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Meta-analysis demonstrates that the NAD(P)H: quinone oxidoreductase 1 (*NQO1*) gene 609 C>T polymorphism is associated with increased gastric cancer risk in Asians

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ABSTRACT. The association between the NAD(P)H: quinone oxidoreductase 1 (*NQO1*) gene C609T polymorphism and gastric cancer has been widely evaluated, yet with conflicting results. Data were available from seven study populations involving 2600 subjects. Overall, comparison of alleles 609T and 609C indicated a significantly increased risk (46%) for gastric cancer (95% confidence interval (95%CI) for odds ratio (OR) = 1.20-1.79) in individuals with the T allele. The tendency was increased in the homozygous comparison (609TT versus 609CC), with an OR = 2.04 (95%CI = 1.37-3.05). Stratified analysis by study design demonstrated stronger associations in population-based studies than in hospital-based studies,

based on OR. Ethnicity-based analysis demonstrated a significant association in Asians but not in Caucasians. Additionally, in the subgroup analyses by the type of gastric cancer, a significantly increased risk was found with all genetic models in the gastric adenocarcinoma subgroup compared to the others. We conclude that the *NQO1* gene C609T polymorphism increases the risk for gastric cancer, especially in Asian populations.

Key words: Gastric cancer; *NQO1* gene; Polymorphism; Risk; Meta-analysis

INTRODUCTION

Gastric cancer is the second most common cause of cancer-related mortality in the world (Parkin et al., 2005), especially in East Asian countries (Long et al., 2010). It is widely accepted that environmental factors, such as high salt diet, tobacco smoking, alcohol consumption, and *Helicobacter pylori* (Hp) infection, contribute to susceptibility to gastric cancer. Of note, Hp infection is recognized as the single most common cause of gastric cancer (Forman et al., 1991; Parsonnet et al., 1991) and is ranked by the WHO as a class I carcinogen (Suerbaum and Michetti, 2002). However, only about 1% Hp-infected people ultimately develop gastric cancer (Suerbaum and Michetti, 2002), indicating that host genetic susceptibility plays an important role in the etiology of gastric cancer. Although great hope has been expressed in genome-wide association studies to unlock the genetic underpinnings of gastric cancer, the results from such research have told us little (Yoshida et al., 2010). Therefore, the evaluation of predetermined candidate genes or loci attracts widespread research interest.

The gene encoding the NAD(P)H: quinone oxidoreductase 1 (*NQO1*, chromosome 16q22.1) is a logical candidate for involvement in the underlying cause of gastric cancer, with its expressed cytosolic enzyme that protects cells from oxidative damage by preventing the generation of semiquinone free radicals and reactive oxygen species (Rauth et al., 1997). Animal models using *NQO1*-knockout mice have suggested that the *NQO1* gene deficiency increases susceptibility to cancer (Long et al., 2000; Iskander et al., 2005). In particular, an exonic polymorphism, C609T (Pro187Ser) in the *NQO1* gene has been widely evaluated. Functional studies have suggested that the *NQO1* protein encoded by the CC homozygous wild-type genotype (Pro/Pro) has full enzymatic activity, while the TT genotype (Ser/Ser) protein completely lacks this activity (Kuehl et al., 1995). In addition, the *NQO1* C609T polymorphism was reported to be associated with Hp seropositivity in Japanese (Goto et al., 2005), and with intestinal metaplasia, an important precursor lesion in the development of gastric cancer in a Singapore-Chinese population (Zhu et al., 2009). Although some studies have attempted to link the *NQO1* gene C609T polymorphism with gastric cancer, the data are often not reproducible. To derive a more precise estimation, we therefore conducted a meta-analysis to investigate the association of the *NQO1* gene C609T polymorphism with the occurrence of gastric cancer, while addressing between-study heterogeneity and publication bias.

MATERIAL AND METHODS

Search strategy for identification of studies

Studies were identified by searches in the PubMed, EMBASE, ISI Web of Knowledge, as well as China WANFANG (www.wanfangdata.com.cn) databases for relevant articles published up to October 2011. Key subjects were sought using the following Boolean combinations: (quinone oxidoreductase OR DT-diaphorase OR quinone reductase OR NAD(P)H: quinone oxidoreductase 1 OR NQO1 OR DTD) AND (gastric cancer OR gastric carcinoma) AND (polymorphism OR allele OR genotype OR variant OR variation). Search results were restricted to human populations and articles written in English or Chinese. The full text of the retrieved articles and reviews was scrutinized to decide whether information on the topic of interest was included. The reference lists of original studies and review articles were also checked to determine the relevance of citations of articles that were not initially identified. If more than one geographic or heterogeneous ethnic group were reported in one article, each group was treated separately.

Inclusion/exclusion criteria

Studies were included if they had data on the *NQO1* gene C609T genotype aiming to estimate odds ratio (OR) and its corresponding 95% confidence interval (95%CI), a case-control design (retrospective or nested case-control), and involved gastric cancer as an end point. Where there were multiple articles of the same study population, the most complete and recent results were extracted.

Extracted information

Data were collected on *NQO1* gene C609T genotype counts, case-control status, as well as first author's last name, publication date, ethnicity of the population studies, study design, baseline characteristics of the study population by authors Y. Zhang and Z. Wang, and were entered into separate databases for comparison. Any discrepancies encountered were adjudicated by discussion and resolved when a 100% consensus was reached.

Statistical analysis

We assessed the association of the *NQO1* gene 609T allele with gastric cancer relative to the 609C allele (allelic model), as well as the homozygous contrast (609TT versus 609CC), the dominant model (609TT plus 609TC versus 609CC), and the recessive model (609TT versus 609CC plus 609TC), respectively. Unadjusted OR and 95%CI were used to compare contrasts of alleles or genotypes between patients and controls. The random-effects model using the DerSimonian and Laird method was implemented to bring the individual effect-size estimates together, and the estimate of heterogeneity was determined using the Mantel-Haenszel model (Cohn and Becker, 2003).

Satisfaction of C609T genotypes with Hardy-Weinberg proportions was calculated using the χ^2 test or the Fisher exact test in control groups. Possible heterogeneity between the results of individual studies or in groups defined by race or by study design or by type of gastric cancer was assessed using the inconsistency index I^2 statistic (ranging from 0 to 100%), with higher values suggesting the existence of heterogeneity (Higgins and Thompson, 2002; Higgins et al., 2003). In the case of between-study heterogeneity, we examined the study characteristics that could stratify the studies into subgroups with homogeneous effects.

Cumulative meta-analysis was conducted to identify the influence of the first published study on the subsequent publications, and the evolution of the combined estimates over time according to the ascending date of publication. Likewise, to identify potentially influential studies, sensitivity analysis was undertaken by removing an individual study each time to check whether any of these estimates could bias the overall estimate.

Funnel plots and the Egger regression asymmetry test were used to examine publication bias. Probability less than 0.05 was judged significant except for the I^2 statistic and the Egger statistic, 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

Search results

Based on our search strategy, primary screening yielded 25 potentially relevant articles, of which 7 met the inclusion criteria with an attempt to evaluate association of the *NOQ1* gene C609T polymorphism with gastric cancer risk (Hamajima et al., 2002; Sarbia et al., 2003; Zhang et al., 2003; Ren et al., 2006; Chen et al., 2007, 2011; Malik et al., 2011). Finally, a total of 1221 gastric cancer patients and 1379 controls were analyzed. Four studies were conducted in a hospital-based design (Hamajima et al., 2002; Sarbia et al., 2003; Zhang et al., 2003; Malik et al., 2011) and 3 studies in a population-based design (Ren et al., 2006; Chen et al., 2007, 2011). Of these 7 articles, four (Hamajima et al., 2002; Sarbia et al., 2003; Zhang et al., 2003; Malik et al., 2011) were published in English and three in Chinese (Ren et al., 2006; Chen et al., 2007, 2011). Besides one study conducted in Germany (Sarbia et al., 2003), the rest were involved Asians (four in Chinese (Zhang et al., 2003; Ren et al., 2006; Chen et al., 2007, 2011), one in Japanese (Hamajima et al., 2002) and one in Indians (Malik et al., 2011)). The detailed selection process and the baseline characteristics of qualified studies are presented in Figure 1 and Table 1, respectively.

The genotype distributions of the *NQO1* gene 609 C>T polymorphism were in agreement with the Hardy-Weinberg equilibrium among control groups of all studies. The frequencies of the *NQO1* gene 609T allele ranged widely from 20.31 to 55% in case patients and from 14.08 to 42.5% in controls.

Overall analyses

In the allelic model, comparison of alleles 609T with 609C generated a significant

46% increased risk for gastric cancer (95%CI = 1.20-1.79; P < 0.001), yet with strong evidence of between-study heterogeneity (I^2 = 62.7%; P = 0.013). Besides the suggestive symmetry of the funnel plot, the Egger test indicated no publication bias for allelic association (P = 0.565). The magnitude of this association was potentially strengthened in the homozygous comparison (609TT versus 609CC) with OR doubled to 2.04 (95%CI = 1.37-3.05; P < 0.001). Similarly, this association was still tinged by heterogeneity (I^2 = 55.9%; P = 0.035), the risk estimates from individual studies were symmetric, and the Egger test suggested a low probability of publication bias (P = 0.858).

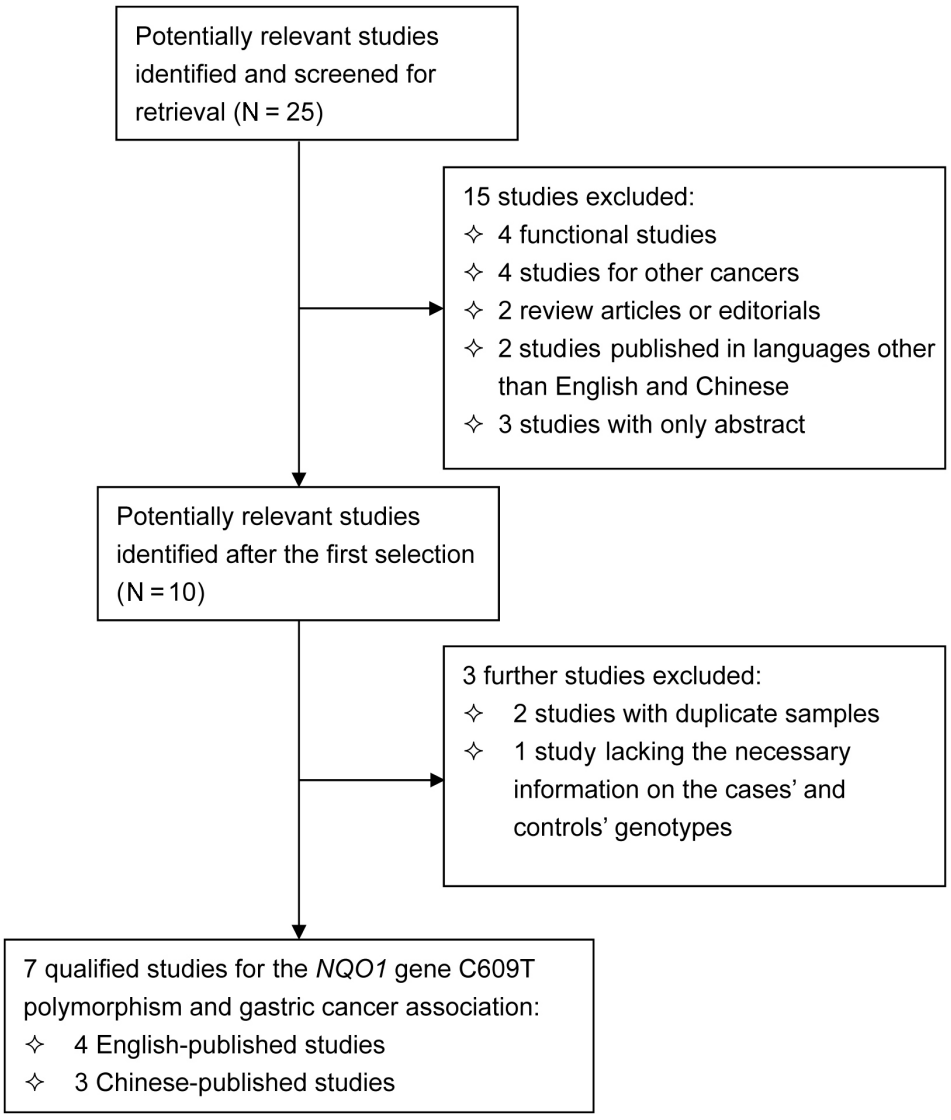

Figure 1. Flow diagram of search strategy and study selection.

Table 1. The baseline characteristics of all eligible studies.

Study	Year	Ethnicity	Study design	Age, mean (SD) (years)		Number (males, %)		609T allele frequency (%)	
				Cases	Controls	Cases	Controls	Cases	Controls
Hamajima et al.	2002	Japanese	Hospital	57.0	54.0	71.33	48.96	41.61	42.12
Sarbia et al.	2003	Germany	Hospital	64.5	39.0	67.18	76.59	20.31	14.09
Zhang et al.	2003	Chinese	Hospital	60.0 (8.24)	52.0 (7.16)	74.19	66.06	45.56	42.42
Ren et al.	2006	Chinese	Population	NA	NA	NA	NA	55.00	42.50
Chen et al.	2007	Chinese	Population	57.38 (8.95)	NA	64.29	64.29	45.54	33.48
Chen et al.	2011	Chinese	Popolation	57.23 (8.67)	NA	65.27	65.27	49.25	33.53
Malik et al.	2011	Indian	Hospital	55.91 (9.73)	57.98 (12.67)	83.33	71.28	34.72	25.13

NA = not available; SD = standard deviation.

Additionally, in view of the heterozygous 609TC genotype, we considered two different models of inheritance. As compared with the allelic model, the slightly elevated associations were identified in both the dominant (OR = 1.51; 95%CI = 1.20-1.90; P < 0.001) and recessive (OR = 1.76; 95%CI = 1.26-2.50; P = 0.001) models, with attenuated between-study heterogeneity (for dominant model: I^2 = 43.5%, P = 0.101; for recessive model: I^2 = 52.5%, P = 0.049). Moreover, there was no publication bias for either model as reflected by funnel plots and statistical tests ($P_{Egger's\ for\ dominant}$ = 0.851 and $P_{Egger's\ for\ recessive}$ = 0.745).

Cumulative and influential analyses

In cumulative meta-analysis, there was no evidence suggesting that the first published study that reported a potentially significant result then trigged a subsequent replication. Also, our influential analysis revealed in general that no single study influenced the pooled results significantly (data not shown).

Subgroup analyses

Considering the strikingly different frequencies of 609T allele between Caucasians and Asians, we performed subgroup analyses by race. Interestingly, there was a significant association among populations of Asian descent in the allele model as well as genetic models, whereas no significance was observed in Caucasians in either the homozygous or recessive model (Table 2).

Additional stratification by study design showed significant association in allele and genetic models, in the population-based subgroup, with no obvious association between the *NQO1* C609T polymorphism and gastric cancer risk in the homozygous model (OR = 1.53, 95%CI = 0.92-2.55, P = 0.104) and recessive model (OR = 1.46, 95%CI = 0.87-2.45, P = 0.152), in the hospital-based subgroup.

In view of the fact that the type of gastric cancer [gastric adenocarcinoma (GAC), cardiac adenocarcinoma (CAC), gastric squamous cell carcinoma (GSCC)] could bias the overall estimate, we conducted subgroup analyses based on the type of gastric cancer, and in general, there were obvious differences. For example, an increased risk association was observed in all genetic models in the GAC subgroup; however, nearly no remarkable changes in ORs was observed in the CAC and GSCC subgroups for the *NQO1* C609T polymorphism.

Table 2. Subgroup analysis of the *NQO1* gene C609T polymorphism and gastric cancer.

Subgroup	Study No.	T *vs* C				TT *vs* CC				Dominant				Recessive			
		OR (95%CI)	P	I^2 (%)	Heterogeneity	OR (95%CI)	P	I^2 (%)	Heterogeneity	OR (95%CI)	P	I^2 (%)	Heterogeneity	OR (95%CI)	P	I^2 (%)	Heterogeneity
Total	7	1.46 (1.20-1.79)	0.000	62.7	0.013	2.04 (1.37-3.05)	0.000	55.9	0.035	1.51 (1.20-1.90)	0.000	43.5	0.101	1.76 (1.26-2.50)	0.001	52.5	0.049
Area																	
Asia	6	1.45 (1.14-1.84)	0.002	68.8	0.007	2.02 (1.30-3.14)	0.002	63.1	0.019	1.48 (1.12-1.96)	0.006	52.0	0.064	1.75 (1.19-2.56)	0.004	60.3	0.027
Europe	1	1.55 (1.13-2.13)	0.006	/	/	2.31 (0.71-7.50)	0.163	/	/	1.66 (1.16-2.37)	0.006	/	/	2.00 (0.62-6.45)	0.246	/	/
Design																	
HB	4	1.27 (1.01-1.62)	0.045	53.0	0.094	1.53 (0.92-2.55)	0.104	44.7	0.143	1.31 (1.02-1.69)	0.034	25.3	0.260	1.46 (0.87-2.45)	0.152	53.6	0.091
PB	3	1.82 (1.53-2.17)	0.000	0.0	0.725	2.87 (2.05-4.02)	0.000	0.0	0.674	1.89 (1.41-2.54)	0.000	14.0	0.313	2.30 (1.71-3.11)	0.000	0.0	0.656
Gastric cancer type																	
GAC	6	1.51 (1.20-1.90)	0.000	64.3	0.016	2.18 (1.36-3.47)	0.001	59.5	0.030	1.59 (1.26-2.00)	0.000	32.0	0.196	1.78 (1.16-2.73)	0.008	60.1	0.028
CAC	2	1.47 (0.87-2.49)	0.150	76.5	0.039	1.81 (0.81-4.02)	0.148	28.5	0.237	1.46 (0.66-3.25)	0.351	82.1	0.018	1.70 (1.00-2.91)	0.051	0.0	0.462
GSCC	1	1.12 (0.55-2.25)	0.757	/	/	1.72 (0.44-6.75)	0.435	/	/	0.93 (0.38-2.29)	0.882	/	/	1.89 (0.50-7.14)	0.345	/	/

HB = Hospital-based; PB = Population-based; GAC = gastric adenocarcinoma; CAC = cardiac adenocarcinoma; GSCC = gastric squamous cell carcinoma; OR = odds ratio; CI = confidence interval.

DISCUSSION

After a comprehensive evaluation of the *NQO1* gene C609T polymorphism among 2600 subjects, we provided, for the first time, evidence that the *NQO1* 609T allele is associated with a significantly increased risk of gastric cancer occurrence, especially in Asians. Although between-study heterogeneity, albeit disturbing, could not be easily eliminated, our results indicated that the *NQO1* gene could be a genetic marker for gastric cancer.

It is generally accepted that genetic heterogeneity is an inevitable problem in any disease identification strategy (Hemminki et al., 2006). In this study, we speculated that the *NQO1* gene 609T polymorphism could play divergent roles across different ethnic populations. On the one hand, there were striking differences in terms of mutant 609T allele frequency in controls between Asians (25.13-42.5%) and Europeans (14.09%), with the latter remarkably lower than the former, suggesting that different genetic backgrounds may account for this discrepancy or that 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). Alternatively, the *NQO1* gene C609T polymorphism may be in close linkage with different nearby causal variants in different populations. On the other hand, in our subgroup analyses by ethnicity, polymorphism C609T showed significant heterogeneous associations with gastric cancer between Asians and Caucasians, with positive association in Asians for all genetic models, whereas negative association in Caucasians in either the homozygous model or recessive model, leaving open the question whether this polymorphism may have a pleiotropic role in the pathogenesis of gastric cancer or interact with other genetic or environmental factors. However, considering the relatively small sample sizes in Caucasians, we believe that confirmation in large, well-designed studies is critical.

In addition, study design may also be a potential source of between-study heterogeneity for the *NOQ1* gene C609T polymorphism. It is universally believed that control for population stratification remains an important consideration in hospital-based studies (Salanti et al., 2005), because in this meta-analysis, most studies had recruited subjects from only one hospital, and thereby, there might have been a narrow socioeconomic profile for both patients and controls. Moreover, in hospital-based studies, poor comparability between cases and controls may 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 may be representative of the true population, leading us to believe that results from population-based studies may hold water. Our results showed a stronger association observed in population-based studies relative to hospital-based subgroup, reinforcing the quality of our conclusion.

Furthermore, possible heterogeneity may also result from different histological types of gastric cancer, such as GAC, CAC and GSCC, which are believed to have great differences in etiology and tumor biology. For example, CAC are strongly correlated with chronic gastroesophageal reflux (Wijnhoven et al., 1999) and with cigarette smoking (Gammon et al., 1997), and have a higher rate of lymph node metastasis and unfavorable prognosis (El-Rifai et al., 2001; Tajima et al., 2007), while Hp infection has been proven to be more relevant to GAC development (Xue et al., 2011). In the subgroup analyses by type of gastric cancer, we found significantly increased risk with all genetic models in GAC subgroup; however, nearly no remarkable changes in risk estimates was observed in CAC and GSCC subgroups for the *NQO1*

gene C609T polymorphisms. Considering the relatively small sample size in each subgroup, much more research within the framework of genetics and biology is needed in various types of gastric cancer.

Finally, despite the clear strengths of our study, including relatively large sample sizes and lack of publication bias, the interpretation of our study, however, should be viewed in light of several technical limitations. Because only published articles were identified and the "grey" literature (articles in languages other than English and Chinese) was not included, publication bias might have been possible, even though our funnel plots and statistical tests showed low possibility. Moreover, the single locus-based meta-analysis precluded the possibility of gene-gene and gene-environment interactions, as well as haplotype-based effects. Furthermore, we only studied the *NQO1* gene C609T polymorphism, and did not cover other genes or polymorphisms. It is likely that the C609T polymorphism itself contributes moderately to risk prediction in gastric cancer subjects, but whether this polymorphism integrated with other risk factors will enhance the prediction requires further research. Thus, the jury must refrain from drawing a conclusion until large, well-performed studies confirm or refute our results.

In summary, we expand previous individual studies on gastric cancer by indicating that the *NQO1* C609T polymorphism may increase the risk of GAC, especially in Asians. Also, our observations leave open the question regarding the heterogeneous effects of the C609T polymorphism across different ethnic populations. Future studies within a genetic and functional framework are warranted to elucidate the relationship between the C609T polymorphism and gastric cancer, and mechanisms of the *NQO1* gene and gastric cancer.

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