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Meta-analysis demonstrates lack of association of the *hOGG1* Ser326Cys polymorphism with bladder cancer risk

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ABSTRACT. The functional polymorphism Ser326Cys (rs1052133) in the human 8-oxoguanine DNA glycosylase (*hOGG1*) gene has been implicated in bladder cancer risk. However, reports of this association between the Ser326Cys polymorphism and bladder cancer risk are conflicting. In order to help clarify this relationship, we made a meta-analysis of seven case-control studies, summing 2521 cases and 2408 controls. We used odds ratios (ORs) with 95% confidence intervals (95%CIs) to assess the strength of the association. Overall, no significant association between the *hOGG1* Ser326Cys polymorphism and bladder cancer risk was found for Cys/Cys *vs* Ser/Ser (OR = 1.10, 95%CI = 0.74-1.65), Ser/Cys *vs* Ser/Ser (OR = 1.07, 95%CI = 0.81-1.42), Cys/Cys + Ser/Cys *vs* Ser/Ser (OR = 1.08, 95%CI = 0.87-1.33), and Cys/Cys *vs* Ser/Cys + Ser/Ser (OR = 1.04, 95%CI = 0.65-1.69). Even when stratified by ethnicity, no significant association was

observed. We concluded that the *hOGG1* Ser326Cys polymorphism does not contribute to susceptibility to bladder cancer.

Key words: Bladder cancer; *hOGG1*; Polymorphism; Meta-analysis; Genetic susceptibility

INTRODUCTION

Bladder cancer ranks ninth in worldwide cancer incidence and is more frequent in men than in women (Murta-Nascimento et al., 2007). The incidence of bladder cancer varies considerably between countries, with the highest incidence rates seen in Western countries and the lowest rates in Asian countries (Kakehi et al., 2010). Researchers have reached a consensus that bladder cancer is an excellent model for studying genetic susceptibility and gene-environment interaction in cancer etiology. Cigarette smoking and occupational exposure to carcinogens are believed to play a critical role in the incidence of bladder cancer (Zeegers et al., 2000; Reulen et al., 2008; Wu et al., 2008). Nevertheless, only a small percentage of individuals with environmental exposure develop bladder cancer, suggesting a genetic contribution to bladder cancer etiology.

DNA damage, which is associated with carcinogenesis, can be removed or repaired through different repair systems. The base excision repair pathway, which is composed of many DNA repair genes, mainly removes DNA damage caused by ionizing radiation and reactive oxidative species (ROS; Yuan et al., 2010). The human 8-oxoguanine DNA glycosylase (*hOGG1*) gene, as a component of the base excision repair pathway, performs the initial step of recognizing the 8-hydroxyguanine damage, which is highly mutagenic and a major form of oxidative DNA damage (Yun et al., 2012). Researchers have found a number of *hOGG1* functional polymorphisms such as Arg46Gln, Arg154His, Ser326Cys, Gly308Glu, and Arg229Gln (Blons et al., 1999; Audebert et al., 2000; Hill and Evans, 2007). In recent years, the common functional polymorphism (Ser326Cys) has been investigated in many studies. The C/G polymorphism at 1245 bp (C1245G) in exon 7 of the *hOGG1* gene results in an amino acid substitution of serine (Ser) with cysteine (Cys) at codon 326 (Ser326Cys, rs1052133) (Zhang et al., 2011). A functional study showed that the 326Cys allele had reduced DNA repair activity (Kohno et al., 1998) and was associated with cancer risk (Weiss et al., 2005). To date, many studies have assessed the association between the *hOGG1* Ser326Cys polymorphism and bladder cancer risk, which have shown inconclusive results (Figueroa et al., 2007; Arizono et al., 2008; Narter et al., 2009; Gangwar et al., 2009). In search of a conclusive association, we carried out a meta-analysis of seven published case-control studies to comprehensively evaluate the role of the *hOGG1* Ser326Cys polymorphism in the susceptibility to bladder cancer.

MATERIAL AND METHODS

Eligible studies and data extraction

The PubMed database was searched using combinations of the following phrases: "hOGG1/OGG1/OGG/human 8-oxoguanine DNA glycosylase", "polymorphism", and "bladder cancer" (last search on July 20, 2011). To retrieve the most eligible studies, we evaluated all associated articles

and their references, which were hand-searched. The inclusion criteria were: 1) English-language articles, 2) case-control studies, 3) evaluation of the Ser326Cys polymorphism and bladder cancer risk, and 4) to contain useful genotype frequency. For each of the eligible publications, the following data was extracted: first author's surname, year of publication, country of study population, ethnicity, total number of cases and controls, genotyping methods, and matching criteria.

Statistical analysis

For the control group of each study, the allelic frequency was calculated, and the observed genotype frequencies of the *hOGG1* Ser326Cys polymorphism were assessed for Hardy-Weinberg equilibrium (HWE) using the chi-square test. The effect measure of choice was odds ratio (OR) with its corresponding 95% confidence interval (95%CI) and the Z-test was used to determine the significance of the summary OR, with $P < 0.05$ considered to be statistically significant. The heterogeneity between studies was tested by the Q-statistic (Zintzaras and Ioannidis, 2005). If $P < 0.10$ was considered significant for heterogeneity between studies, the summary OR estimate of each study was calculated by the random-effect model (the DerSimonian and Laird method). Otherwise, fixed-effect models (Mantel-Haenszel) were used (Lau et al., 1997).

The genotype frequencies of the *hOGG1* Ser326Cys polymorphism were examined using heterozygote comparison (Ser/Cys *vs* Ser/Ser), homozygote comparison (Cys/Cys *vs* Ser/Ser), dominant model (Ser/Cys + Cys/Cys *vs* Ser/Ser), and recessive model (Cys/Cys *vs* Ser/Cys + Ser/Ser). Funnel plots and the Egger linear regression test were used to determine potential publication bias (Egger et al., 1997). All analyses were done with the Stata software (version 10.0; StataCorp LP, College Station, TX, USA), and all tests were two-sided.

RESULTS

Characteristics of studies

There were 284 published articles relevant to the search words and manual search. Figure 1 showed the process of inclusion and exclusion of associated studies. Finally, a total of 7 articles including 2521 cases and 2408 controls were selected in our meta-analysis (Kim et al., 2005; Wu et al., 2006; Karahalil et al., 2006; Figueroa et al., 2007; Arizono et al., 2008; Narter et al., 2009; Gangwar et al., 2009). The characteristics of the eligible studies are summarized in Table 1. Seven independent studies consisted of 3 Asian and 4 European. A classic polymerase chain reaction-restriction fragment length polymorphism assay was conducted in 5 of the 7 studies. The other two studies used the TaqMan method to detect the genotypes. Bladder cancer was confirmed histologically or pathologically in most studies. In addition, the controls were all hospital-based and mainly matched on age and gender. The distribution of genotypes among the controls of the studies was in agreement with HWE for all except two studies (Karahalil et al., 2006; Narter et al., 2009).

Quantitative synthesis

In the present study, we did not observe any significant association between the *hOGG1*

Ser326Cys polymorphism and bladder cancer risk. The results showed that individuals carrying the Cys/Cys genotype did not have an increased bladder cancer risk compared to the Ser/Ser genotype (OR = 1.10, 95%CI = 0.74-1.65); similarly, no significant association was found in the recessive genetic model (OR = 1.04, 95%CI = 0.65-1.69), and dominant genetic model (OR = 1.08, 95%CI = 0.87-1.33) (Table 2). In the stratified analysis by ethnicity, significant results were still not observed in any of the genetic models (Table 2). Excluding the two articles that were not in HWE ($P < 0.05$), we saw that the results were similar (data not shown).

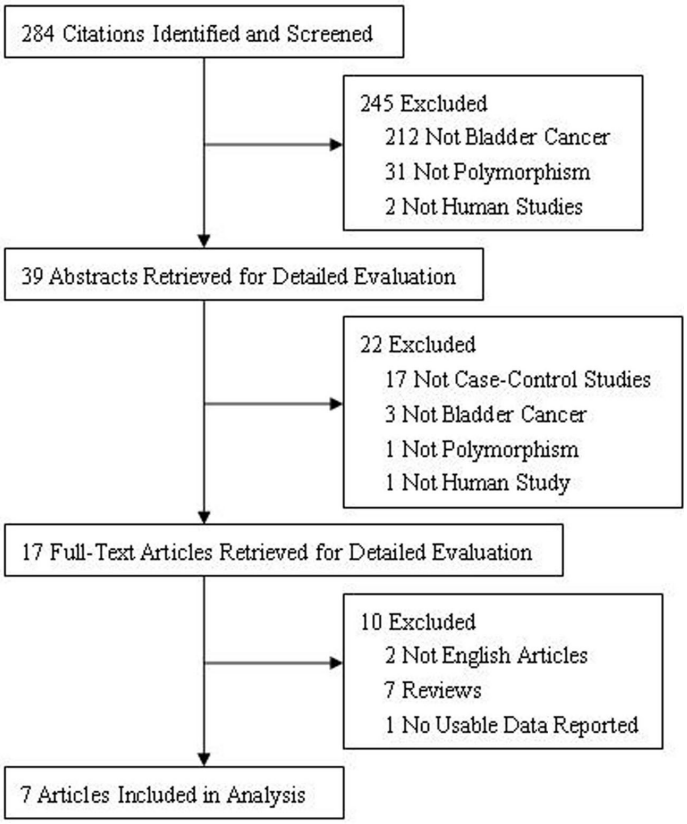

Figure 1. Inclusion and exclusion criteria in the associated studies.

Table 1. Characteristics of studies selected in the meta-analysis.

First author	Year	Country	Ethnicity	Control source	Genotyping method	Cases	Controls	HWE
Kim	2005	Korea	Asian	Hospital	PCR-RFLP	153	153	0.304
Arizono	2008	Japan	Asian	Hospital	PCR-RFLP	251	251	0.198
Gangwar	2009	India	Asian	Hospital	PCR-RFLP	212	250	0.216
Karahalil	2006	Turkey	European	Hospital	PCR-RFLP	146	100	<0.001
Wu	2006	USA	European	Hospital	TaqMan	613	600	0.747
Figueroa	2007	Spain	European	Hospital	TaqMan	1088	1018	0.521
Narter	2009	Turkey	European	Hospital	PCR-RFLP	58	36	0.046

PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; HWE = Hardy-Weinberg equilibrium.

Table 2. Stratified analysis of the *hOGG1* Ser326Cys polymorphism and bladder cancer risk.

Variables	N	Ser/Cys *vs* Ser/Ser		Cys/Cys *vs* Ser/Ser		Ser/Cys + Cys/Cys *vs* Ser/Ser (dominant)		Cys/Cys *vs* Ser/Cys + Ser/Ser (recessive)	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Total	7	1.07 (0.81-1.42)*	0.001	1.10 (0.74-1.65)*	0.009	1.08 (0.87-1.33)*	0.024	1.04 (0.65-1.69)*	0.000
Ethnicities									
Asian	3	1.06 (0.82-1.37)	0.478	1.34 (0.64-2.83)*	0.010	1.16 (0.91-1.47)	0.848	1.26 (0.50-3.17)*	0.000
European	4	1.07 (0.67-1.71)*	0.000	0.88 (0.66-1.16)	0.410	0.97 (0.76-1.25)*	0.006	0.85 (0.65-1.11)	0.260

The P value was evaluated by the Q-test for heterogeneity. *The random-effect model was used when the P value for heterogeneity <0.10; otherwise, the fixed-effect model was used. OR = odds ratio; 95%CI = confidence interval.

Publication bias

Funnel plots and the Egger test showed no evidence of publication bias in any comparison model (P > 0.05).

DISCUSSION

ROS may be generated as a by-product of normal cellular metabolism as well as by exposure to exogenous compounds (Weiss et al., 2005). ROS may cause oxidative DNA damage and increase susceptibility to bladder cancer if they are not removed. 8-OHdG is a highly mutagenic base produced in DNA as a result of exposure to ROS and it can be excised by hOGG1 (Weiss et al., 2005). The *hOGG1* Ser326Cys polymorphism has been shown to be associated with hOGG1 activity. Functional studies have shown that suppression of spontaneous mutagenesis is significantly lower for *hOGG1* Cys326 than Ser326 (Kohno et al., 1998). Moreover, Tarng et al. (2001) and Chen et al. (2003) found that 8-OHdG levels were significantly higher among patients with the Cys/Cys genotype compared to other genotypes. *OGG1* mutant mice exhibit a relatively higher level of 8-oxoguanine and an increase in mutation frequency during the cell cycle (Luna et al., 2005). A number of studies have shown that Cys/Cys increases bladder cancer risk (Karahalil et al., 2006; Arizono et al., 2008; Gangwar et al., 2009), a finding contrary to the results obtained by Kim et al. (2005). Meanwhile, several other studies have indicated that there is no association between the *hOGG1* Ser326Cys polymorphism and bladder cancer risk (Wu et al., 2006; Figueroa et al., 2007; Narter et al., 2009). Meta-analysis, which is a powerful statistical method, can provide a quantitative approach for pooling the results of different investigations on the same topic, estimating and explaining their diversity (Ioannidis et al., 2001; Munafo, 2004). Thus, we conducted the present meta-analysis to evaluate the association between the *hOGG1* Ser326Cys polymorphism and bladder cancer risk. We found no statistical evidence of an overall effect of the Ser326Cys polymorphism on bladder cancer risk in all the genetic models. The results may come from chance because studies with small sample sizes may be underpowered to detect a slight effect or may have generated a fluctuating risk estimate.

Lifestyle and genetic susceptibility are both important risk factors for the development of bladder cancer (Kakehi et al., 2010). Thus, subanalysis with regard to different ethnicity was performed. However, the results showed no difference between the European population and Asian population, which may suggest that those ethnic differences in genetic backgrounds and the environmental/life style context do not play a crucial role in the associa-

tion of the *hOGG1* Ser326Cys polymorphism with bladder cancer risk. Moreover, significant between-study heterogeneity was still detected in both populations in stratified analyses by ethnicity, and we conducted analyses using random-effect models. Thus, we obtained a wider confidence interval and a larger P value, which may have distorted the result.

There are still some limitations in this meta-analysis. First, selection bias could have played a role because the genotype distribution of this polymorphism among control subjects deviated from HWE in two studies (Karahalil et al., 2006; Narter et al., 2009) and all of the controls were hospital-based, which may not be representative of the general population. Second, the number of cases and controls in the included studies was relatively low (data shown in Table 1). Third, lack of information on well-documented smoking status may influence the results because cigarette smoking is an established risk factor for bladder cancer (Moss, 1971), which may interact with the *hOGG1* Ser326Cys polymorphism on bladder cancer risk (Huang et al., 2007). Finally, the fact that studies included in the analysis used different genotyping methods that had different quality control issues may have also influenced the results. Therefore, the results of this study should be interpreted with caution.

In conclusion, our results suggest that the *hOGG1* Ser326Cys polymorphism is not associated with bladder cancer risk. Well-designed studies with larger sample size are needed to validate these findings.

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