

RESEARCH COMMUNICATION

Lack of Association between the hOGG1 Ser326Cys Polymorphism and Gastric Cancer Risk: a Meta-analysis

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Abstract

Aim: To clarify any association between the hOGG1 Ser326Cys polymorphism and susceptibility to gastric cancer. **Methods:** A meta-analysis based on 11 eligible case-control studies involving 5,107 subjects was carried out to summarize the data on the association between hOGG1 Ser326Cys polymorphism and gastric cancer risk. **Results:** No association was found between hOGG1 Ser326Cys polymorphism and gastric cancer risk (dominant model: OR = 0.95, 95% CI: 0.83-1.09, $p = 0.486$, $I^2 = 0.419$; additive model: OR = 1.02, 95% CI: 0.81-1.30, $p = 0.850$, $I^2 = 0.181$; recessive model: OR = 1.09, 95% CI: 0.80-1.48, $p = 0.586$, $I^2 = 0.053$). Subgroup analysis based on ethnicity (Asian and Caucasian) and smoking status (ever smoker and never smoker) did not present any significant association. Sensitivity analysis did not perturb the results. **Conclusions:** This study strongly suggested there might be no association between the hOGG1 Ser326Cys polymorphism and gastric cancer risk. However, larger scale studies are needed for confirmation.

Keywords: hOGG1 - polymorphism - gastric cancer - risk factors - meta-analysis

Asian Pacific J Cancer Prev, 13, 1145-1149

Introduction

Oxidative DNA damage induced by reactive oxidative species (ROS) contributes to the generation and development of cancer (Marnett, 2000). One of the most common forms of ROS-generated DNA damage is 8-hydroxy-2'-deoxyguanosine (8-OHdG). It prefers to mismatching with deoxyadenosine instead of deoxycytosine, which leads to a base transversion from GC to AT at the end of a replication cycle (Cheng et al., 1992). when this mutation occurs within oncogenes or tumor suppressor genes, carcinogenesis may initiate (Hoeijmakers, 2001).

Base excision repair (BER) pathway, which prevents genes from mutating by removing modified base before DNA replication, is an important mechanism for repairing oxidatively damaged DNA. Human 8-hydroxydeoxyguanosine glycosylase 1 (hOGG1), specifically repairing 8-OHdG, is a key component in the BER pathway (Yang et al., 2006). This catalytic enzyme is encoded by the hOGG1 gene located on chromosome 3p26 which is highly polymorphic. The functional polymorphism Ser326Cys, resulting from a C to G transversion at 1245 position in exon 7, is a hotspot widely studied (Kohno et al., 1998). It is reported that ser326 allele exhibited higher catalytic activity in BER pathway than the cys326 variant (Kohno et al., 1998; Hill et al., 2006). Therefore, the hOGG1 Ser326Cys polymorphism may influence the capacity of the host to repair DNA damage

and be relevant to susceptibility to tumor (Goode et al., 2002). Studies indicated a role of the hOGG1 Ser326Cys polymorphism in many cancers including oro-laryngeal cancer (Elahi et al., 2002; Yang et al., 2008), esophageal cancer (Xing et al., 2001), lung cancer (Lan et al., 2004), gastric cancer (Hanaoka et al., 2001), renal cell carcinoma (RCC) (Zhao et al., 2011), gallbladder cancer (Jiao et al., 2007), bladder cancer (Arizono et al., 2008), prostate cancer (Zhang et al., 2010) and acute lymphoblastic leukemia (Stanczyk et al., 2011).

Gastric cancer (GC) is one of the four most common cancers and the second leading cause of cancer deaths worldwide (Jemal et al., 2009). GC development is a multistep process and many factors and mechanisms are proposed to be involved in it. Oxidative DNA damage caused by ROS is thought to be one of the pathogeneses (Farinati et al., 1998), and thus hOGG1 Ser326Cys polymorphism, responsible for repairing ROS generating DNA damage, may associate to susceptibility to GC. However, published studies conducted to observe the relations showed inconsistent results, including lack of association (Shinmura et al., 1998; Hanaoka et al., 2001; Poplawski et al., 2006; Arai et al., 2008; Capella et al., 2008; Malik et al., 2010; Palli et al., 2010; Sun et al., 2010; Engin et al., 2011) and positive association interacting with other factors (Takezaki et al., 2002; Tsukino et al., 2004; Farinati et al., 2008; Li et al., 2009). In order to decisively conclude, a meta-analysis was performed to evaluate the association between hOGG1 Ser326Cys

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polymorphism and the susceptibility of GC. To our knowledge, no meta-analysis regarding to this issue has been reported until now.

Materials and Methods

Study identification and selection

Before the study, inclusion criteria were defined as follows: (a) articles evaluating the association between hOGG1 Ser326Cys polymorphism and gastric cancer risk; (b) study designed as case-control; (c) sufficient data available to estimate an odds ratio (OR) with its 95% confidence interval (95% CI). A literature search of PubMed and EMBASE (updated to 2011/09/01) was conducted using the following terms: 'OGG1', 'polymorphism(s)', 'gastric cancer' or 'gastric carcinoma', without restriction on language. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis by the two authors (Li BR and Zhou GW) independently. The reference lists of reviews and retrieved articles were searched simultaneously to find additional eligible studies. If studies had partly overlapped subjects, only the one with a larger sample size was selected. Any disagreement was resolved by discussion between the two authors.

Data extraction

The following variables were extracted from each study if available: first author's surname, publication year, ethnicity, matching criteria, sample size, and numbers of cases and controls in different hOGG1 Ser326Cys genotypes.

Statistical analysis

The strength of association between hOGG1 Ser326Cys polymorphism and gastric cancer risk was assessed by OR with the corresponding 95% CI. And the pooled OR was calculated by a fixed-effects model (the Mantel-Haenszel method) when between-study heterogeneity was absent (Mantel et al., 1959). Otherwise, a random-effects model (the DerSimonian and Laird method) (DerSimonian et al., 1986) was selected. Statistical between-study heterogeneity was checked by the Q test (Cochran, 1954) and it was considered

statistically significant with $P < 0.10$. The OR and its 95% CI in each comparison was assessed in dominant (Ser/Cys+Cys/Cys versus Ser/Ser), additive (Cys/Cys versus Ser/Ser), and recessive (Cys/Cys versus Ser/Ser+Ser/Cys) genetic models. In addition, subgroup analyses for ethnicity (Caucasian and Asian) were conducted, and influence analysis was performed by omitting each study to find potential outliers (Tobias, 1999). In the control populations, Hardy-Weinberg equilibrium (HWE) was tested, but a deviation from HWE was allowed in a mixed control population. Sensitivity analysis was also conducted by excluding the HWE-violating studies. The potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested by Egger's test ($P < 0.05$ was considered a significant publication bias) (Egger et al., 1997). This meta-analysis was performed using the software STATA version 10.0.

Results

Study characteristics

A total of fourteen publications met the inclusion criteria. Of these studies, three (Poplawski et al., 2006; Arai et al., 2008; Li et al., 2009) were excluded because these studies didn't report available data. As a result, a total of eleven publications (Shinmura et al., 1998; Hanaoka et al., 2001; Takezaki et al., 2002; Tsukino et al., 2004; Capella et al., 2008; Farinati et al., 2008; Canbay et al., 2010; Malik et al., 2010; Palli et al., 2010; Sun et al., 2010; Engin et al., 2011) involving 5,107 subjects were included in this meta-analysis. Table 1 lists the main characteristics of these studies. Among these publications, there were four studies of Caucasian descent and six of Asian descent, and three studies presented available data in dominant genetic model to explore the interaction effect between hOGG1 Ser326Cys polymorphism and smoke status on gastric risk (Hanaoka et al., 2001; Tsukino et al., 2004; Malik et al., 2010). All of the cases were histologically confirmed as gastric cancer. Controls were mainly healthy populations, and matched with age or cancer-free. Genotype distributions in the controls of all studies were in agreement with HWE except one (Takezaki et al., 2002).

Table 1. Main Characteristics of Studies Included in this Meta-analysis

References	Country	Ethnicity	Source of controls	Matching criteria	Sample size (case/control)	Genotype (case/control)			HWE*
						Ser/Ser	Ser/Cys	Cys/Cys	
Shinmura, 1998	Japan	Asian	Population-based	-	35/42	9/15	16/20	10/7	Yes
Hanaoka, 2001	Brazil	Asian	Hospital-based	Age, sex	96/192	20/44	29/56	9/27	Yes
		Caucasian	Hospital-based	Age, sex	236/236	133/123	67/74	8/8	Yes
Takezaki, 2002	Japan	Asian	Population-based	Age, sex	101/198	20/30	61/120	20/48	No
Tsukino, 2004	Japan	Asian	Population-based	Cancer-free	153/302	32/74	75/141	35/56	Yes
Capella, 2008	Spain	Caucasian	Population-based	-	246/1175	156/688	76/391	11/59	Yes
Farinati, 2008	Italy	Caucasian	Hospital-based	Cancer-free	50/43	33/36	7/15	2/0	Yes
Canbay, 2010	Turkey	Caucasian	Population-based	Age, sex	40/247	24/171	13/69	3/7	Yes
Malik, 2010	India	Asian	Population-based	Cancer-free	108/195	50/94	51/89	7/12	Yes
Sun, 2010	China	Asian	Population-based	Cancer-free	73/255	21/72	19/119	33/64	Yes
Palli, 2010	Italy	Caucasian	Population-based	random	314/548	192/325	101/191	11/29	Yes
Engin, 2011	Turkey	Caucasian	Hospital-based	random	106/116	53/51	42/47	11/18	Yes

*HWE Hardy-Weinberg equilibrium

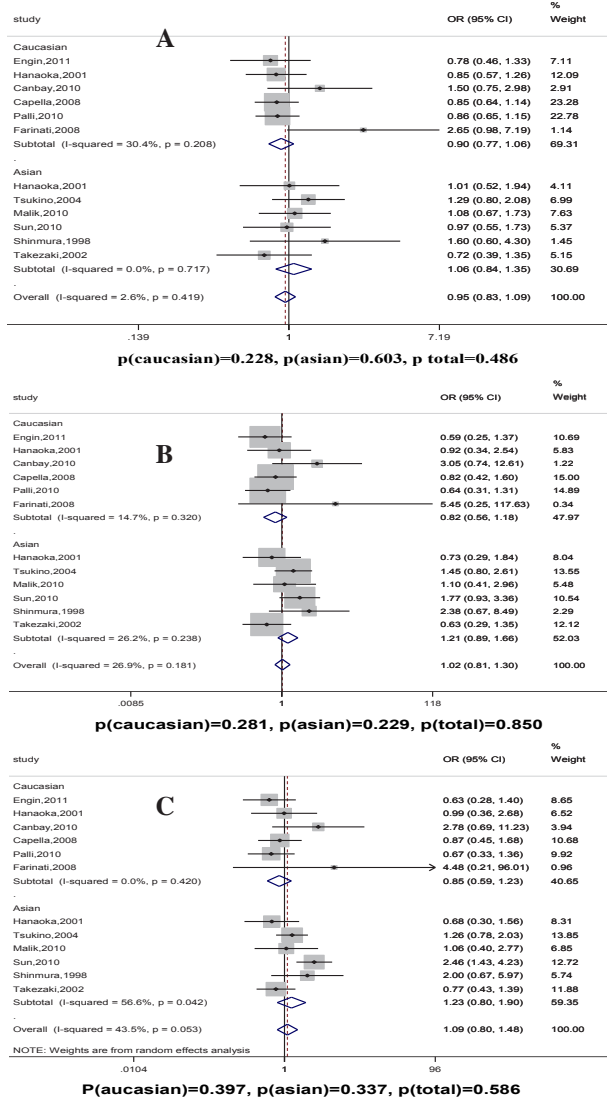


Figure 1. Meta-analysis of the Association Between hOGG1 Ser326Cys Polymorphism and Gastric Cancer Risk. Subgroup analyses were conducted according to specific ethnicities. A: dominant genetic model, B: additive genetic model, C: recessive genetic model

Meta-analysis results

As shown in Figure 1, no heterogeneity among studies was detected in dominant and additive models. In recessive model, there was significant heterogeneity in overall comparison and Asian subgroup analysis and therefore random-effect model was used. When all the eligible studies were pooled into the meta-analysis, no association was found between hOGG1 Ser326Cys polymorphism and gastric cancer risk (dominant model: OR = 0.95, 95% CI: 0.83-1.09, p = 0.486, I^2 (p values for heterogeneity) = 0.419; additive model: OR = 1.02, 95% CI: 0.81-1.30, p = 0.850, I^2 = 0.181; recessive model: OR = 1.09, 95% CI: 0.80-1.48, p = 0.586, I^2 = 0.053). In the subgroup analysis according to specific ethnicity, no significant association was found in neither Asian (dominant model: OR = 1.06, 95% CI: 0.84-1.35, p = 0.603, I^2 = 0.717; additive model: OR = 1.21, 95% CI: 0.89-1.66, p = 0.229, I^2 = 0.238; recessive model: OR = 1.23, 95% CI: 0.80-1.90, p = 0.337, I^2 = 0.042) nor Caucasian populations (dominant model: OR = 0.90, 95% CI: 0.77-1.06, p = 0.228, I^2 = 0.208; additive model: OR =

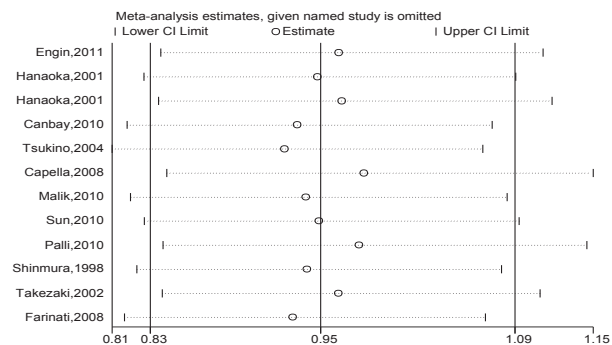


Figure 2. Influence Analysis for Ser/Cys+ Cys/Cys versus Ser/Ser in the Overall Meta-analysis. This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate its 95% CI. Every hollow round indicates the pooled OR when the left study is omitted in this meta-analysis. The two ends of every broken line represent the 95% CI

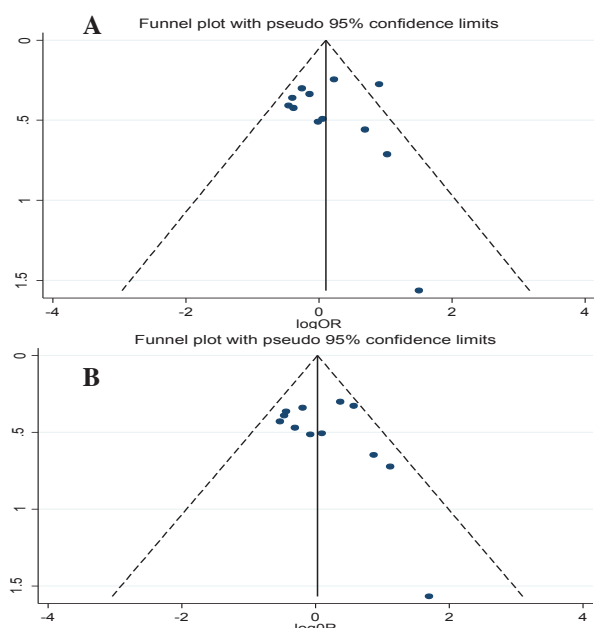


Figure 3. Funnel Plot of hOGG1 Ser326Cys Polymorphism and Gastric Cancer Risk for Publication Bias. A: recessive genetic model, B: additive genetic model

0.82, 95% CI: 0.56-1.18, p = 0.281, I^2 = 0.320; recessive model: OR = 0.85, 95% CI: 0.59-1.23, p = 0.397, I^2 = 0.420). In the subgroup analysis according to smoke status, negative results were obtained in dominant genetic model (ever smoke: OR = 1.04, 95% CI: 0.71-1.55, p = 0.831, I^2 = 0.289; never smoke: OR = 1.09, 95% CI: 0.75-1.57, p = 0.655, I^2 = 0.798).

Sensitivity analysis

Influence analysis was performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggested that no individual study significantly affected the pooled ORs (Figure 2). Sensitivity analysis by excluding HWE-violating study didn't perturb the overall results.

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias. The shapes of the funnel plot

did not indicate any evidence of obvious asymmetry in additive and recessive model (Figure 3) and the Egger's test suggested the absence of publication bias (additive model: $p = 0.347$; recessive model: $p = 0.800$).

Discussion

Although most previous studies evaluating the association between the hOGG1 Ser326Cys polymorphism and gastric cancer risk failed to demonstrate that any hOGG1 Ser326Cys variants were relevant to increased risk of GC, a few studies were reported to indicate a role of the hOGG1 Ser326Cys polymorphism in gastric cancer susceptibility. The conflicting results may result from the relatively small sample size and different genetic and environmental background. With a relatively large number of subjects, we performed a meta-analysis to precisely clarify the conclusion. The present meta-analysis combined 11 case-control studies focused on associations between GC and hOGG1 Ser326Cys polymorphism. The overall ORs were not significantly influenced by the hOGG1 Ser326Cys polymorphism.

Mutations at codon 326 of hOGG1 change the enzymatic activity of the hOGG1 proteins. With the cys326 variant, the ability of the host to repair the oxidative DNA damages seems to be lowered and consequently the host is relatively easier to get GC. However, the deduction above is based on the hypothesis that the ability of the host to repair the oxidative DNA damage is reduced by the low activity of the mutated hOGG1 proteins. Maybe the mutated hOGG1 proteins still active enough to maintain a low level of the oxidative damaged DNA and keep the host away from GC generating point. As evidence supporting no increased level of oxidative damaged DNA with mutated hOGG1 proteins, referred results have been reported in gastric and lung cancer cell lines (Kohno et al., 1998). Studies to observe the level of 8-OHdG in vivo in the population with different hOGG1 genotypes are needed for further identification. Also, as response to DNA damage, there are several maintenance systems both at the cellular and molecular level. Reduced repairing potential from one of the molecular level systems can be compensated by other systems. So the overall effect is negative even if genotype is changed. Moreover, insignificant association between hOGG1 Ser326Cys variations and GC risk may due to lack of analysis of these variants in combination with other DNA repair polymorphisms. Carriers with multiple mutations of DNA repair genes show significantly increased risk of GC (Palli et al., 2010).

And according to the stratified analysis, effect of hOGG1 Ser326Cys polymorphism interacting with smoking status on GC was not detected. Similarly, analysis in different races indicates hOGG1 Ser326Cys polymorphism did not significantly contribute to the GC susceptibility.

The effect of SNP is often influenced by its genetic background and different races are with different genomic genotypes. Given this, we analyze the combined data by dividing the samples into subgroups according to the race. But results of all race subgroups indicated no

statistically significant association between GC and hOGG1 Ser326Cys polymorphism. This also may be explained by no enough decreased DNA repair activity of mutated hOGG1 proteins and the compensated effects of other DNA damage repairing enzymes.

Cigarette is a well-known risk factor for GC, through increasing oxidative stress, activating NF-kappa B and GRP78, inducing apoptosis and sensitizing cells to genotoxic/xenobiotic stresses by a multiple stress inducer (Crowley-Weber et al., 2003). So in this meta-analysis, we evaluated the role of interactions between cigarette status and hOGG1 Ser326Cys polymorphism in GC susceptibility. hOGG1 Ser326Cys variations failed to reach significantly statistical difference either in the no-smoking group and the smoking group. As well as the above-mentioned explanations, to some extent, genetics background and different lifestyles may play potential roles through affecting the oxidative metabolism.

Pathology of GC is complex and is not completely clear and many factors are involved in it. The presently detected association between GC and hOGG1 Ser326Cys polymorphism may be influenced by other GC risk factors. Besides race and cigarette status, other lifestyle factors such as vegetable intake and consumption of salt tea may act as moderating roles of hOGG1 variants in GC development (Ivankovic et al., 1998) by releasing compounds that are antioxidant or ROS-inducing may affect the evaluation of the role of hOGG1 Ser326Cys in GC susceptibility.

With a relatively large number of subjects, results of this meta-analysis are reliable. Heterogeneity in this study was not significant and Publication bias was not observed. Sensitivity analysis was conducted and the combined ORs were not influenced by any individual study.

There are limitations in this study. Firstly, sources of subjects in control groups are inconsistent, either hospital-based or population-based. Secondly, the present study only involved in the races of Asian and Caucasian and analyses of other races are absent. Thirdly, with studies published so far, sub-group analysis concerning the infection of *Helicobacter pylori* is unfeasible. And also the association between hOGG1 Ser326Cys polymorphism and GC of different histological types is undetectable in this meta-analysis. Lastly, in GC patients, mutations in the hOGG1 are infrequent (Shinmura et al., 1998), which suggests that a huge number of subjects are needed to detect the role of hOGG1 Ser326Cys polymorphism in GC.

In conclusion, the present study supported no overall association between GC susceptibility and hOGG1 Ser326Cys polymorphism. And taken the races and smoking status into consideration, hOGG1 Ser326Cys polymorphism was not relevant to the increased GC susceptibility. Extensive studies are needed to evaluate the association between GC susceptibility and hOGG1 Ser326Cys polymorphism in both gene-gene and gene-environment methods.

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