Modulating influence of cytochrome *P*-450 *MspI* polymorphism on serum liver function profiles in coke oven workers

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Abstract

Objectives—It was reported previously that topside oven workers with heavy exposure to coke oven emissions had increased serum activities of hepatic aminotransferase in one coke oven plant. This study was conducted to investigate the modifying effect of *CYP1A1 MspI* polymorphism on liver function profiles in coke oven workers.

Methods—88 coke oven workers from a large steel company in Taiwan were studied in 1995–6. Exposure was categorised by work area: topside oven workers and sideoven workers. Liver function profiles including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and total bilirubin (BIL) were examined in the morning after personal exposure measurements. The *MspI* polymorphism was determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP).

Results—Five of 23 (22%) topside oven workers and seven of 65 (11%) sideoven workers had the *CYP1A1 MspI* homozygous variant genotype. With sideoven workers with the combined wild type and heterozygous variant as the reference group in multiple regression models, it was found that topside oven workers with the combined traits had mean AST and ALT activities that were 21% and 46% higher (95% confidence interval (95% CI) 4% to 42% and 12% to 91%, respectively) than the reference group after adjusting for appropriate confounders. Also, topside oven workers with the homozygous variant trait had mean AST, ALT, and GGT activities that were 59%, 68%, and 157% higher (95% CI 21% to 109%, 6% to 168%, and 39% to 374%, respectively) than the reference group. The prevalence of an abnormal hepatocellular pattern (AST >37 IU/l or ALT >39 IU/l) was more common in the topside oven workers with the homozygous variant than in the sideoven workers with the other combined genotypes (adjusted odds ratio 9.9, 95% CI 1.2 to 82.3) after adjusting for appropriate confounders.

Conclusions—The *CYP1A1 MspI* polymorphism may modify the biotransformation of coke oven emissions, which

results in hepatocellular damage in coke oven workers.

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Keywords: *CYP1A1* genotype; liver function; coke oven workers

Coke oven workers are constantly exposed to coke oven emissions. These include a wide variety of volatile organic solvents and particulates, especially polycyclic aromatic hydrocarbons (PAHs).^{1–3} Recent studies have shown that phase I enzymes such as P4501A1 metabolise organic compounds to reactive compounds which can damage cells and DNA.^{4–6} Previous studies have suggested that variant alleles of *CYP1A1 MspI* polymorphism are associated with malignancies, particularly lung cancer,^{7–10} but the effect of this polymorphism on serum activities of hepatic enzymes has not been well characterised. Our earlier studies have found that topside oven workers with heavy exposure to coke oven emissions had higher serum activities of hepatic aminotransferases, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), than sideoven workers in a coke oven plant in Taiwan.^{11,12} Therefore, in this study we investigated whether the *CYP1A1 MspI* polymorphism modifies liver function profiles in coke oven workers.

Materials and methods

SUBJECTS

We studied the older of two coke oven plants in the largest steel company in Taiwan. The study design has been described in detail elsewhere.¹¹ Eighty eight coke oven workers who were currently working and had been employed for at least 3 months in the older of two coke oven plants were recruited in this study.

AMBIENT BENZENE SOLUBLE FRACTION, QUESTIONNAIRE INFORMATION, AND LABORATORY TESTS

Personal breathing zone air samples for benzene soluble fraction (BSF) of total particulates, used as a surrogate for coke oven emissions, were collected from study subjects for 3 consecutive days between August 1995, and February 1996. Our earlier study showed that the median (range) of ambient BSF of total particulates was 372 (51–18,181) $\mu\text{g}/\text{m}^3$ in topside oven workers and 53 (1–2965) $\mu\text{g}/\text{m}^3$ in sideoven workers.¹¹

A self administered questionnaire was given during the second or third day of the personal

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air samplings to collect information on the potential risk factors for increased liver enzymes, including age, height, weight, nutritional history, past liver diseases, smoking, alcohol consumption, job classifications, job histories, and regular use of respirators.¹¹ Quetelet's index (kg/m^2) was used to measure the degree of obesity. Nutritional history included vitamin B complex, multiple vitamin, or other medications that potentially affect the liver. Subjects were asked about their average weekly alcohol consumption of spirits, wine, and beer over the past 6 months. Their weekly consumption of the different beverages was totalled as g 100% alcohol.

Liver function profiles including AST, ALT, γ -glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and total bilirubin (BIL), and hepatitis B surface antigens (HBsAg) and antihepatitis C antibodies (Anti-HCV) were measured in the company clinic.

CYP1A1 *m*spi GENOTYPE ANALYSES

The *MspI* polymorphism in *CYP1A1* 3' flanking region was determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP), according to the method of Hayashi *et al.*¹³ The DNA sample was amplified with 2 primers: 5'-CAGTGAAGA GGTGTAGCCGC-3' (upstream) and 5'-TAGGAGTCTTGTCTCATGCC-3' (downstream) (Perkin Elmer, Taipei, Taiwan). The PCR amplification was carried out with 1 μg DNA in 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 3 mM MgCl_2 , 0.3 mM deoxyribonucleotide triphosphates (Boehringer Mannheim GmbH, Mannheim, Germany), 0.2 μM of each primer and 1.5 units Taq polymerase (AmpliTa; Perkin Elmer) in a total volume of 50 μl . Amplification was performed with an initial denaturation at 94°C for 5 minutes, followed by 30 cycles at 94°C for 1 minute, 61°C for 1 minute, and 72°C for 1 minute, and a final extension at 72°C for 7 minutes.

Amplification product (10 μl) was digested with 3 units *MspI* (New England Biolabs, Beverly, MA) in 50 mM NaCl, 10 mM Tris-HCl, 10 mM MgCl_2 , and 1 mM dithiothreitol (DTT) at 37°C incubation for 4 hours. Then, fragment lengths were analysed on a 2.5% agarose gel. When an *MspI* restriction site was present, the fragment of 340 base pairs (bp) was digested into two lengths: 140 bp and 200 bp. Homozygous wild type people lacked the 140 bp and 200 bp fragment (*AA*), and heterozygous people had three bands (*Aa*); homozygous rare allele people lacked the large parent band and had the smaller bands (*aa*).

STATISTICAL ANALYSES

The distribution of demographic data by genotype (*AA* and *Aa* *v* *aa*) was examined with χ^2 statistics. Liver function profiles were categorised by genotype and work area (topside oven *v* sideoven workers). To evaluate the effect of genotype and work area on the activity of hepatic enzymes, multiple linear regression models with log transformation of liver function profiles and logistic regression models were used. Logistic regression was used to ana-

Table 1 Demographic data (n (%)) by genotype among coke oven workers during 1995 and 1996, Taiwan

	<i>AA</i> or <i>Aa</i> (n=76)	<i>aa</i> (n=12)
Age (y):		
<38	25 (33)	4 (33)
38–43	26 (34)	3 (25)
>43	25 (33)	5 (42)
Quetelet's index (kg/m^2):		
<22	20 (26)	2 (17)
22–25	31 (41)	6 (50)
>25	25 (33)	4 (33)
Nutrition history (tablet/wk):†		
≤1	48 (63)	10 (83)
>1	28 (37)	2 (17)
Viral infection:‡		
No	63 (83)	8 (67)
Yes	13 (17)	4 (33)
Alcohol consumption (g/wk):		
Never and former	52 (68)	7 (58)
≤120	12 (16)	4 (33)
>120	12 (16)	1 (8)
Smoking status (cigarettes/day):*		
Never and former	39 (51)	3 (25)
1–15	25 (33)	4 (33)
>15	12 (16)	5 (42)
Regular use of respirators:		
No	24 (32)	7 (58)
Yes	52 (68)	5 (42)

* $\chi^2=4.73$, $\text{df}=2$, $p=0.03$.

AA=homozygous wild type; *Aa*=heterozygous; *aa*=homozygous variant.

†Vitamin B complex, multiple vitamin, or tablets containing liver enzymes.

‡No viral infection: both hepatitis B antigens and antihepatitis C antibody were negative.

lyse abnormal hepatocellular pattern, when either AST or ALT were above the references (abnormal: AST >37 IU/l, ALT >39 IU/l), and abnormal hepatobiliary pattern, when any of AST, ALT, GGT, ALP, or BIL were above the reference values (abnormal: GGT >54 IU/l, ALP >240 IU/l, or BIL >1.2 mg/dl).¹¹

In regressions, core models were initially established with potential confounders suggested by the previous study.¹¹ Then, genotype was forced into the models. Covariates in the models included age, Quetelet's index, viral infection, alcohol consumption, and work area for multiple regression and Quetelet's index, nutrition history, alcohol consumption, and work area for logistic regression.¹¹ The final models included the interaction factors between genotype and work area, with *AA* and *Aa* sideoven workers as the reference group. For regression models, the estimated percentage changes were calculated by taking the exponentials of the regression coefficients, subtracting 1, and multiplying the results by 100 in multiple regression models. For example, the regression coefficient of $\ln(\text{AST})$ in the topside oven workers with the *AA* and *Aa* group was estimated to be 0.154 units higher than that in the sideoven workers with *AA* and *Aa* in a crude analysis. Thus, the percentage changes on the AST were estimated to be $(\exp(0.154)-1) \times 100 = 17\%$. Confidence intervals (95% CI) were similarly converted to percentage changes. Trend tests were used to test the liver enzyme differences in decreasing order as follows: topside oven workers with the *aa* trait, sideoven workers with the *aa* trait, topside oven workers with the *AA* and *Aa* traits, and sideoven workers with the *AA* and *Aa* traits.

Table 2 Liver function profiles by genotype and work area among coke oven workers

	<i>AA</i> or <i>Aa</i>				<i>aa</i>			
	<i>Sideoven workers</i> (n=58)		<i>Topside oven workers</i> (n=18)		<i>Sideoven workers</i> (n=7)		<i>Topside oven workers</i> (n=5)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
AST	24 (7)	23 (12–43)	27 (6)	26 (19–44)	30 (14)	31 (17–57)	39 (20)	32 (21–70)
ALT	27 (14)	22 (8–66)	36 (23)	27 (15–112)	41 (20)	30 (23–77)	49 (40)	40 (14–113)
GGT	33 (25)	23 (10–124)	63 (127)	26 (13–559)	46 (24)	39 (27–95)	142 (218)	49 (36–532)
ALP	157 (47)	155 (72–354)	146 (26)	142 (116–202)	156 (33)	145 (111–202)	193 (69)	184 (108–301)
BIL	0.8 (0.3)	0.8 (0.3–1.8)	0.8 (0.3)	0.7 (0.5–1.3)	0.9 (0.2)	0.8 (0.6–1.3)	0.7 (0.1)	0.7 (0.6–0.8)
Abnormal hepatocellular pattern (n (%))*	11 (19)		6 (33)		3 (43)		3 (60)	
Abnormal hepatobiliary pattern (n (%))†	21 (36)		9 (50)		3 (43)		4 (80)	

*Abnormal hepatocellular pattern: either AST >37 or ALT >39.

†Abnormal hepatobiliary pattern: any of AST >37, ALT >39, GGT >54, ALP >240, or BIL >1.2.

AST (IU/l)=aspartate aminotransferase; ALT (IU/l)=alanine aminotransferase; GGT (IU/l)= γ -glutamyl transferase; ALP (IU/l)=alkaline phosphatase; BIL (mg/dl)=total bilirubin. Other abbreviations as in table 1.

Results

We first investigated the effect of various *CYP1A1 MspI* genotypes on the activity of hepatic enzymes. The heterozygous variant (*Aa*) and homozygous wild type (*AA*) were similar in having no effect in hepatic enzyme activities. Therefore, we combined the wild type and heterozygous variant for the remaining analysis.

Table 1 shows the distribution of the demographic data and other potential confounders categorised by genotype. Except for a higher prevalence of heavy smokers (>15 cigarettes/day) in the group with homozygous variant alleles (*aa*) than the combined alleles (*AA* and *Aa*) ($\chi^2=4.73$; $df=2$; $p=0.03$), other variables were not significantly different in these two groups.

Categorised by work area and genotype, five of 23 (22%) topside oven workers and seven of 65 (11%) sideoven workers, have the *CYP1A1 MspI* homozygous variant genotype (*aa*). Mean, median, and range of liver function profiles and frequency of abnormal liver patterns are presented in table 2 and figure. A positive trend was evident for AST, ALT, and GGT in decreasing order from topside oven workers with the *aa* trait, sideoven workers with the *aa* trait, topside oven workers with the *AA* and *Aa* traits to sideoven workers with *AA* and *Aa* traits (figure).

In the regression models, we used sideoven workers with the combined wild type and heterozygous variant (*AA* and *Aa*) as the reference group. We found that topside oven workers with the *AA* and *Aa* traits had mean AST and ALT activities that were 21% and 46% higher (95% CI 4% to 42% and 12% to 91%, respectively) than the reference group after controlling for age, Quetelet's index, viral infection, and alcohol consumption (table 3). Also, topside oven workers with the homozygous variant trait (*aa*) had mean AST, ALT, and GGT activities that were 59%, 68%, and 157% higher (95% CI 21% to 109%, 6% to 168%, and 39% to 374%, respectively) than the reference group after controlling for covariates. The results were similar even after further adjustment for nutritional history, smoking, and regular use of respirators (data not shown).

Selected liver function profiles categorised by genotype and work area among 88 coke oven workers (abbreviations are defined in tables 1 and 2). *After adjustment for age, Quetelet's index, viral infection, and alcohol consumption.

Table 3 Relation of selected liver function profiles in serum samples (natural log transformed data) with genotype and work area among 88 coke oven workers in multiple linear regression models (sideoven workers with *AA* or *Aa* were the reference group)

Dependent variables	Crude analyses		Adjusted analyses*	
	Changes (%)	95% CI	Changes (%)	95% CI
AST:				
Sideoven workers with <i>AA</i> or <i>Aa</i>	0		0	
Topside oven workers with <i>AA</i> or <i>Aa</i>	17	(0 to 36)	21	(4 to 42)
Sideoven workers with <i>aa</i>	24	(-2 to 56)	20	(-6 to 54)
Topside oven workers with <i>aa</i>	56	(19 to 104)	59	(21 to 109)
ALT:				
Sideoven workers with <i>AA</i> or <i>Aa</i>	0		0	
Topside oven workers with <i>AA</i> or <i>Aa</i>	34	(2 to 77)	46	(12 to 91)
Sideoven workers with <i>aa</i>	58	(5 to 138)	46	(-4 to 121)
Topside oven workers with <i>aa</i>	60	(-1 to 158)	68	(6 to 168)
GGT:				
Sideoven workers with <i>AA</i> or <i>Aa</i>	0		0	
Topside oven workers with <i>AA</i> or <i>Aa</i>	20	(-17 to 74)	18	(-17 to 68)
Sideoven workers with <i>aa</i>	53	(-11 to 164)	45	(-17 to 152)
Topside oven workers with <i>aa</i>	168	(42 to 406)	157	(39 to 374)

Abbreviations as in tables 1 and 2.

*Adjusting for age, Quetelet's index to viral infection, and alcohol consumption as described in table 1.

However, these associations were not found for ALP or BIL.

The prevalence of an abnormal hepatocellular pattern was more common in topside oven workers with the *aa* trait than in the sideoven workers with the *AA* and *Aa* traits (adjusted odds ratio (OR) 9.9, 95% CI 1.2 to 82.3) after adjustment for Quetelet's index, nutritional history, and alcohol consumption. This significant result remained after further adjustment for age, viral infection, smoking, and regular use of respirators (adjusted OR 19.6, 95% CI 1.5 to 253.8). Topside oven workers with the *aa* trait had an increased prevalence of an abnormal hepatobiliary pattern (adjusted OR 9.0, 95% CI 0.9 to 93.7) after adjusting for Quetelet's index, nutritional history, and alcohol consumption, although this association was not significant. Also, the prevalence of an abnormal hepatocellular pattern was more common in the topside oven workers with the *AA* and *Aa* traits and sideoven workers with the *aa* trait than in the sideoven workers with the *AA* and *Aa* traits both in the crude and adjusted analyses, although these differences did not reach significance (table 4).

Of the other predictor variables, the most predictive of the liver function profiles included Quetelet's index and alcohol consumption. The results were similar in the previous analyses.¹¹ Quetelet's index was most significantly associated with ALT and GGT activities (for ALT 22–25 v <22: percentage changes 10%, 95% CI -16% to 43%; >25 v <22: percentage changes 50%, 95% CI 13% to 98%; for GGT 22–25 v <22: percentage changes 22%, 95% CI -14% to 74%; >25 v <22: percentage changes 72%, 95% CI 19% to

149%). Current drinkers of >120 g/week had GGT activities that were 59% higher (95% CI 6% to 139%) than those of never and former drinkers, whereas current drinkers of <120 g/week had GGT activities that were 44% higher (95% CI -2% to 111%) than those of never and former drinkers after controlling for other confounders.

Discussion

Our earlier two studies have suggested that heavy exposure to coke oven emissions has an adverse effect on the liver.^{11 12} In this study, we also found that the *CYP1A1* *MspI* polymorphism may have a modulating effect on the activities of hepatic enzymes in coke oven workers. Topside oven workers with the homozygous variant trait (*aa*) had higher AST, ALT, and GGT activities than those in the sideoven workers with the combined wild type and heterozygous variant (*AA* and *Aa*). Similar results were also found in the prevalence of an abnormal hepatocellular pattern. We also found that topside oven workers with *AA* and *Aa* had significantly increased mean AST and ALT compared with the sideoven workers with *AA* and *Aa* (table 3). Although the prevalence of an abnormal hepatocellular pattern was more common in the topside oven workers with *AA* and *Aa* than in the sideoven workers with *AA* and *Aa*, it did not reach significance (table 4). This may be due to the small sample size of this study.

Coke oven emissions contain a large amount of organic compounds, particularly PAHs, some of which are potentially hepatotoxic in both humans and animals.^{2 14 15} The compounds are originally lipophilic forms, which

Table 4 Dose-response relation between abnormal liver patterns and interaction of genotype and work area in 88 coke oven workers (sideoven workers with *AA* or *Aa* were the reference group)

Status	Hepatocellular pattern		Crude odds ratio		Adjusted odds ratio*	
	Normal	Abnormal	95% CI		95% CI	
Sideoven workers with <i>AA</i> or <i>Aa</i>	47	11	1.0	1.0		
Topside oven workers with <i>AA</i> or <i>Aa</i>	12	6	2.1	(0.7 to 6.9)	3.0	(0.8 to 10.9)
Sideoven workers with <i>aa</i>	4	3	3.2	(0.6 to 16.4)	2.9	(0.5 to 17.1)
Topside oven workers with <i>aa</i>	2	3	6.4	(1.0 to 43.1)	9.9	(1.2 to 82.3)

Abbreviations as in tables 1 and 2.

*Adjusting for Quetelet's index, alcohol consumption, and nutrition history.

are poorly excreted by the kidneys. The liver plays an important part in transforming them into hydrophilic forms for excretion.⁶ Most of these compounds are not primarily toxic to the liver. However, their intermediate metabolites may result in hepatic injury because of bioactivation by different P-450 enzymes in the liver.⁶

A P-450 enzyme with aryl hydrocarbon hydroxylase (AHH) activity, CYP1A1, catalyses the oxygenation of PAHs. Kiyohara *et al* examined the relation between AHH inducibility (3-methylcholanthrene (MC) induced AHH activity/non-induced AHH activity) and the frequency of *CYP1A1 MspI* in peripheral lymphocytes in 84 healthy Japanese male subjects *in vitro*.¹⁶ They found that age adjusted AHH inducibility (mean (SEM)) of the wild type, heterozygous, and homozygous variants of the *CYP1A1 MspI* gene was 4.89 (0.36), 4.82 (0.29), and 13.61 (1.44), respectively, and the homozygous variants had significantly higher AHH inducibility than the combined wild type and heterozygous subjects. By contrast, Crofts *et al* did not find similar results among 51 healthy subjects including 22 Asian, 23 white, and six African-American people.¹⁷ These data may indicate interethnic differences in the function of *CYP1A1* polymorphisms. Hence, caution is warranted in extrapolating the association of genetic polymorphisms to the occurrence of a particular form of disease from one ethnic group to another.¹⁸ Although several groups have reported that the *CYP1A1 MspI* homozygous variant genotype was significantly associated with lung cancer in Japanese populations,^{7,8} to our knowledge, there are no published studies on the effect of this polymorphism on liver function in humans who are heavily exposed to PAHs. Our results need to be extended and confirmed by a mechanistic explanation of this polymorphism on the liver *in vitro* and *in vivo*.

Our earlier study found that AST and ALT activities were increased 26% (95% CI 9% to 46%) and 45% (95% CI 14% to 86%), respectively, among 23 topside oven workers compared with 65 sideoven workers after controlling for appropriate confounders.¹¹ In the current study, the results were similar in that AST and ALT activities were increased 21% (95% CI 4% to 42%) and 46% (95% CI 12% to 91%), respectively, among 18 topside oven workers with the combined wild type and heterozygous variant compared with 58 sideoven workers with the combined genotypes after controlling for the same confounders. Both results support our hypothesis that heavy exposure to coke oven emissions results in increased serum activities of hepatic aminotransferases in coke oven workers.

We conclude that current heavy exposure to coke oven emissions can affect serum aminotransferase activities among topside oven workers. These adverse hepatic effects may be modified by the *CYP1A1 MspI* genotype. Topside oven workers with the homozygous variant have the highest serum activities of hepatic enzymes. Given the limited number of subjects in this study, a large population should be examined to assess the effects of both phase I and phase II metabolic gene polymorphisms on the liver.

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- Schulte KA, Larsen DJ, Hornung RW, *et al*. Analytical methods used in a study of coke oven effluent. *Am Ind Hyg Assoc J* 1975;36:131-9.
- World Health Organization. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: polynuclear aromatic compounds, part 3, Industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding*. Lyon: IARC, 1984;34:101-31.
- Bieniek G, Cisowska G, Luisak T, *et al*. Evaluation of exposure to benzene and naphthalene in coke plant workers. *Medycyna Pracy* 1993;44:579-86.
- Boyland E, Sims P. Metabolism of polycyclic compounds—the metabolism of pyrene in rats and rabbits. *Biochem J* 1964;90:391-8.
- Jongeneelen FJ, Anzion RBM, Henderson PT. Determination of hydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. *J Chromat* 1987;413:227-32.
- Sturgill MG, Lambert GH. Xenobiotic-induced hepatotoxicity: mechanisms of liver injury and methods of monitoring hepatic function. *Clin Chem* 1997;43:1512-26.
- Kawarjiri K, Nakachi K, Imai K, *et al*. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P-4501A1 gene. *FEBS Lett* 1990;263:131-3.
- Nakachi K, Imai K, Hayashi S, *et al*. Genetic susceptibility to squamous cell carcinoma of the lung in relation to cigarette smoking dose. *Cancer Res* 1991;51:5177-80.
- Hayashi S, Watanabe J, Kawarjiri K. High susceptibility to lung cancer analyzed in terms of combined genotype P-4501A1 and Mu-class glutathione-S-transferase genes. *Jpn J Cancer Res* 1992;83:866-70.
- Xu X, Kelsey KT, Wiencke JK, *et al*. Cytochrome P-450 CYP1A1 *MspI* polymorphism and lung cancer susceptibility. *Cancer Epidemiol Biomark Prev* 1996;5:687-92.
- Wu MT, Mao IF, Wypij D, *et al*. Serum liver function profiles in coking workers. *Am J Ind Med* 1997;32:478-86.
- Wu MT, Christiani DC. Elevated serum hepatic aminotransferase in coking workers after exposure to coke oven emissions. *J Occup Environ Med* 1998;40:303-5.
- Hayashi SI, Watanabe J, Nakachi K, *et al*. Genetic linkage of lung cancer-associated *MspI* polymorphisms with amino acid replacement in the heme binding region of the human cytochrome P-4501A1 gene. *J Biochem* 1991;110:407-11.
- Yoshikawa T, Ruhr LP, Flory W, *et al*. Toxicity of polycyclic aromatic hydrocarbons: I. Effects of phenanthrene, pyrene, and their ozonized products on blood chemistry in rats. *Toxicol Appl Pharmacol* 1985;79:218-26.
- Yoshikawa T, Flory W, Ruhr LP, *et al*. Toxicity of polycyclic aromatic hydrocarbons: II. Effects of NO₂-nitrated phenanthrene and pyrene on blood chemistry in rats. *Vet Hum Toxicol* 1987;29:25-30.
- Kiyohara C, Hirohata T, Inutsuka S. The relationship between aryl hydrocarbon hydroxylase and polymorphisms of the CYP1A1 gene. *Jpn J Cancer Res* 1996;87:18-24.
- Crofts F, Taioli E, Trachman J, *et al*. Functional significance of different human CYP1A1 genotypes. *Carcinogenesis* 1994;15:2961-3.
- Ingelman-Sundberg M, Johansson I, Persson I, *et al*. Genetic polymorphism of cytochromes P-450: interethnic differences and relationship to incidence of lung cancer. *Pharmacogenetics* 1992;2:264-71.