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COMBINED EFFECTS OF *NQO1* PRO187SER OR *SULT1A1* ARG213HIS POLYMORPHISM AND SMOKING ON BLADDER CANCER RISK: TWO META-ANALYSES

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Abstract

Objectives: Cigarette smoking is the major risk factor of bladder cancer via exposure to chemical carcinogens. Nicotinamide adenine dinucleotide phosphate ($NADP^+$): quinine oxidoreductase 1 (NQO1) and sulfotransferase 1A1 (SULT1A1) have been reported to involve in the metabolism of polycyclic aromatic hydrocarbons (PAHs) and aromatic amines. Therefore, the risk of bladder cancer (BC) may be influenced by polymorphisms in the genes that modulate metabolic detoxification in particular by interacting with cigarette smoking. Considering the limited power by the individual studies with a relatively small sample size, especially when analyzing the combined effect of polymorphisms in *NQO1* and *SULT1A1* genes and smoking, these 2 meta-analyses have aimed to clarify the combined effects of them on BC risk by integrating related studies. **Material and Methods:** Two meta-analyses included 1341 cases and 1346 controls concerning *NQO1* Pro187Ser and smoking, and 1921 cases and 1882 controls on *SULT1A1* Arg213His and smoking were performed. Odds ratios (OR) and 95% confidence intervals (CI) were used for assessing the strength of the association. **Results:** The result has demonstrated that smokers with *NQO1* Pro/Ser or Ser/Ser genotypes have a prominent association with the risk of BC as compared with non-smokers with *NQO1* Pro/Pro genotype, with OR equal to 3.71 (95% CI: 2.87–4.78, $p_{heterogeneity} = 0.376$). Besides, smokers carrying *SULT1A1* Arg/Arg genotypes were observed to confer 2.38 fold increased risk of BC (95% CI: 1.44–3.93, $p_{heterogeneity} = 0.001$) when compared with non-smokers with *SULT1A1* Arg/Arg or His/His genotypes. **Conclusions:** These findings have suggested that the *NQO1* Pro187Ser or *SULT1A1* Arg213His polymorphism combination with smoking significantly confer susceptibility to BC. Int J Occup Med Environ Health 2017;30(5):791–802

Key words:
Polymorphisms, Meta-analysis, *NQO1*, Urinary bladder neoplasms, Smoking, *SULT1A1*

INTRODUCTION

Bladder cancer (BC) has remained the eleventh most common cancer worldwide, accounting for a global incidence rate of 429 793 and mortality rate of 165 084 in 2012 [1]. The incidence rate of colorectal cancer has still been increasing, especially in the western world. The etiology of bladder cancer has been complicated, with both host genetic variants and environmental factors contributing to its development. Extensive evidence has indicated that several environmental factors, including cigarette smoking, aromatic amines, aniline dyes, nitrates, acrolein, coal, and arnicare are involved in the development of BC [2,3].

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Among the environmental factors, cigarette smoking has been established as the major risk factor for BC, which confers around two- to four-fold increased risk of BC, according to previous epidemiology studies and the meta-analysis [4,5]. It has been estimated that with the elimination of smoking, the incidence of bladder cancer could be reduced by approximately 50% for men and 25% for women [6].

The important chemical carcinogens of cigarette smoke, including polycyclic aromatic hydrocarbons, heterocyclic aromatic amines and N-nitroso may induce the process of carcinogenic by several of molecular mechanisms in the development of BC. Most chemical carcinogens contained in cigarettes are metabolized and detoxified by phase II enzymes such as nicotinamide adenine dinucleotide phosphate ($NADP^+$): quinine oxidoreductase 1 (NQO1) and sulfotransferase 1A1 (SULT1A1) and are then excreted in urine [7]. The AD(P)H:quinone oxidoreductase (NQO1) is a detoxification enzyme that plays a crucial role in the protection against oxidative damage by preventing the generation of reactive oxygen species and reducing certain chemical carcinogens [8,9].

Besides, *SULT1A1* plays an important role in the bioactivation and detoxification of many environmental mutagens and procarcinogens, including chemical carcinogens in cigarettes [10]. Functional polymorphisms of the *NQO1* or *SULT1A1* gene which influence the activities of the corresponding enzymes might be associated with susceptibility to BC. A common single nucleotide polymorphism in codon 187 of *NQO1* (rs1800566, a C to T transition) causes the Pro to Ser amino acid substitution, and the Ser187 variant shows lower enzyme activity as compared with the Pro187 variant [9,11]. In addition, a non-synonymous SNP of *SULT1A1* gene has been identified in the codon 213 in exon 7 (rs9282861, a G to A transition), which results in an Arg to His amino acid substitution, and the His213 allele has been shown to have lower enzyme activity and thermal stability [12,13].

Furthermore, great numbers of association studies have been conducted to explore the relationship between *NQO1* Pro187Ser or *SULT1A1* Arg213His polymorphism and the risk of BC. Moreover, the increased effects of *NQO1* Pro187Ser or *SULT1A1* Arg213His polymorphism on the risk of various cancers including BC have been clarified by the previous meta-analyses [14–20]. Importantly, a certain amount of the original study has not only investigated the individual effect of *NQO1* Pro187Ser or *SULT1A1* Arg213His on the risk of BC but has also examined the genetic effect of *NQO1* Pro187Ser or *SULT1A1* Arg213His modified by smoking on BC risk. Furthermore, the controversial results have been yielded by the previous studies considering the limited power by the studies with a relatively small sample size especially when analyzing the combined effect of *NQO1* Pro187Ser or *SULT1A1* Arg213His and smoking. Consequently, it has been necessary to calculate the pooled effect of Pro187Ser or *SULT1A1* Arg213His and smoking on the risk of BC by integrating individual studies. Therefore, we have carried out 2 meta-analyses to derive more precise risk estimations for the combined effects of the 2 polymorphisms on bladder cancer risk.

MATERIAL AND METHODS

Search strategy and study selection

We systematically browse through the online electronic databases (PubMed, EMBASE, ISI Web of Science and Chinese Biomedical (CBM) database) for published papers up to June, 2016, using the search terms "bladder cancer," "*NQO1*," "polymorphism" and "smoking" for the analysis between smoking-*NQO1* Pro187Ser interaction and bladder cancer risk. Meanwhile, we have used the following search terms "bladder cancer," "sulfotransferase 1A1," "polymorphism," and "smoking" for the analysis between smoking-*SULT1A1* Arg213His interaction and bladder cancer risk. The entire search has been limited to the English and Chinese language papers.

Additional studies have been supplied by a hand search of the references of retrieved articles and reviews.

The inclusion criteria have been as follows:

– case-control study design,
– genotype frequencies on *NQO1* Pro187Ser polymorphisms or *SULT1A1* Arg213His stratified by smoking which are permitted to calculate odds ratio (OR) with 95% confidence interval (CI) for estimation of the combined effects of the 2 polymorphism and smoking,
– the distribution of genotypes in the controls conformed to Hardy-Weinberg equilibrium ($p > 0.05$).

No control population, duplicate of previous publication, animal studies, reviews and unpublished reports have been excluded.

Data extraction

All the included data was extracted independently by 2 reviewers. The following information was extracted from the eligible studies: first author's surname, year of publication, country, ethnicity, source of controls, sample size, genotyping method, smoking status and genotype frequencies in both case and control groups stratified by smoking.

Statistical analysis

The crude ORs and their 95% CIs were calculated to assess the strength of the association for the *NQO1* Pro187Ser or *SULT1A1* Arg213His interaction with smoking in the risk of bladder cancer risk. The pooled ORs were evaluated by comparing the combination of smoking status and *NQO1* Pro187Ser or *SULT1A1* Arg213His genotypes with the other combination. Furthermore, we used dominant model for *NQO1* Pro187Ser and recessive model for *SULT1A1* Arg213His to estimate the pooled ORs in this meta-analysis. The Chi^2-based Cochran's Q statistic test and I^2 statistics were employed to test between-study heterogeneity, and heterogeneity was considered significant when $p < 0.05$ for Q statistic. Fixed-effects model (Mantel-Haenszel method) was used for calculating the pooled ORs when no significant heterogeneity was detected; otherwise, random-effects model (DerSimonian-Laird method) was applied. Publication bias was assessed by the funnel plot and Egger's test [21]. All p values are two-tailed with a significant level at 0.05. All statistical analyses were conducted by using STATA 10.0 (Stata Corporation, College Station, USA).

RESULTS

Characteristics of included studies

After extensive searching, a total of 7 studies have contained 1341 cases with 1346 controls on *NQO1* Pro187Ser and 1921 smoking cases with 1882 controls on *SULT1A1* Arg213His. Smoking is retrieved based on the search criteria for BC susceptibility [12,22–33]. Study characteristics were summarized in the Table 1. For *NQO1* Pro187Ser polymorphism and smoking, 4 studies have focused on Caucasian descendants, and 3 studies of Asian descendants. For *SULT1A1* Arg213His polymorphism and smoking, 2 studies have focused on Caucasian descendants, and 5 studies of Asian descendants.

Combined effects of gene-smoking for the combined effects of *NQO1* Pro187Ser and smoking status

In the meta-analysis, we did further analysis to explore the potential combined effects between *NQO1* Pro187Ser polymorphism and smoking on the risk of bladder cancer which has been shown in the Table 2 and Figure 1. When compared with non-smokers with *NQO1* Pro/Pro genotype, non-smokers carried *NQO1* Pro/Ser or Ser/Ser genotypes exhibited an increased risk of BC, with OR of 1.76 (95% CI: 1.34–2.31); and smokers with *NQO1* Pro/Pro genotype were observed to confer 2.88 fold increased risk of BC (95% CI: 2.24–3.70). More importantly, the association was even more prominent for smokers with *NQO1*

Table 1. Characteristics of studies included in the meta-analysis of *NQO1* Pro187Ser or *SULT1A1* Arg213His polymorphisms with risk of bladder cancer

Study	Year of publication	Country (region)	Ethnicity	Control source	Respondents [n]		Genotyping method	Smoking status	HWE in control group
					study group	control group			
NQO1 Pro187Ser									
Park et al. [22]	2003	United States	Caucasian	HB	232	239	PCR-RFLP	reported	Y
Moore et al. [23]	2004	Argentina	Caucasian	PB	106	108	PCR-RFLP	reported	Y
Hung et al. [24]	2004	Italy	Caucasian	HB	201	214	PCR-RFLP	reported	Y
Terry et al. [25]	2005	United States	Caucasian	HB	239	215	mass spectrometry	reported	Y
Wang et al. [26]	2008	China (Taiwan)	Asian	HB	300	300	PCR-RFLP	reported	Y
Pandith et al. [27]	2011	Kashmiri	Asian	HB	104	120	PCR-RFLP	reported	Y
Huang et al. [28]	2014	China	Asian	HB	159	150	PCR-RFLP	reported	Y
SULT1A1 Arg213His									
Zheng et al. [12]	2003	United States	Caucasian	HB	384	386	PCR-RFLP	reported	Y
Hung et al. [24]	2004	Italy	Caucasian	HB	201	214	PCR-RFLP	reported	Y
Wang et al. [26]	2008	China (Taiwan)	Asian	HB	300	300	PCR-RFLP	reported	Y
Cui et al. [32]	2013	Japan	Asian	HB	282	257	PCR-RFLP	reported	Y
Tsukino et al. [31]	2004	Japan	Asian	HB	306	306	PCR-RFLP	reported	Y
Ozawa et al. [29]	2002	Japan	Asian	HB	149	189	PCR-RFLP	reported	Y
Tung et al. [33]	2014	China (Taiwan)	Asian	HB	299	230	PCR-RFLP	reported	Y

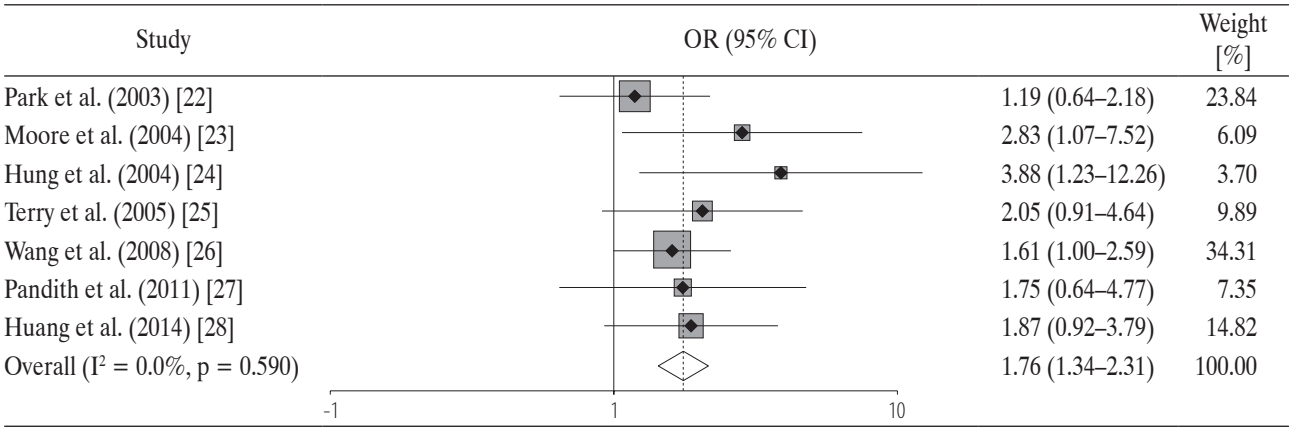
NQO1 – quinine oxidoreductase 1; *SULT1A1* – sulfotransferase 1A1.
HWE – Hardy-Weinberg equilibrium; HB – hospital-based study; PB – population-based study; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Summary odds ratios with confidence intervals between smoking-*NQO1* Pro187Ser interaction and bladder cancer risk

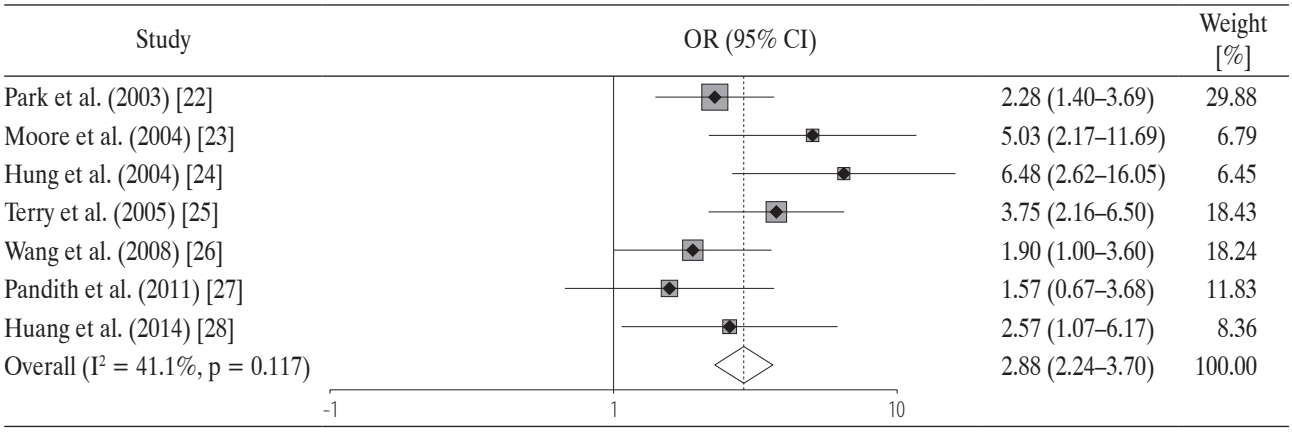
Smoking-*NQO1* Pro187Ser	Studies [n]	Respondents [n]		Heterogeneity		Model for meta-analysis	OR (95% CI)	$p_{Egger's\ test}$ [b]
		study group	control group	I^2 [%]	$p_{heterogneity}$ [b]			
–/(CT+TT) vs. –/CC	7	398	634	0.0	0.590	F	1.76 (1.34–2.31)	0.049
+/CC vs. –/CC	7	623	733	41.1	0.117	F	2.88 (2.24–3.70)	0.387
+/(CT+TT) vs. –/CC	7	594	620	6.7	0.376	F	3.71 (2.87–4.79)	0.092
+/(CT+TT) vs. –/(CT+TT)	7	714	612	32.4	0.181	F	1.99 (1.48–2.69)	0.683
+/(CT+TT) vs. +/CC	7	939	711	66.4	0.007	R	1.34 (0.93–1.95)	0.423

NQO1 – quinine oxidoreductase 1.
OR – odds ratio; CI – confidence interval.
F – fixed-effects model; R – random-effects model.
[a] p value of Q-test for heterogeneity test.
[b] p value for Egger's test.

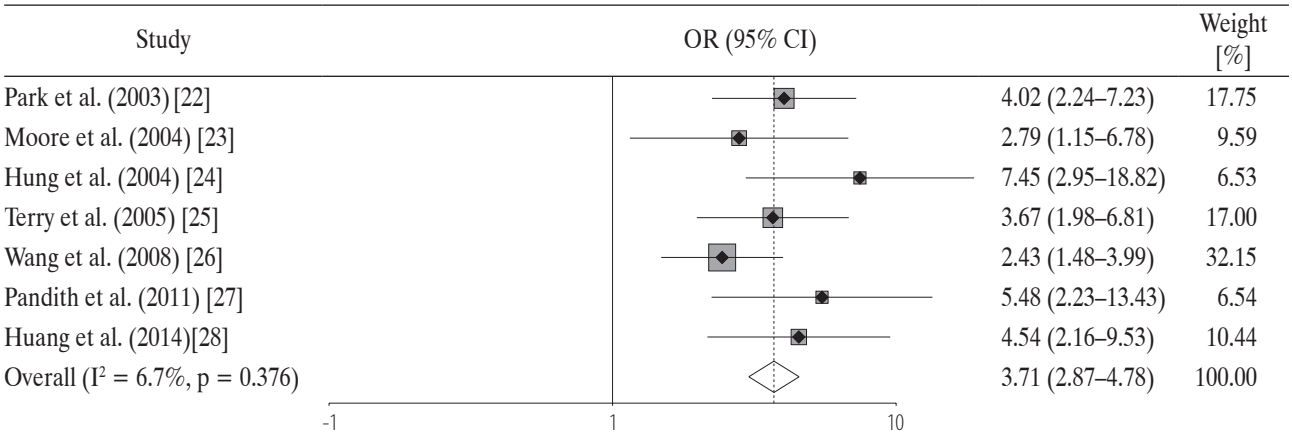
a)



b)



c)



NQO1 – quinine oxidoreductase 1.
OR – odds ratio; CI – confidence interval.

Fig. 1. Forest plot of the combined effects of *NQO1* Pro187Ser polymorphism and smoking on the risk of bladder cancer:
a) non-smokers carried *NQO1* Pro/Ser or Ser/Ser genotypes vs. non-smokers with *NQO1* Pro/Pro genotype,
b) smokers carried *NQO1* Pro/Pro genotype vs. non-smokers with *NQO1* Pro/Pro genotype,
c) smokers carried *NQO1* Pro/Ser or Ser/Ser genotypes vs. non-smokers with *NQO1* Pro/Pro genotype

Pro/Ser or Ser/Ser genotypes compared with non-smokers with *NQO1* Pro/Pro genotype, with OR equal to 3.71 (95% CI: 2.87–4.78).

In addition, we also compared smokers with *NQO1* Pro/Ser or Ser/Ser genotypes with non-smoker carrying *NQO1* Pro/Ser or Ser/Ser genotypes, the associated OR equaled 1.99 (95% CI: 1.48–2.69). Among smokers, *NQO1* Pro/Ser or Ser/Ser genotypes showed no significant association with the risk of BC when compared with *NQO1* Pro/Pro genotype (OR = 1.34, 95% CI: 0.93–1.95).

For the combined effects of *SULT1A1* Arg213His and smoking status

The Table 3 and Figure 2 show the potentially combined effects between *SULT1A1* Arg213His polymorphism and smoking on the risk of bladder cancer. When compared with non-smokers with *SULT1A1* Arg/His or His/His genotypes, non-smokers carrying *SULT1A1* Arg/Arg show an increased risk of BC, with OR of 1.52 (95% CI: 1.18–1.96); and smokers carrying *SULT1A1* Arg/His or His/His genotypes with the OR of 2.00 (95% CI: 1.54–2.60) show the increased risk of BC. Interestingly, smokers carrying *SULT1A1* Arg/Arg genotypes have been observed to confer 2.38 fold increased risk of BC (95% CI: 1.44–3.93). Similarly, we have also compared smokers with *SULT1A1* Arg/Arg genotypes with non-smokers carrying *SULT1A1* Arg/Arg, the associated OR equals 1.49 (95% CI: 1.27–1.75). Among smokers, *SULT1A1* Arg/Arg genotypes show significant association with the risk of BC when compared with *SULT1A1* Arg/His or His/His genotypes (OR = 1.21, 95% CI: 1.01–1.46).

Publication bias

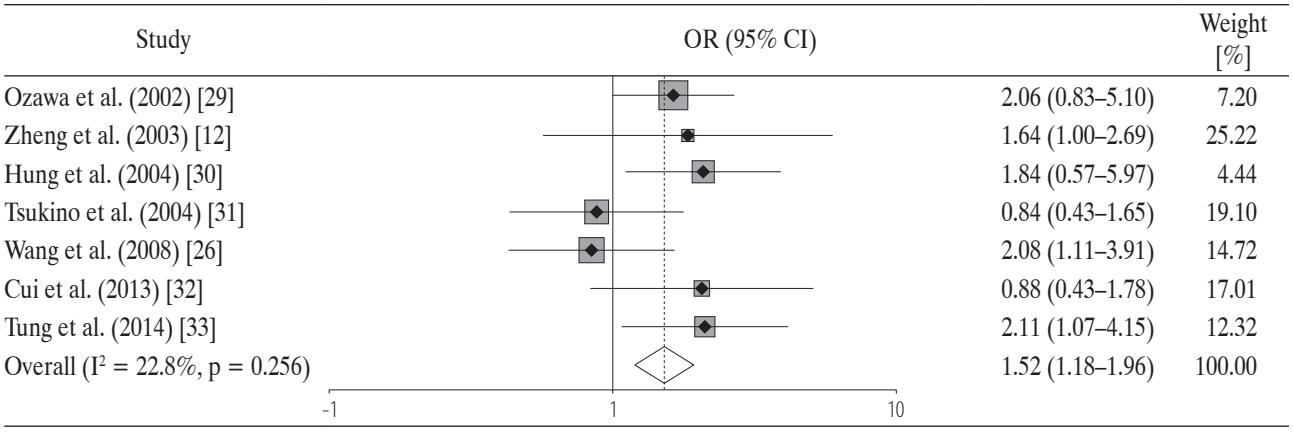
Begg's funnel plot (Figure 3) and Egger's test were performed to assess the publication bias in related literature (Table 2 and Table 3). For *NQO1* Pro187Ser and smoking status, the shape of funnel plots seemed asymmetrical for non-smokers carrying *NQO1* Pro/Ser or Ser/Ser genotypes vs. non-smokers, with p, that was used in Egger's test, equaling 0.049. Besides, the shape of the funnel plots for smokers carrying *NQO1* Pro/Pro genotype vs. non-smokers with *NQO1* Pro/Pro genotype did not show either any evidence of the funnel plot asymmetry or publication bias detected by using Egger's test, with p values equaling

Table 3. Summary odds ratios with confidence intervals between smoking-*SULT1A1* Arg213His interaction and bladder cancer risk

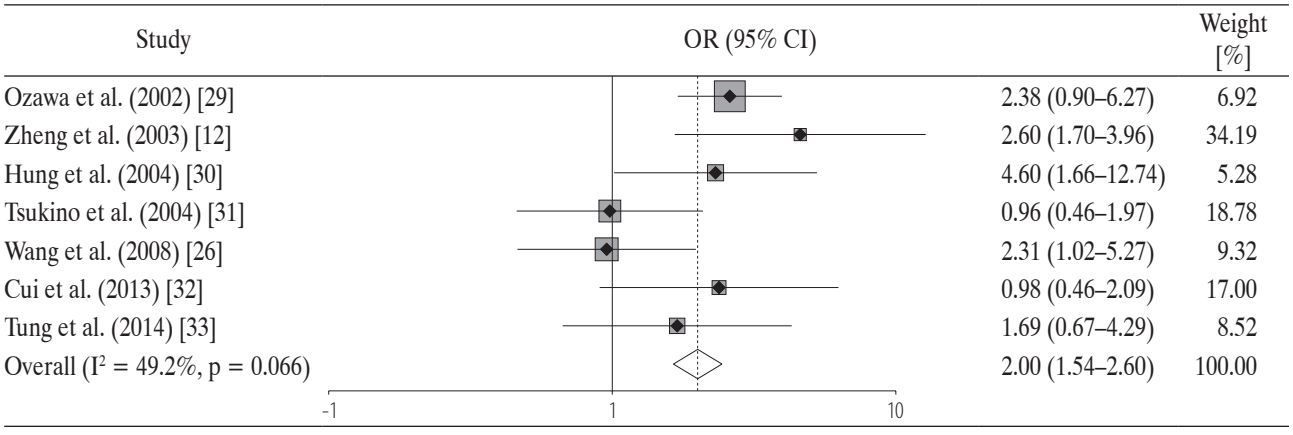
Smoking-*SULT1A1* Arg213His	Studies [n]	Respondents [n]		Heterogeneity		Model for meta-analysis	OR (95% CI)	$p_{Egger's\ test}$ [b]
		study group	control group	I^2 [%]	$p_{heterogneity}$ [a]			
–/(Arg/Arg) vs. –/(Arg/His+His/His)	7	652	819	22.8	0.256	F	1.52 (1.18–1.96)	0.777
+/(Arg/Arg+His/His) vs. –/(Arg/His+His/His)	7	502	596	49.2	0.066	F	2.00 (1.54–2.60)	0.834
+/(Arg/Arg) vs. –/(Arg/His+His/His)	7	1 039	973	74.7	0.001	R	2.38 (1.44–3.93)	0.530
+/(Arg/Arg) vs. –/(Arg/Arg)	7	1 419	1 286	46.5	0.082	F	1.49 (1.27–1.75)	0.074
+/(Arg/Arg) vs. +/(Arg/His+His/His)	7	1 269	1 063	0.0	0.683	F	1.21 (1.01–1.46)	0.256

Abbreviations as in Tables 1 and 2.

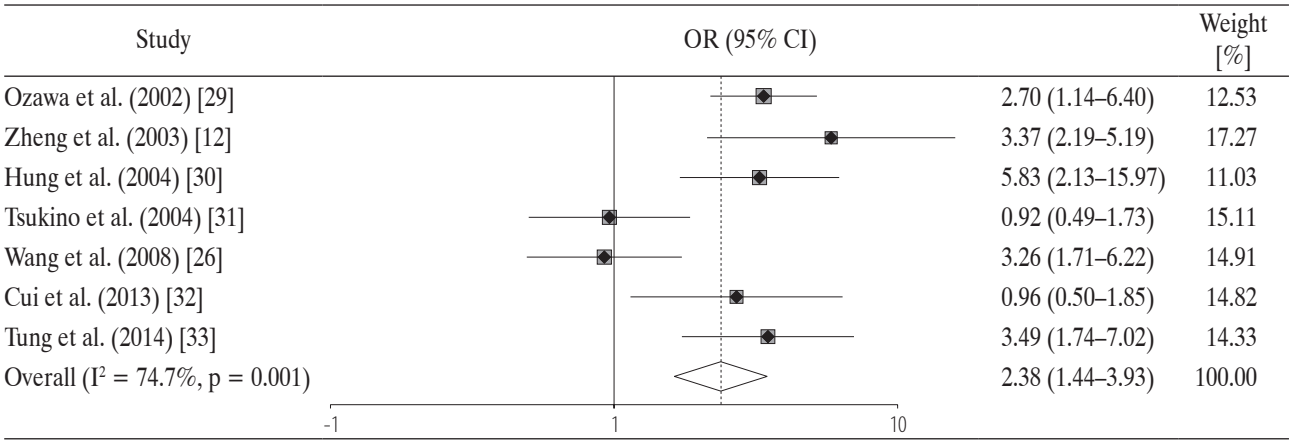
a)



b)

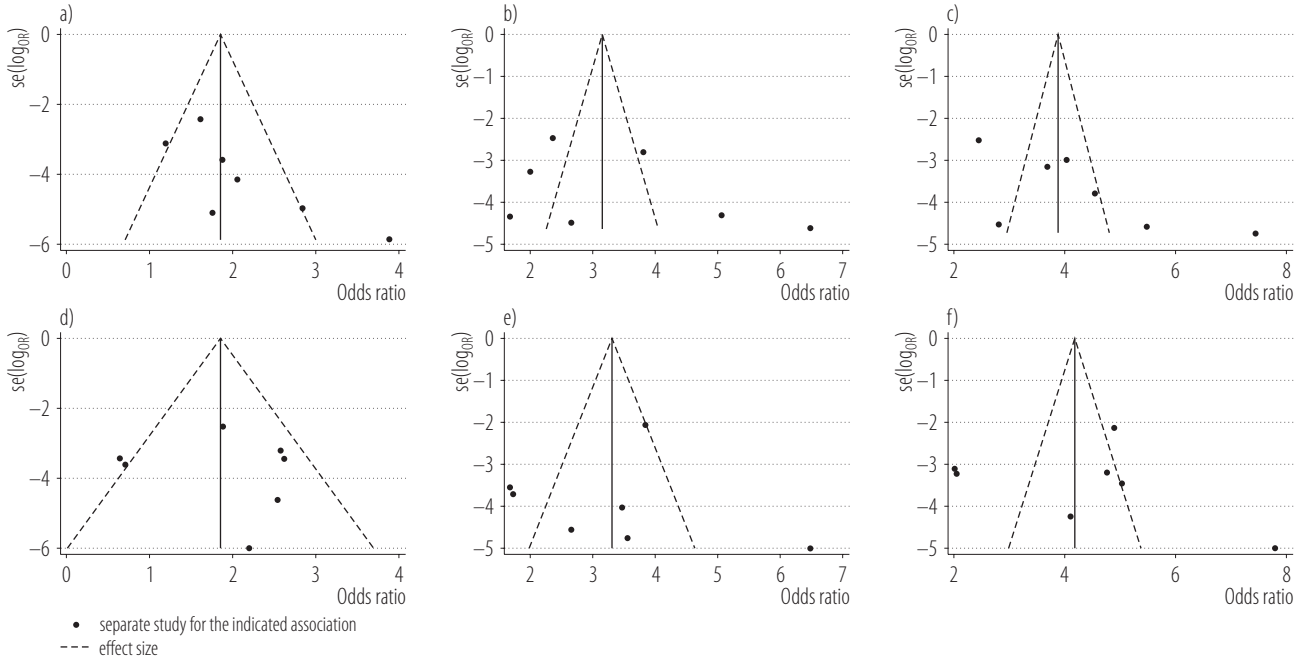


c)



SULT1A1 – sulfotransferase 1A1.
OR – odds ratio; CI – confidence interval.

Fig. 2. Forest plot of the combined effects of *SULT1A1* Arg213His polymorphism and smoking on the risk of bladder cancer:
a) non-smokers carried *SULT1A1* Arg/Arg genotypes vs. non-smokers with *SULT1A1* Arg/His or His/His genotype,
b) smokers with *SULT1A1* Arg/His or His/His genotype vs. non-smokers with *SULT1A1* Arg/His or His/His genotype,
c) smokers with *SULT1A1* Arg/Arg vs. non-smokers with *SULT1A1* Arg/His or His/His genotypes



log$_{OR}$ – natural logarithm of odds ratio (OR).

Fig. 3. Begg's funnel plot for publication bias test – smoking-*NQO1* Pro187Ser interaction: a) –/(CT+TT) vs. –/CC, b) +/CC vs. –/CC; c) +/(CT+TT) vs. –/CC; smoking-*SULT1A1* Arg213His interaction: d) –/(Arg/Arg) vs. –/(Arg/His+His/His); e) +/(Arg/Arg+His/His) vs. –/(Arg/His+His/His); f) +/(Arg/Arg) vs. –/(Arg/His+His/His)

0.387. Similarly, the shape of funnel plots seemed symmetrical for smokers carrying *NQO1* Pro/Ser or Ser/Ser genotypes vs. non-smokers with *NQO1* Pro/Pro genotype, with p, that was used in Egger's test, equaling 0.092.

For *SULT1A1* Arg213His and smoking status, all the shapes of funnel plots seemed symmetrical, with p, that was used in Egger's test, equaling 0.777 for non-smokers carrying *SULT1A1* Arg/Arg genotypes vs. non-smokers with, 0.834 for smokers with *SULT1A1* Arg/His or His/His genotype vs. non-smokers with, and 0.530 for smokers with *SULT1A1* Arg/Arg vs. non-smokers with *SULT1A1* Arg/His or His/His genotype.

DISCUSSION

We conducted 2 meta-analyses including 1341 cases and 1346 controls concerning *NQO1* Pro187Ser and smoking, and 1921 cases and 1882 controls on *SULT1A1* Arg213His and smoking. The combined effects of the 2 missense polymorphisms and smoking on bladder cancer risk were firstly explored by meta-analyses. The result demonstrated that smokers with *NQO1* Pro/Ser or Ser/Ser genotypes had a prominent association with the risk of BC as compared with non-smokers with *NQO1* Pro/Pro genotype, with OR equaling 3.71 (95% CI: 2.87–4.78). Besides, smokers carrying *SULT1A1* Arg/Arg genotypes were observed to confer 2.38 fold increased risk of BC (95% CI: 1.44–3.93) when compared with non-smokers with *SULT1A1* Arg/Arg or His/His genotypes.

The NQO1 enzyme has been phase II enzyme and involves in the detoxification of chemical carcinogens generated from cigarette smoking. So far, several previous studies have investigated the genetic effect of *NQO1* Pro187Ser modified by smoking on BC risk. However, the reported associations of *NQO1* Pro187Ser and smoking with BC risk have been inconsistent. As far as the limited power of the individual studies is concerned, we

have analyzed the pooled effect of Pro187Ser and smoking on the risk of BC by integrating individual studies. In the meta-analysis, non-smokers carrying *NQO1* Pro/Ser or Ser/Ser genotypes have exhibited an increased risk of BC, with OR at 1.76 (95% CI: 1.34–2.31) as compared with non-smokers with *NQO1* Pro/Pro genotype whereas smokers with *NQO1* Pro/Ser or Ser/Ser genotypes have shown no significant association with the risk of BC as compared to smokers with *NQO1* Pro/Pro genotype (OR = 1.34, 95% CI: 0.93–1.95).

However, a similar trend has been observed in the case of non-smokers and smokers. The joint effects between *NQO1* Pro187Ser and smoking have been observed. Smokers with *NQO1* Pro/Ser or Ser/Ser genotypes have shown more prominent association with the risk of BC as compared with non-smokers with *NQO1* Pro/Pro genotype, with OR equaling 3.71 (95% CI: 2.87–4.78). The joint effect has suggested that *NQO1* Pro/Ser or Ser/Ser genotypes confer some benefit for smokers as opposed to smokers with the Pro/Pro genotype. Additionally, publication biases have been comprehensively examined by using Begg's funnel plot and Egger's tests. Border line publication bias has only been detected for non-smokers carrying *NQO1* Pro/Ser or Ser/Ser genotypes vs. non-smokers ($p = 0.049$) and no publication bias has been detected for the other comparison. In view of this, we are convinced that the results of our meta-analysis, in essence, are sound and reliable.

Sulfotransferase 1A1 which is involved in detoxification pathways is responsible for metabolizing a wide range of endogenous and exogenous carcinogens. The genotypes containing *SULT1A1* His213 allele have been observed less efficiently at DNA adduct formation than *SULT1A1* Arg/Arg genotype [34]. Moreover, results of the previous meta-analysis have proven that *SULT1A1* Arg/Arg genotype is significantly associated with increased BC risk [17,18]. The combined effects of *SULT1A1* Arg213His and smoking on BC risk have been investigated by individual studies, but the result has not been inconsistent.

CONCLUSIONS

Therefore, we conducted a meta-analysis to estimate the pooled effect of *SULT1A1* Arg213His and smoking on the risk of BC by integrating individual studies. The results show that non-smokers carrying *SULT1A1* Arg/Arg show an increased risk of BC, with OR at 1.52 (95% CI: 1.18–1.96) when compared with non-smokers with *SULT1A1* Arg/His or His/His genotypes. Among smokers, *SULT1A1* Arg/Arg genotypes also show significant association with the risk of BC as compared with *SULT1A1* Arg/His or His/His genotypes (OR = 1.21, 95% CI: 1.01–1.46). We can see from the result that *SULT1A1* Arg/Arg genotype is consistently associated with increased BC risk when stratified by smoking status.

Meanwhile, smokers carrying *SULT1A1* Arg/Arg genotypes have been observed to confer 2.38 fold increased risk of BC as compared with non-smokers with *SULT1A1* Arg/His or His/His genotypes. The joint effect of *SULT-1A1* Arg213His and smoking has been observed from the result. We have noted that the effect of *SULT1A1* Arg213His polymorphism on BC risk is likely to be enhanced in relation to smoking. Fortunately, biological plausibility exists for an elucidation of the combined effect between *SULT1A1* Arg213His and smoking [13,33].

Similarly, publication biases have been comprehensively examined by using Begg's funnel plot and Egger's tests. No publication bias has been detected for all the comparison about the combined effect of smoking and *SULT1A1* Arg213His. Therefore, the results of our meta-analysis are sound and reliable.

To the best of our knowledge, the 2 meta-analyses have firstly explored the combined effects of *NQO1* Pro187-Ser or *SULT1A1* Arg213His polymorphisms and smoking on BC risk, which seem biologically plausible. The strengths of our meta-analysis could be summarized as follows: firstly, the publications have been systematically browsed through by various searching approaches and satisfactory studies, which have met our inclusion criterion, have been finally selected. Secondly, all the comparisons

about the combined effect of *NQO1* Pro187Ser or *SULT-1A1* Arg213His polymorphisms and smoking have been performed to estimate the pooled OR.

Besides, the effect of *NQO1* Pro187Ser or *SULT1A1* Arg-213His polymorphisms stratified by smoking has also been examined by combining all the included studies. Our results further provide some support that *NQO1* Pro187Ser or *SULT1A1* Arg213His polymorphism combination with smoking significantly increase the risk of BC. The biological function analysis should be performed to validate the combined effect between *NQO1* Pro187Ser or *SULT-1A1* Arg213His polymorphism and smoking in modulation of BC risk. Furthermore, well-designed studies with a sufficient sample size are warranted to further confirm the associated OR modified by smoking.

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