RESEARCH COMMUNICATION

SULT1A1 Arg213His Polymorphism and Lung Cancer Risk: a Meta-analysis

Shao-Guang Liao[&], Lu Liu[&], Ying-Yi Zhang, Ying Wang, Ya-Jie Wang*

Abstract

<u>Background</u>: The SULT1A1 Arg213His polymorphism is reported to be associated with lung cancer risk. However, this relationship remains controversial. For better understanding a meta-analysis was therefore performed. <u>Methods</u>: An extensive search was performed to identify all case-control studies investigating association between SULT1A1 Arg213His polymorphism and lung cancer risk. The strength was assessed by odds ratio (OR) with the corresponding 95% confidence interval (95%CI). <u>Results</u>: A total of five publications covering 1,669 cases and 1,890 controls were included in this meta-analysis. No significant association between SULT1A1 Arg213His polymorphism and lung cancer risk was observed in overall comparisons in all genetic models (dominant model: OR=1.33, 95%CI=1.00-1.76, P=0.05; additive model: OR=1.30, 95%CI=0.93-1.81, P=0.12; recessive model: OR=1.21, 95%CI=0.89-1.66, P=0.23). However, on subgroup analysis, an elevated risk in mixed populations with variant His allele was revealed in the dominant model (OR=1.66, 95% CI=1.06-2.62, P=0.03). Furthermore, the SULT1A1 Arg213His polymorphism was associated with an increased risk of lung cancer in both females and males in the dominant model (females: OR=1.72, 95%CI=1.29-2.27, P=0.00; males: OR=1.46, 95%CI=1.19-1.78, P=0.00). No significant association between this polymorphism and different smoking status (smokers and non-smokers) and the other ethnicities (Asians and Caucasians) was shown. <u>Conclusions</u>: The results of this meta-analysis indicate that the SULT1A1 Arg213His polymorphism is not associated with lung cancer risk in Asians and Caucasians, but possible elevation for genotype (GA/AA) in mixed populations and males and females needs further investigation.

Keywords: SULT1A1 - lung cancer - genetic polymorphisms - meta-analysis

Introduction

Sulfotransferases (SULTs) are involved in the phase II metabolism of endogenous and exogenous compounds including drugs, thyroid and steroid hormones, catecholamines and procarcinogenic agents (Falany, 1997; Richard et al., 2001). Sulfotransferase 1A1 (SULT1A1), an important member of this enzyme superfamily, has high activity towards a wide range of substrates including environmental and tobacco carcinogens. SULT1A1 catalyze the sulfonation of N-hydroxy derivatives of arylamines and heterocyclic amines, which are presented in tobacco smoke, to form more reactive DNA-damaging electrophiles (Ozawa et al., 1994; Chou et al., 1995). Sulfonation can also activate another major class of tobacco carcinogens, polycyclic aromatic hydrocarbons (PAHs) and nitro PAHs (Watabe et al., 1982; Surh et al., 1995; Arlt et al., 2002). Therefore, reduced activity of SULT enzymes may result in accumulation of potential carcinogens.

Several single nucleotide polymorphisms have been identified in the SULT1A1 gene (Raftogianis et al.,

1997; Ozawa et al., 1998; Hirata et al., 2008). Among these, a common polymorphism (G638A) at codon 213 in exon 7 of SULT1A1 gene causes an Arg to His amino acid substitution. The mutation in the SULT1A1 gene would affect an individual's capacity to efficiently sulfate endogenous compounds, drugs and xenobiotics, and consequently result in an individual's susceptibility to cancer (Coughtrie et al., 1999; Raftogianis et al., 1999). Some studies have demonstrated that genetic polymorphisms of SULT1A1 Arg213His are associated with susceptibility to several cancer types including lung cancer (Wang et al., 2002; Wong et al., 2002; Han et al., 2004; Nowell et al., 2004; Bardakci et al., 2008).

Lung cancer is a major cause of cancer death related to tobacco smoke in the world (Greenlee et al., 2000). In recent years, several studies to address the association between SULT1A1 Arg213His polymorphism and lung cancer risk were conducted, with contradictory results. Liang's study (Liang et al., 2004) reported that the variant SULT1A1 genotype (638GA or AA) was associated with a significantly increased risk for overall lung cancer, while in Tamaki's study (Tamaki et al., 2011) no association

*Department of Oncology, Changhai Hospital, Second Military Medical University, Shanghai, China &Equal contributors *For correspondence: yajiewa0459@163.com*

was found. For better understanding of the association between SULT1A1 Arg213His polymorphism and lung cancer risk, a meta-analysis was performed.

Materials and Methods

Identification of eligible studies

We performed an extensive search of studies that examined the association of the SULT1A1 polymorphisms with lung cancer. All eligible studies were identified by searching the PubMed database. The following terms were used: "SULT1A1" or ''sulfotransferase'', "polymorphism(s)'', "lung cancer" or "lung carcinoma''. No language or country restrictions were applied. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis by the two authors (Liao and Liu) independently. References of cited articles were reviewed to identify additional studies not indexed by Medline. Included studies were required to meet the following criteria: (a) articles evaluating the association between SULT1A1 Arg213His polymorphism and lung 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).

Data extraction

Information was carefully extracted from all eligible publications independently by two authors (Liao and Liu), according to the inclusion criteria. Disagreement was resolved by discussion between the authors. If these two authors could not reach a consensus, a third author was consulted to resolve the dispute and a final majority decision was made. The following variables were extracted from each study if available: first author's surname, publication year, country in which the study was performed, ethnicity of the study population, matching criteria, numbers of cases and controls, and genotype distributions in both cases and controls.

Statistical analysis

We calculated summary odd ratios (ORs) corresponding to a 95% confidence interval (CI) to assess the strength of association between SULT1A1 Arg213His polymorphism and lung cancer. 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. The between-study heterogeneity was assessed by the $\chi 2$ test-based Q statistic (Cochran et al., 1954). A P value greater than 0.10 for the Q-test indicates a lack of heterogeneity among studies.

The OR and its 95%CI in each comparison was assessed in dominant (GA/AA vs. GG), additive (AA vs. GG) and recessive (AA vs. GG/GA) genetic models. In addition, subgroup analyses for ethnicity (mixed, Asian and Caucasian population), smoking status (smokers and non-smokers) and gender (males and females) were conducted.

The potential publication bias was examined visually
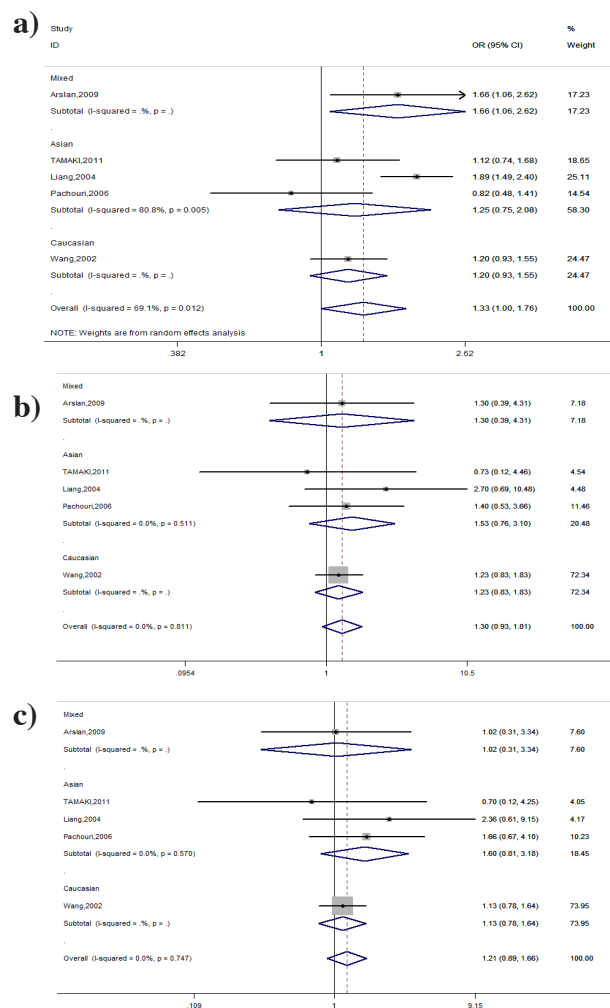
Figure 1. Meta-Analysis of SULT1A1 Arg213His Polymorphism and Lung Cancer Risk. a) dominant model; b) additive model; c) recessive model

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). In the control populations, Hardy–Weinberg equilibrium (HWE) was tested. This meta-analysis was performed using the software STATA version 11.2.

Results

Characteristics of eligible studies

A total of five publications (Wang et al., 2002; Liang et al., 2004; Pachouri et al., 2006; Arslan et al., 2009; Tamaki et al., 2011) containing 1,669 cases and 1,890 controls were included in this meta-analysis. Table 1 lists the main characteristics of these studies. Four of these studies (Wang et al., 2002; Liang et al., 2004; Pachouri et al., 2006; Arslan et al., 2009) presented SULT1A1 Arg213His polymorphism genotype distributions according to the smoking status (smokers and non-smokers). And three of these studies (Wang et al., 2002; Liang et al., 2004; Arslan et al., 2009) presented SULT1A1 Arg213His polymorphism genotype distributions according to the sex (males and females). All of the cases were histologically confirmed as lung cancer. Controls were mainly healthy or hospital-based populations. Genotype distributions in

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

Study	Country	Ethnicity	Sample size(case control)	Genotype (case/control)			HWE
				GG	GA	AA	
Arslan et al., 2009	Turkey	Mixed	106/271	50/162	52/99	4/10	Yes
Tamaki et al., 2011	Japan	Asian	192/203	120/132	70/68	2/3	Yes
Liang et al., 2004	China	Asian	805/809	581/672	217/134	7/3	Yes
Pachouri et al., 2006	India	Asian	103/122	42/44	49/69	12/9	No
Wang et al.,2002	America	Caucasian	463/485	195/226	201/196	67/63	Yes

Ph, P values for heterogeneity from Q test; *A significant association was detected (P<0.05)

Table 2. Results of Meta-analysis for SULT1A1 Arg213His Polymorphism and Lung Cancer Risk

Analysis	Cases/ controls	Dominant model (GA/AA vs. GG)			Additive model (AA vs. GG)			Recessive model (AA vs. GG/GA)		
		OR (95% CI)	P	Ph	OR (95% CI)	P	Ph	OR (95% CI)	P	Ph
Overall	1669/1890	1.33(1.00-1.76)	0.05	0.01	1.30(0.93-1.81)	0.12	0.81	1.21(0.89-1.66)	0.23	0.75
Ethnicity										
Mixed	106/271	1.66(1.06-2.62)*	0.03	-	1.30(0.39-4.31)	0.67	-	1.02(0.31-3.34)	0.97	-
Asian	1100/1134	1.25(0.75-2.08)	0.39	0.01	1.53(0.76-3.10)	0.23	0.51	1.60(0.81-3.18)	0.18	0.57
Caucasian	463/485	1.20(0.93-1.55)	0.16	-	1.23(0.83-1.83)	0.30	-	1.13(0.78-1.64)	0.51	-

Table 3. Subgroup Analysis of SULT1A1 Arg213His Polymorphism and Lung Cancer Risk

Analysis	Sample size (case/control)	Dominant model (GA/AA vs. GG) OR(95% CI)	Model	P- heterogeneity	P value
Smoking status					
Smokers	1085/971	1.50(0.99-2.24)	R	0.02	0.06
Non-smokers	370/675	1.35(1.00-1.83)		0.61	0.05
Gender					
Females	454/551	1.72(1.29-2.27)	F	0.15	0.00
Males	920/1014	1.46(1.19-1.78)		0.11	0.00

F, fixed effect model; R, random effect model
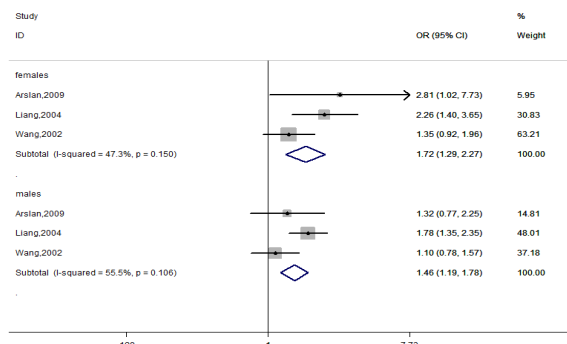
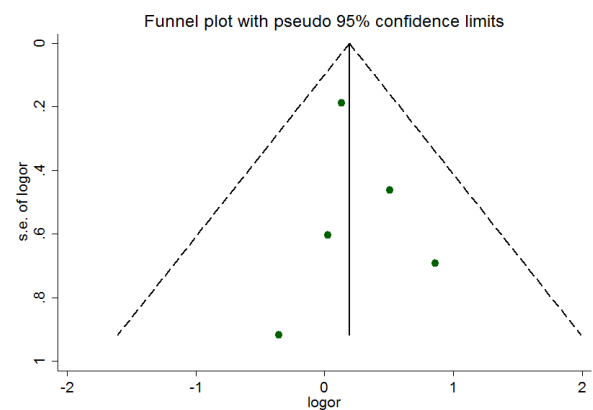**Figure 2. Meta-Analysis of SULT1A1 Arg213His Polymorphism and Lung Cancer Risk in Different Gender (Dominant Model)**

Figure 3. Funnel Plot of SULT1A1 Arg213His Polymorphism and Lung Cancer Risk for Publication Bias

the controls of all studies were in agreement with HWE, except one study (Pachouri et al., 2006).

Meta-analysis

When all the eligible studies were pooled into the meta-analysis, SULT1A1 Arg213His polymorphism did not reveal any relationship with lung cancer susceptibility in dominant, additive and recessive model (dominant model: OR=1.33, 95%CI=1.00-1.76, P=0.05; additive model: OR=1.30, 95%CI=0.93-1.81, P=0.12; recessive model: OR=1.21, 95%CI=0.89-1.66, P=0.23; Table 4; Figure 1). In the subgroup analysis on ethnicity, no significant association was found except for the mixed population in dominant model (OR=1.66, 95% CI=1.06-2.62, P=0.03; Figure 1).

Next, the association between the SULT1A1

Arg213His polymorphism and lung cancer risk was evaluated according to different smoking status and gender in dominant model. In the subgroup analysis on smoking status, the results were negative (Table 3). However, stratification by gender indicated that the SULT1A1 Arg213His polymorphism was associated with an increased risk of lung cancer in both females and males (females: OR = 1.72, 95%CI = 1.29-2.27, P=0.00; males: OR = 1.46, 95%CI = 1.19-1.78, P=0.00; Table 3; Figure 2).

Evaluation of publication bias

Funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plot did not indicate any evidence of obvious asymmetry (Figure 3) and the Egger's test suggested the absence of publication bias (Dominant model: P=0.35; Additive model: P=0.69; Recessive model: P=0.67).

Discussion

SULT1A1 gene, located in chromosome 16p12.1-p11.2, encodes the SULT1A1 enzyme which is an important enzyme in the metabolism of endogenous and exogenous carcinogens. The G638A polymorphism in SULT1A1 which causes an Arg to His amino acid substitution

results in reduced enzyme activity and thermostability, and consequently results in an individual's susceptibility to cancer (Raftogianis et al., 1997; Coughtrie et al., 1999). Regarding the association between SULT1A1 Arg213His polymorphism and lung cancer susceptibility, five case–control studies were found by searching PubMed, with inconclusive results. To resolve these problems, a meta-analysis was performed. The result of this meta-analysis suggested that the SULT1A1 Arg213His polymorphism was not significantly associated with lung cancer susceptibility in all genetic models. However, in dominant model, there was a borderline increased risk for mutant genotype (GA/AA) for lung cancer. Furthermore, in dominant model of the subgroup analysis by ethnicity, increased risk was found in mixed population, while no association was detected in Asians and Caucasians populations. Further investigation may be needed to confirm the result.

Cigarette smoking is thought to be responsible for 90% of lung carcinomas in men and 78% in women (Shopland et al., 1991).Processed tobacco contains more than 3,000 compounds, including 30 carcinogens (Hecht, 1999). SULT1A1 was known to be involved in the metabolism of procarcinogens such as heterocyclic amines and polycyclic aromatic hydrocarbons, both of which are present in tobacco smoke. In some studies, smokers with His213 allele have been shown to possess higher risk of developing lung cancer (Wang et al., 2002; Liang et al., 2004). Thus, we perform a subgroup analysis for smoking status (smokers and non-smokers). Similarly, in dominant model, we found a borderline increased risk for mutant genotype (GA/AA) for lung cancer both in smokers and non-smokers. This result needs further large-scale studies to confirm.

The most important pathway involves in the formation of estrogen is sulfatase pathway which involves conversion of inactive estrone sulfate into active estrone (Wang et al., 2005). Sulfotransferases (SULT) sulfonate estrone to inactive estrone sulfate, whereas steroid sulfatase (STS) hydrolyzes estrone sulfate to estrone. Thus the SULT1A1 polymorphisms are believed to modulate susceptibility to estrogen-mediated carcinogenesis such as breast cancer (Jiang et al., 2010;Wang et al., 2010; Sun et al., 2011). Differential regulation of the SULT1A1 enzymes may also account for the difference in lung cancer risk between males and females. Hence, gender status was considered as a potential source of heterogeneity. In the subgroup analysis by gender of this meta-analysis, SULT1A1 Arg213His polymorphism was associated with an increased risk of lung cancer in both males and females in dominant model. Interestingly, when all the eligible studies were pooled into the meta-analysis, only a borderline increased risk for lung cancer in dominant model was found. That may because of two of these studies were excluded in this subgroup analysis for lacking related information. Therefore, the conclusion about this association should be further investigated.

However, there are still some limitations exist in this meta-analysis. Between-study heterogeneity, resulting from different defined controls or some other factors, may impact on the results of this analysis. The matching criteria of the control group, such as age, smoking status, and environment exposures, are different between studies. The varied risk of lung cancer in these different populations may impact on the results. And OR value was obtained without adjusting. More accurate OR should be adjusted by age, smoking status, gender and other factors.

In conclusion, no significant association between SULT1A1 Arg213His polymorphism and lung cancer risk was revealed in overall comparisons. And subgroup analysis on smoking status in dominant model also shows a negative result. However, subgroup analysis showed an elevated risk in mixed population and both males and females with variant His allele in dominant genetic model. Further detailed investigation with large numbers of worldwide participants is needed to clarify the role of this polymorphism in lung cancer.

Acknowledgements

References

Arlt VM, Glatt H, Muckel E, et al (2002). Metabolic activation of the environmental contaminant 3-nitrobenzanthrone by humanacetyltransferases and sulfotransferase. *Carcinogenesis*, **23**, 1937-45.

Arslan S, Silig Y, Pinarbasi H (2009). An investigation of the relationship between SULT1A1 Arg(213) his polymorphism and lung cancersusceptibility in a Turkish population. *Cell Biochem Funct*, **27**, 211-5.

Bardakci F, Arslan S, Bardakci S, et al (2008). Sulfotransferase 1A1 (SULT1A1) polymorphism and susceptibility to primary brain tumors. *J Cancer Res Clin Oncol*, **134**, 109–14.

Cochran WG (1954). The combination of estimates from different experiments. *Biometrics*, **10**, 101-29.

Chou HC, Lang NP, Kadlubar FF (1995). Metabolic activation of the N-hydroxy derivative of the carcinogen 4-aminobiphenyl by human tissue sulfotransferases. *Carcinogenesis*, **16**, 413-7.

Coughtrie MW, Gilissen RA, Shek B, et al (1999). Phenol sulphotransferase SULT1A1 polymorphism: molecular diagnosis and allele frequencies in Caucasian and African populations. *Biochem J*, **337**, 45-9.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.

Falany CN (1997). Enzymology of human cytosolic sulfotransferases. *FASEB J*, **11**, 206-16.

Greenlee RT, Murray T, Bolden S, et al (2000). Cancer statistics. *CA Cancer J Clin*, **50**, 7-33.

Hecht SS (1999). DNA adduct formation from tobacco-specific N-nitrosamines. *Mutat Res*, **424**, 127-42.

Han DF, Zhou X, Hu MB, et al (2004). Sulfotransferase 1A1 (SULT1A1) polymorphism and breast cancer risk in Chinese women. *Toxicol Lett*, **150**, 167-77.

Hirata H, Hinoda Y, Okayama N, et al (2008). CYP1A1, SULT1A1, and SULT1E1 polymorphisms are risk factors for endometrial cancer susceptibility. *Cancer*, **112**, 1964-73.

Jiang Y, Zhou L, Yan T, et al (2010). Association of sulfotransferase SULT1A1 with breast cancer risk: a meta-analysis of case-

control studies with subgroups of ethnic and menopausal statue. *J Exp Clin Cancer Res*, **29**, 101.

Liang G, Miao X, Zhou Y, et al (2004). A functional polymorphism in the SULT1A1 gene (G638A) is associated with risk of lung cancer in relation to tobacco smoking. *Carcinogenesis*, **25**, 773-8.

MANTEL N, HAENSZEL W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.

Nowell S, Ratnasinghe DL, Ambrosone CB, et al (2004). Association of SULT1A1 phenotype and genotype with prostate cancer risk in African-Americans and Caucasians. *Cancer Epidemiol Biomarkers Prev*, **13**, 270-6.

Ozawa S, Chou HC, Kadlubar FF, et al (1994). Activation of 2-hydroxyamino-1-methyl-6-phenylimidazo[4,5-b] pyridine by cDNA-expressed human and rat arylsulfotransferases. *Jpn J Cancer Res*, **85**, 1220-8.

Ozawa S, Tang YM, Yamazoe Y, et al (1998). Genetic polymorphisms in human liver phenol sulfotransferases involved in the bioactivation of N-hydroxy derivatives of carcinogenic arylamines and heterocyclic amines. *Chem Biol Interact*, **109**, 237-48.

Pachouri SS, Sobti RC, Kaur P, et al (2006). Impact of polymorphism in sulfotransferase gene on the risk of lung cancer. *Cancer Genet Cytogenet*, **171**, 39-43.

Raftogianis RB, Wood TC, Otterness DM, et al (1997). Phenol sulfotransferase pharmacogenetics in humans: association of common SULT1A1 alleleswith TS PST phenotype. *Biochem Biophys Res Commun*, **239**, 298-304.

Raftogianis RB, Wood TC, Weinshilboum RM (1999). Human phenol sulfotransferases SULT1A2 and SULT1A1: genetic polymorphisms, allozyme properties, and human liver genotype-phenotype correlations. *Biochem Pharmacol*, **58**, 605-16.

Richard K, Hume R, Kaptein E, et al (2001). Sulfation of thyroid hormone and dopamine during human development: ontogeny of phenol sulfotransferases and arylsulfatase in liver, lung, and brain. *J Clin Endocrinol Metab*, **86**, 2734-42.

Shopland DR, Eyre HJ, Pechacek TF (1991). Smoking-attributable cancer mortality in 1991: is lung cancer now the leading cause of deathamong smokers in the United States? *J Natl Cancer Inst*, **83**, 1142-8.

Surh YJ, Tannenbaum SR (1995). Sulfotransferase-mediated activation of 7,8,9,10-tetrahydro-7-ol, 7,8-dihydrodiol, and 7,8,9,10-tetraol derivatives of benzo[a]pyrene. *Chem Res Toxicol*, **8**, 693-8.

Sun Y, Zang Z, Xu X, et al (2011). The association of SULT1A1 codon 213 polymorphism and breast cancer susceptibility: meta-analysis from 16 studies involving 23,445 subjects. *Breast Cancer Res Treat*, **125**, 215-9.

Tamaki Y, Arai T, Sugimura H, et al (2011). Association between cancer risk and drug-metabolizing enzyme gene (CYP2A6, CYP2A13, CYP4B1, SULT1A1, GSTM1, and GSTT1) polymorphisms in cases of lung cancer in Japan. *Drug Metab Pharmacokinet*, **26**, 516-22.

Watabe T, Ishizuka T, Isobe M, et al (1982). A 7-hydroxymethyl sulfate ester as an active metabolite of 7,12-dimethylbenz[alpha]anthracene. *Science*, **215**, 403-5.

Wang Y, Spitz MR, Tsou AM, et al (2002). Sulfotransferase (SULT) 1A1 polymorphism as a predisposition factor for lung cancer: a case-control analysis. *Lung Cancer*, **35**, 137-42.

Wong CF, Liyou N, Leggett B, et al (2002). Association of the SULT1A1 R213H polymorphism with colorectal cancer. *Clin Exp Pharmacol Physiol*, **29**, 754-8.

Wang LQ, James MO (2005). Sulfotransferase 2A1 forms estradiol-17-sulfate and celecoxib switches the dominant product fromestradiol-3-sulfate to estradiol-17-sulfate. *J Steroid Biochem Mol Biol*, **96**, 367-74.

Wang Z, Fu Y, Tang C, et al (2010). SULT1A1 R213H polymorphism and breast cancer risk: a meta-analysis based on 8,454 cases and 11,800 controls. *Breast Cancer Res Treat*, **122**, 193-8.