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SULT1A1 Arg213His Polymorphism is Associated with Bladder Cancer Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The evidence of an association between the Sulfotransferase 1A1 (SULT1A1) Arg213His polymorphism (rs9282861) and bladder cancer risk is still conflicting. We conducted a meta-analysis to assess the association between this polymorphism and bladder cancer risk.

Material/Methods: PubMed, EMBASE, HuGE Navigator, and Web of Science databases were searched for correlative articles. The risk (odds ratio, OR) was used to estimate the association between SULT1A1 Arg213His polymorphism and bladder cancer risk. All of the studies used either fixed-effects or random-effects models. For assessing the credibility of an association, we applied the Venice criteria.

Results: Seven published case-control studies with 1688 cases and 2842 controls were included in this meta-analysis. There were 5 studies of Caucasians and 2 studies of Asians. Four studies reported data on smoking behavior. The percentage of Arg/Arg was higher in Asians and non-smokers than that in Caucasians and smokers, respectively. A significant association of this polymorphism with bladder cancer was found (OR=1.45, 95% CI 1.18–1.78, $P=0.0004$). In the subgroup analysis by ethnicity, a significant association was found among Caucasians (OR=1.43, 95% CI 1.16–1.77, $P=0.0008$) but not among Asians (OR=1.89, 95% CI 0.68–5.26, $P=0.22$). In the subgroup analysis by smoking behavior, increased bladder cancer risk was found in the smokers (OR=1.39, 95% CI 1.01–1.91, $P=0.04$) and non-smokers (OR=1.74, 95% CI 1.24–2.43, $P=0.001$).

Conclusions: In conclusion, this meta-analysis indicated that SULT1A1 Arg213His polymorphism is associated with bladder cancer risk.

MeSH Keywords: Genetics • Meta-Analysis • Urinary Bladder Neoplasms • Epidemiology

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Background

Bladder cancer is the most common malignancy of the urinary tract, with an estimated incidence of 73 510 cases and 14 880 deaths in the United States for 2012 [1]. Despite recent multi-disciplinary advances in its treatment, bladder cancer continues to carry unacceptably high rates of morbidity and mortality [2,3]. Thus, the identification of subjects at high risk of bladder cancer is a major concern for clinicians. Recently, several lines of evidence have indicated that inherited genetic factors influence the development and progression of bladder cancer.

Sulfotransferase 1A1 (SULT1A1) is expressed in the liver, as well as in many extrahepatic tissues (e.g., colonic mucosa), and is a component in the detoxification pathway of numerous xenobiotics [4]. It plays an important role in the metabolism and bioactivation of many dietary and environmental mutagens, including heterocyclic amines implicated in carcinogenesis of bladder cancer [5]. A non-synonymous SNP in the SULT1A1 gene has been identified in the coding region at nucleotide 638 (a G to A transition). This base change leads to an amino-acid substitution at codon 213 (Arg to His). Several studies have investigated the association between SULT1A1 Arg213His polymorphism (rs9282861) and bladder cancer risk. However, the results are contradictory [6–11]. The purpose of this meta-analysis was to assess the overall relationship between SULT1A1 Arg213His polymorphism and bladder cancer risk.

Material and Methods

This meta-analysis was performed according to a predetermined protocol described in the following paragraph, using standard systematic review techniques, as outlined in the HuGE Review Handbook [12].

Publication search

Two investigators independently obtained relevant articles through searches of PubMed, EMBASE, HuGE Navigator, and Web of Science databases using the following search terms: “Sulfotransferase 1A1”, “polymorphism”, and “bladder cancer”. The following MeSH terms were used in PubMed: “SULT1A1 protein, human” and “polymorphism, genetic” and “Urinary Bladder Neoplasms”. The search was last updated in May 2014. No language restrictions were applied. A study was included in the current meta-analysis if: (1) it was a case-control study of the SULT1A1 Arg213His polymorphism and bladder cancer, and (2) genotype distributions in both cases and controls were available for estimating an odds ratio (OR) with 95% confidence interval (CI). We excluded studies in which family members were studied. When there were multiple studies from the same population, only the largest study was included.

Data extraction

The following data were collected from each study: first author's surname, year of publication, ethnicity, age, sex, smoking behavior, and sample size. Authors of the relevant studies were contacted via email if further study data were needed.

Qualitative assessment

The quality of included studies was assessed independently by 2 investigators. The quality scoring system was based on traditional epidemiological considerations and genetic issues [13]. The criteria covered the representativeness of cases and controls, the ascertainment of cases and controls, genotyping examination, Hardy-Weinberg equilibrium (HWE), and association assessment. Scores ranged from 0 to 13.

Statistical analysis

The strength of the associations between the SULT1A1 Arg213His polymorphism and bladder cancer was measured by ORs and 95% CIs. Because most of the studies reported ORs and the corresponding 95% CIs in a recessive model, we chose the recessive genetic model and pooled the results. The between-study heterogeneity was assessed across by the chi-square-based Q statistics and I^2 test. Heterogeneity was considered at either a P value of <0.10 or $I^2 > 50\%$. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Departure from HWE in controls was tested by the chi-square test. Subgroup analyses were carried out by ethnicity and smoking. We estimated the difference between the estimates of the subgroups according to tests for interaction. Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. Potential publication bias was estimated using Egger's linear regression test by visual inspection of the Funnel plot [14]. All statistical tests were performed using STATA 11.0 software (Stata Corporation, College Station, TX, USA). A P value <0.05 was considered statistically significant.

Estimating the credibility of statistically significant association

Nominally statistically significant results of the meta-analysis were graded on the basis of the Human Genome Epidemiology Network Venice criteria for the assessment of cumulative evidence of genetic associations [15]. These criteria take into account the amount of evidence (sample size measured as the number of minor alleles), consistency of replication (heterogeneity across studies measured as I^2), and protection from bias (the bias reason, in particular including sensitivity analysis as

Table 1. Characteristics of the studies included in this meta-analysis.

First author/year	Ethnicity	Age	Sex	Smoking habit	Case number	Control number	Score
Zheng/2002	Caucasian	63	Reported	Reported	384	386	8
Hung/2004	Caucasian	65	Mixed	Reported	201	214	7
Kellen/2007	Caucasian	70	Mixed	Mixed	200	385	7
Covolo/2008	Caucasian	50	Mixed	Mixed	197	211	9
Lumbreras/2008	Caucasian	NA	Mixed	Mixed	124	1089	9
Wang/2008	Asian	63	Mixed	Reported	300	300	8
Cui/2013	Asian	60	Mixed	Reported	282	257	7

HWE – Hardy-Weinberg equilibrium.

outlined above, assessments of the strength of the association, small-study bias, and evidence of an excess of statistically significant results). On the basis of the analysis, the overall epidemiological credibility was graded as strong (grade A), moderate (grade B), or weak (grade C).

Results

Study characteristics

A total of 7 case-control studies with 1688 cases and 2842 controls on the association between SULT1A1 Arg213His polymorphism and bladder cancer risk were included in this meta-analysis [6–11]. There were 5 studies of Caucasians and 2 studies of Asians. Four studies reported information on smoking behavior. The quality scores ranged from 7 to 9, suggesting that the methodological quality was generally acceptable. All studies were in HWE. The characteristics of each case-control study are presented in Table 1. Genotype numbers and HWE examination results are listed in Tables 2 and 3. The percentage of Arg/Arg was higher in Asians than that in Caucasians (79.1% vs. 47.3%, $P=0.001$). The percentage of Arg/Arg was higher in non-smokers than that in smokers (63.8% vs. 52.3%, $P=0.006$).

Meta-analysis results

Our results suggest that SULT1A1 Arg213His polymorphism is significantly associated with bladder cancer risk (OR=1.45, 95% CI 1.18–1.78, $P=0.0004$; Figure 1). In the subgroup analysis by ethnicity, a significant association was found among Caucasians (OR=1.43, 95% CI 1.16–1.77, $P=0.0008$) but not among Asians (OR=1.89, 95% CI 0.68–5.26, $P=0.22$). In the subgroup analysis by smoking behavior, increased bladder cancer risk was found in the smokers (OR=1.39, 95% CI 1.01–1.91, $P=0.04$) and non-smokers (OR=1.74, 95% CI 1.24–2.43, $P=0.001$), respectively. No

significant difference was observed between subgroup analyses of ethnicity and smoking habit by the test of interaction ($P=0.61$ and 0.34 , respectively). Summary results of comparisons are listed in Table 4. The sensitivity analysis did not influence the results excessively by omitting any single study (Figure 2). The shape of the funnel plot was symmetrical (Figure 3). The result of Egger's linear regression test showed no evidence of publication bias ($P=0.388$).

2 Estimating the credibility of association

To assess the credibility of genetic associations, we considered the Venice criteria, which indicated that the association represented a strongly credible association.

Discussion

To our knowledge, this meta-analysis is the first study to systematically assess the association between SULT1A1 Arg213His polymorphism and bladder cancer risk. Results of this meta-analysis showed that SULT1A1 Arg/Arg genotype was significantly associated with increased bladder cancer risk. Although the percentage of Arg/Arg genotype was higher in Asians than in Caucasians, a significant association was found in Caucasians in the subgroup analysis by ethnicity. No significant association was observed in Asians. However, there was no significant interaction in this subgroup analysis. Thus, the positive association between Asians and bladder cancer could not be ruled out, because studies with small sample size may have insufficient statistical power to detect a slight effect. Since only 2 of the studies were done in Asian populations, more studies with Asians should be performed to determine the relationship between SULT1A1 Arg213His polymorphism and bladder cancer risk. The percentage of Arg/Arg genotype was higher in non-smokers than in smokers. Results of a previous study

Table 2. Distribution of SULT1A1 Arg213His genotype among patients and controls.

Studies	Patients			Controls			HWE
	Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His	
Zheng	196	155	33	164	174	48	Yes
Hung	121	72	8	116	88	10	Yes
Kellen	111	79	18	191	151	47	Yes
Covolo	120	77*		114	97*		Yes
Lumbreras	57	54	13	513	451	125	Yes
Wang	261	37	2	240	54	6	Yes
Cui	218	59	5	201	52	4	Yes

* Combined numbers of Arg/His and His/His genotypes. HWE – Hardy-Weinberg equilibrium.

Table 3. The SULT1A1 Arg213His genotype and bladder cancer risk stratified by smoking behavior.

Studies	Smoking status	Patients			Controls		
		Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His
Zheng	Smoker	286	282*		186	238*	
	Non-smoker	53	47*		71	103*	
Hung	Smoker	109	68	7	86	69	6
	Non-smoker	12	4	1	30	19	1
Wang	Smoker	124	23*		88	23*	
	Non-smoker	137	16*		152	37*	
Cui	Smoker	155	42*		139	37*	
	Non-smoker	63	22*		62	19*	

* Combined numbers of Arg/His and His/His genotypes.

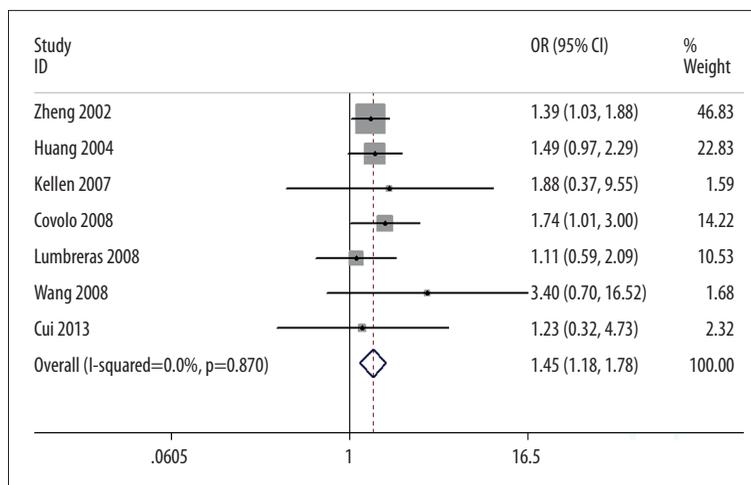


Figure 1. Association between SULT1A1 Arg213His polymorphism and bladder cancer risk.

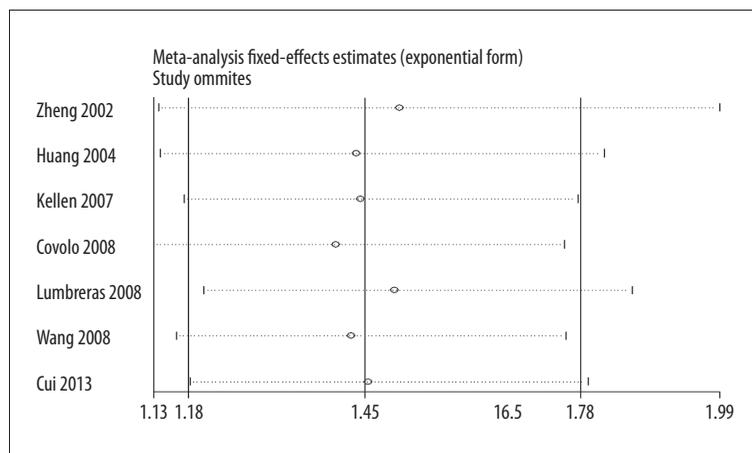
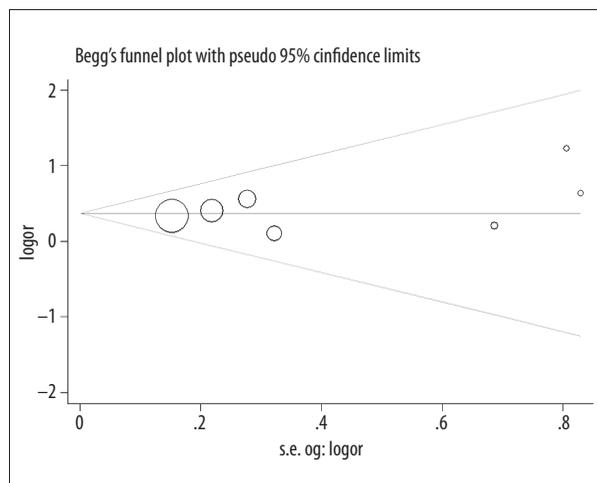
were similar to our results [16]. In the subgroup analysis by smoking behavior, this polymorphism was associated with increased bladder cancer risk in both smokers and non-smokers.

Furthermore, there was also no significant interaction in this subgroup analysis. These results suggest that smoking does not change the role of SULT1A1 Arg213His polymorphism in

Table 4. The genetic effect of SULT1A1 Arg213His polymorphism on bladder cancer.

Comparison	Characteristics	Model	Test of association			P for interaction
			OR (95% CI)	I ² (%)	P value	
Arg/Arg vs. Arg/His + His/His	Overall	F	1.45 (1.18–1.78)	0	0.0004	
Arg/Arg vs. Arg/His + His/His	Asian	F	1.89 (0.68–5.26)	0	0.22	0.61
Arg/Arg vs. Arg/His + His/His	Caucasian	F	1.43 (1.16–1.77)	0	0.0008	
Arg/Arg vs. Arg/His + His/His	Smoker	F	1.39 (1.01–1.91)	0	0.04	0.34
Arg/Arg vs. Arg/His + His/His	Non-smoker	F	1.74 (1.24–2.43)	0	0.001	

F – fixed-effects model.

**Figure 2.** Sensitivity analysis between SULT1A1 Arg213His polymorphism and bladder cancer risk.**Figure 3.** Funnel plot between SULT1A1 Arg213His polymorphism and bladder cancer risk.

the development of bladder cancer. However, this result should be confirmed by further studies.

Recently, studies have suggested that the SULT1A1 Arg/Arg genotype is associated with an increased risk for development of cancers of the esophagus, breast, and lung [17–19]. The

single-nucleotide G/A transition at codon 213 in exon 7 results in an Arg to His amino acid substitution and this polymorphism has been shown to have a functional impact in humans. The allele encoding histidine at position 213 was uniformly associated with lower sulfotransferase activity and lower thermal activity [20]. Thus, it is possible that the SULT1A1 Arg213His polymorphism influences the risk of bladder cancer.

Some limitations should be pointed out. One limitation is the insufficient sample size used in this meta-analysis, especially for the sex subgroup analysis. A second limitation is that lack of original data of each study may prevent more detailed analyses, such as joint effects of SNP-SNP. The third limitation is that in our meta-analysis all the case-control data were used without adjustment by detailed individual information such as age, sex, and lifestyle. The fourth limitation is that we did not include data from genome-wide association studies (GWAS).

Conclusions

This meta-analysis suggests that there is a significant association between SULT1A1 Arg213His polymorphism and bladder cancer risk. Future large-scale, population-based association

studies are warranted to verify the risk identified in the current meta-analysis and to investigate the potential gene-gene and gene-environment interactions involving the SULT1A1 Arg213His polymorphism and bladder cancer.

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Conflicts of interest

None.