et al., 2010), two from Italy (Farinati et al., 2008; Palli et al., 2010), and one from Brazil (non-Japanese Brazilian) (Hanaoka et al., 2001), Poland (Poplawski et al., 2006), Europe (multicenter) (Capellá et al. ,2008), Turkey (Canbay E et al., 2010), India (Malik et al., 2010), respectively. The baseline characteristics of qualified studies are summarized in Table 1. The frequencies of 326Ser allele in GC patients ranged from 41.78% to 89.29%, and that in controls ranged from 45.45% to 91.86%. The genotype distributions in controls were in agreement with the Hardy-Weinberg equilibrium across all studies at the significant level of 0.05.

Meta-Analysis

In Figure 1, compared with 326Cys allele carriers, those with 326Ser allele had a 4% reduced risk for GC (OR=0.96; 95% CI: 0.82–1.13; P=0.66) under the random-effects model. After assigning 326Cys/Cys genotype as a reference, this protective effect was slightly potentiated

Table 1. The Baseline Characteristics of All Eligible Studies

Study	Year	Ethnicity	Study design	Age, mean (SD) (years)		Number (males, %)		Ser Allele freq. (%)	
				Cases	Controls	Cases	Controls	Cases	Controls
Shinmura K et al.	1998	Japanese	Hospital	NA	NA	35	42	48.57	59.52
		Japanese Brazilian	Hospital	65(13)	65(12)	58(66.00)	127(68.00)	59.48	56.69
Hanaoka T et al.	2001	Non-Japanese Brazilians	Hospital	59(8)	58(8)	208(70.00)	205(71.00)	80.05	78.05
Takezaki T et al.	2002	Han Chinese	Hospital	60.85	60.05	101(76.23)	198(65.15)	50.00	45.45
Tsukino H et al.	2004	Japanese	Hospital	57.5(9.5)	57.1(9.5)	142(69.70)	271(70.50)	48.04	53.32
Poplawski T et al.	2006	Poles	Hospital	62.4	NA	28(70.00)	33(NA)	89.29	77.27
Capellá G et al.	2008	Europeans	Hospital	35-70	35-70	243(NA)	1138(NA)	79.84	77.64
Farinati F et al.	2008	Italians	Hospital	68	46	50(64.00)	43(69.77)	81.00	91.86
Canbay E et al.	2010	Turks	Hospital	60.07	52.8	40(NA)	247(NA)	76.25	83.20
Sun LM et al.	2010	Han Chinese	Hospital	59.6(11.2)	43.6(10.3)	73(65.80)	255(60.00)	41.78	51.57
Malik MA et al.	2010	Indians	Population	55.9(9.7)	58.0(12.7)	108(83.30)	195(71.30)	69.91	71.03
Palli D et al.	2010	Italians	Population	68.8(9.9)	55.5(7.0)	304(56.40)	545(49.30)	79.77	77.16

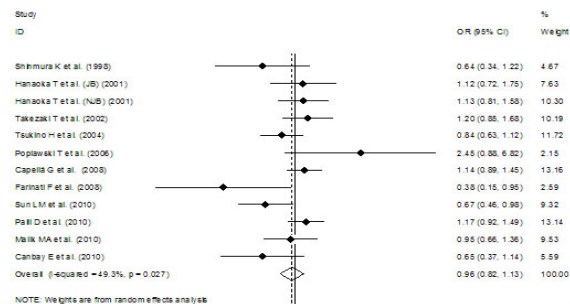Abbreviations: SD, standard deviation; NA, not available; freq., frequency.

Figure 1. The Contrast of OGG1gene 326Ser Allele Versus 326Cys Allele
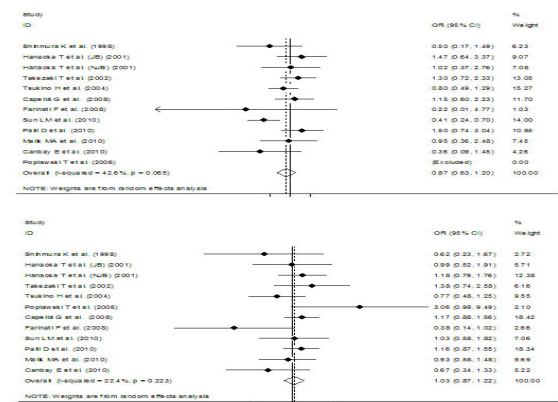

Figure 2. Comparison of the OGG1 Ser/Ser+Ser/Cys Genotypes Versus Cys/ Cys Genotype (Upper) and OGG1 Ser/Ser Genotype Versus Cys/Cys +Ser/Cys Genotypes (Lower) Under the Random-Effects Model

for 326Ser/Ser genotype carriers (OR=0.92; 95% CI: 0.68–1.24; P=0.58).

This tendency preserved after combining 326Ser/Cys and 326Ser/Ser genotypes together in association with GC compared with the 326Cys/Cys genotype (OR=0.87; 95% CI: 0.63–1.20; P=0.40) (Figure 2). Likewise, comparison of 326Ser/Ser genotype with 326Cys allele was reversed with no attainable significance (OR=1.03; 95% CI: 0.87–1.22; P=0.72) (Figure 2).

Subgroup Analysis

Considering the fact that study design and geographic differences might bias the overall estimates, we therefore conducted separate analyses based on these factors. As
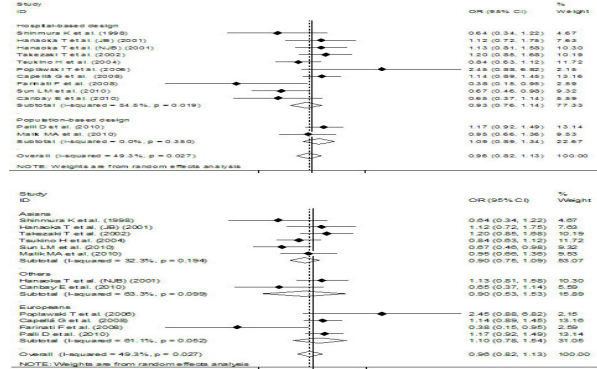

Figure 3. The Contrast of OGG1gene 326Ser Allele Versus 326Cys Allele According to Study Design (Upper) and Ethnicity (Lower)

for the ethnicity, we classified 12 study populations into Asians (Chinese, Japanese, Indians and Japanese Brazilians) (Shinmura K et al., 1998; Hanaoka T et al. ,2001; Takezaki T et al., 2002 ;Tsukino H et al., 2004; Sun LM et al., 2010; Malik MA et al., 2010), Europeans (Italians and Poles and multicenter Europeans) (Poplawski T et al., 2006; Capellá G et al. 2008; Farinati F et al. 2008; Palli D et al., 2010), Turks (Canbay E et al., 2010) and Brazilians (non-Japanese Brazilians) (Hanaoka T et al., 2001). As shown in Table 2, albeit nonsignificant, comparison of 326Ser versus 326Cys generated a weakly protective tendency for GC in Asians (OR=0.90; 95% CI: 0.75–1.09; P=0.29) and Turks (OR=0.65; 95% CI: 0.37–1.14; P=0.13), but a contrary tendency in Europeans (OR=1.10; 95% CI: 0.78–1.54; P=0.60) and Brazilians (OR=1.13; 95% CI: 0.81–1.58; P=0.48) (Figure 3). Similar tendencies were noted for comparisons of 326Ser/Ser versus 326Cys/Cys, 326Ser/Cys plus 326Ser/Ser versus 326Cys/Cys, as well as 326Ser/Ser versus 326Cys/Cy plus Ser/Cys genotypes (Table 2).

With regard to the study design, we divided the studies into two subgroups according to the sources of controls. No significant association was detected in the comparison between hospital-based group and population-based group. However, these two groups exhibited contrary tendency (Table 2).

Meta-Regression Analysis

To evaluate the extent to which different variables

Table 2. Subgroup Analysis of OGG1 Gene Ser326Cys Polymorphism and GC

| Subgroup	Study number	Ser vs. Cys		Ser/Ser vs. Cys/Cys		Ser/Cys+Ser/Ser vs. Cys/Cys		Ser/Ser vs. Cys/Cys+ Ser/Cys	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Ethnicity									
Asians	6	0.90(0.75,1.09)	0.29	0.84(0.57,1.23)	0.36	0.81(0.53,1.25)	0.34	0.94(0.74,1.19)	0.62
Europeans	4	1.10(0.78,1.54)	0.60	1.30(0.80,2.10)	0.29	1.25(0.77,2.01)	0.36	1.12(0.75,1.67)	0.57
Turks	1	0.65(0.37,1.14)	0.13	0.33(0.08,1.35)	0.12	0.36(0.09,1.45)	0.15	0.67(0.34,1.33)	0.25
Brazilians	1	1.13(0.81,1.58)	0.48	1.08(0.39,2.97)	0.88	1.02(0.37,2.76)	0.98	1.18(0.79,1.76)	0.41
Study design									
Population	2	1.09(0.89,1.34)	0.38	1.30(0.73,2.32)	0.38	1.27(0.72,2.26)	0.41	1.09(0.85,1.40)	0.49
hospital	10	0.93(0.76,1.14)	0.48	0.85(0.60,1.20)	0.34	0.80(0.56,1.16)	0.24	1.00(0.80,1.25)	0.99
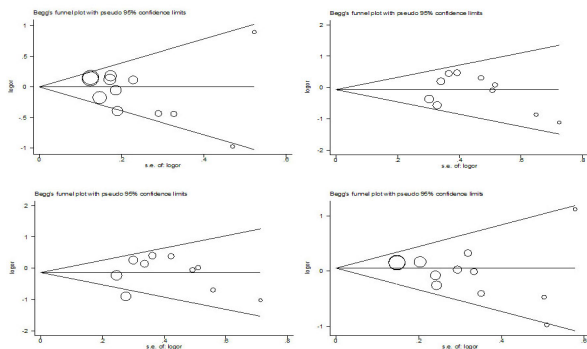
Figure 4. Begg's Funnel Plot of Publication Bias Test for the OGG1 Ser326Cys Polymorphism. (4a for 326Ser Allele Versus 326Cys Allele; 4b for Ser/Ser Versus Cys/ Cys; 4c for Ser/Ser+Ser/Cys Genotypes Versus Cys/ Cys Genotype and 4d for Ser/Ser Genotype Versus Cys/Cys +Ser/Cys Genotypes)

explained heterogeneity among the individual ORs, we performed meta-regression model of the OGG1 gene Ser326Cys polymorphism on study design, geographic region, and the average of age, gender and smoking status of both groups, and we unfortunately failed to detect any statistical significance concerning OGG1 gene Ser326Cys polymorphism across all genetic models (data not shown).

Publication Bias

As reflected by the funnel plots (Figure 4) and Egger's test, there was a low probability of publication bias for OGG1 gene Ser326Cys polymorphism (P=0.241).

Discussion

This study, including 4689 subjects from 12 populations, to our knowledge, is the first meta-analysis examining the relationship between OGG1 gene Ser326Cys polymorphism and GC. Although some statistical biases could not be eliminated and there was evidence of between-study heterogeneity, our results suggested that OGG1 Ser326Cys polymorphism might not be a potential candidate for the development of gastric cancer, whereas the study design and ethnicity were identified as potentially significant sources of between-study heterogeneity in this meta-analysis. Even through, there is a low probability of publication bias for all allelic/ genotypic comparisons, indicating the robustness of our results.

Genetic heterogeneity is an inevitable problem in any disease identification strategy (Hemminki et al., 2006). As shown in this study, we speculated that OGG1 gene

Ser326Cys polymorphism might have different roles across different ethnic populations. On one hand, there were striking differences in terms of mutant 326Ser allele frequency between Asians (41.78-71.03%) and Europeans (77.16-91.86%), with the latter remarkably higher than the former, suggesting that different genetic backgrounds may cause this discrepancy or different populations may have different linkage disequilibrium patterns. A polymorphism may be in close linkage with another nearby causal variant in one ethnic population but not in another (Yu et al., 2010). The OGG1 gene Ser326Cys polymorphism may be in close linkage with different nearby causal variants in different populations. On the other hand, in our subgroup analyses by ethnicity, Ser326Cys polymorphism showed significant heterogeneous associations with GC across different ethnic groups, with 326Ser in Asians and Turks being completely at odds with that in Europeans (Whites) and Brazilians, suggesting that this polymorphism might have a pleiotropic role in the pathogenesis of GC or interact with other genetic and environmental factors. However, considering the relatively small sample sizes in Turks and Brazilians, we suggest that confirmation in large, well-designed studies is critical.

Besides the disturbing influence of ethnicity in this meta-analysis, it should still be treated with caution because of different study designs. Our results indicated that magnitude of association was potentially reversed in population-based studies relative to in hospital-based studies, although no significance was identified. In this regard, we agree that control for population stratification remains an important consideration in hospital-based studies(Salanti G et al., 2005), because in this meta-analysis, most studies have recruited subjects from only one hospital, and thus there might be a narrow socioeconomic profile for both patients and controls. Moreover, in hospital-based studies, poor comparability between cases and controls might exert a confounding effect on the true association in light of a regional specialty for the disease under study and the differential hospitalization rates between cases and controls (Ruano-Ravina et al., 2008). In contrast, subjects drawn from community or a fixed group might be representative of the true population, leading us to believe that results from population-based studies might hold the water. Considering the wider confidence intervals of estimates and small sample sizes in population-based studies, more studies are required to quantify this effect size reliably.

Despite the clear strengths of our study including

relatively large sample sizes and low probability of publication bias, interpretation of our current study, however, should be viewed in light of several technical limitations. Because only published studies were retrieved in this meta-analysis and the "grey" literature (articles in languages other than English) was not included, publication bias might be possible, even though our funnel plots and statistical tests did not show it. Moreover, the single-locus-based nature of meta-analysis precluded the possibility of gene-gene and gene-environment interactions, as well as haplotype-based effects, suggesting that additional studies assessing these aspects will be necessary. Furthermore, we only centered on OGG1 gene Ser326Cys polymorphism, and did not cover other genes or polymorphisms. It seems likely that the Ser326Cys polymorphism individually makes a moderate contribution to risk prediction in GC patients, but whether this polymorphism integrated with other risk factors will enhance the prediction requires additional research. Thus, the jury must refrain from drawing a conclusion until large, well-performed studies confirm or refuse our results.

Taken together, we expand previous individually underpowered studies by suggesting that OGG1 Ser326Cys polymorphism might not be a potential candidate for the development of gastric cancer. Also our observations leave open the question of heterogeneous effect of 326Ser allele across different ethnic populations. Nevertheless, for practical reasons, we hope that this study will not remain just another endpoint of research instead of a beginning to establish the background data for further investigation on association of OGG1 gene with GC.

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