



CYP1A1 and GSTM1 polymorphisms in relation to lung cancer risk in Chinese women

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Received 28 April 2004; received in revised form 24 June 2004; accepted 25 June 2004

Abstract

We examined CYP1A1 (I462V) and GSTM1 null polymorphisms in 200 female cases and 144 female controls selected from a population-based case-control study of lung cancer conducted in northeast China, where the rates of lung cancer among Chinese women are especially high. The CYP1A1 codon 462 point mutation in exon 7 (I462V) causes an Ile-Val substitution near the heme binding site. This mutation correlates with inducibility of aryl hydrocarbon hydrolase (AHH) activity, which activates polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke and in indoor air pollution from coal-burning stoves, a risk factor for lung cancer in this study population. We found that the CYP1A1 I462V genotype (combined ile/val and val/val) was significantly associated with lung cancer risk. The odds ratio (OR) was 2.5 (95% confidence interval [CI], 1.55–4.03) after adjustment for significant risk factors such as age, ever smoking status, family history of cancer, and eye irritation when cooking. The association was more pronounced among non-smokers (OR = 3.67; 95% CI, 1.85–7.28) than among smokers (OR = 1.74, 95% CI, 0.85–3.54). In contrast, we did not find a significant association with the GSTM1 null genotype. In summary, our case-control study of lung cancer among women in northeast China revealed an elevated risk associated with the CYP1A1 I462V genotype, but no interaction with smoking or indoor air pollution was found.

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Keywords: CYP1A1 I462V; GSTM1; Lung cancer; Chinese women

1. Introduction

The rate of lung cancer among Chinese women, particularly in northeast China, is among the highest in the world [1]. Previous studies have identified tobacco smoking, exposure to cooking oil fumes [2],

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and indoor air pollution from burning coal [1,3] as risk factors for lung cancer among Chinese women. In view of the dominant effect of environmental factors on lung cancer risk, a mechanistic consideration prompted a search for susceptibility genes in this population. Of particular interest are the reported associations between lung cancer risk and the polymorphisms of cytochrome P450 1A1 (CYP1A1) and glutathione S-transferase M1 (GSTM1), which, respectively, activate and detoxify chemical carcinogens, including those found in products of coal combustion and tobacco smoke [4–6]. In particular, the CYP1A1 gene polymorphism plays a central role in the metabolic activation of procarcinogens, including polycyclic aromatic hydrocarbons (PAHs) and aromatic amines, and is expressed in the human lung [7,8].

Several polymorphisms have been identified at the CYP1A1 locus, including a MspI polymorphism and a point mutation at codon 462 in exon 7 of CYP1A1, which results in a substitution of valine for isoleucine near the heme binding site [9]. In meta-analyses, the MspI polymorphism of CYP1A1, which is in tight linkage disequilibrium with CYP1A1 I462V, has been related to lung cancer risk in Caucasians but not in Asians [10]. On the other hand, the CYP1A1 I462V polymorphism is rare in Caucasians but more common in Japanese populations, in whom an association with lung cancer has been reported [11–13].

Little is known about the relation of CYP1A1 polymorphisms to the risk of lung cancer in Chinese populations, especially among females. A significant association between the I462V polymorphism and smoking-related lung cancer risk was reported in a case-control study in China [14]. However, a cohort study in Chinese men found no overall association, although a subset analysis suggested an effect at lower levels of cigarette smoking among subjects with the GSTM1 null genotype [15]. In another case-control study in a Chinese population, there was a synergistic effect between CYP1A1 I462V and GSTM1-null on lung cancer risk [16]. GSTM1 is a family member of the glutathione S-transferases (GSTs), which conjugate electrophilic compounds with reduced glutathione, so that homozygous deletion of the GSTM1 gene could increase cancer risk by impeding the elimination of tobacco

carcinogens [17]. Recent meta-analyses suggest that the GSTM1 null genotype marginally contributes to lung cancer risk [18,19], but an effect in Chinese populations has not been well studied.

We therefore investigated the relation between CYP1A1 and GSTM1 polymorphisms and lung cancer risk based on a case-control study of women in Shenyang, China, where the elevated rates were linked to smoking habits and to indoor air pollution from coal-burning stoves [1,20]. To the extent permitted by the sample size, we looked for possible effect modification of these exposures by CYP1A1 genotypes.

2. Subjects and methods

2.1. Study population

All cases of incident primary lung cancer diagnosed between September 1985 and September 1987 among residents of urban Shenyang aged 30–69 years were invited to participate. In the original case-control study, 1249 lung cancer cases aged 30–69 (729 males, 520 females) were enrolled [20]. A total of 1345 controls (788 men, 577 women) were randomly selected from population rosters available for each of the nearly 1500 neighborhood committees in Shenyang. Between March and August, 1986, a series of 218 female lung cancer cases were selected for blood collection, along with contemporaneously identified controls. Fifty-seven samples were eliminated because lung cancer could not be confirmed or blood was hemolyzed. Additional cases were identified between January and March, 1986, resulting in 200 confirmed cases and 144 controls with available DNA. The age distribution of the controls closely matched that of the cases, and the median age among women in the sub-study was 56.

2.2. Questionnaire

A structured, pre-coded questionnaire was administered by trained interviewers who conducted personal interviews with the participants in their homes or work sites or in the hospital/clinic. The interview included information on demographic factors, active and passive smoke exposure, lifetime

residential and occupational histories, diet and cooking practices, personal history of non-malignant lung diseases, history of tuberculosis (TB), history of cancer in first-degree relatives, and reproductive factors. Questions on smoking included the amount and types of tobacco products smoked, age when smoking started, and, for ex-smokers, age when smoking stopped. The amount and duration of passive smoking at work and at home were also assessed. The subjects were questioned in detail about heating and cooking practices, including methods for heating and cooking and types of fuels used. Several questions were asked about 'Kang', brick beds used in the northeastern part of China, which are heated usually by pipes connected to coal-burning stoves. In addition, information on outcome of each pregnancy, age at menarche, and age at menopause was collected. As a quality-control measure, interviews were recorded for review by a field supervisor.

2.3. Genotyping

Phenol–chloroform DNA extraction from whole blood was performed according to the standard procedures. The TaqMan assay was used for detecting CYP1A1 I462V and the Primer Express software package was used for primer design. Briefly, oligonucleotide probes were labeled with two different fluorescent dyes to discriminate between the two alleles. Each of two of oligonucleotide probes anneals perfectly with one allele at the site of the SNP. During the reaction, the Taq enzyme recognizes the perfect match and cleaves the dye molecule off of the probe, releasing it into solution. The mismatched probe remains quenched by the quencher dye attached to the other end of the probe. The increased level of fluorescent emission of each dye indicates the corresponding homozygous genotype. Heterozygous individuals have increased emission of both dyes. Reactions with no template and with DNA of known genotype were run to control for contamination and calibrate signal processing for genotype determination by the software. SNP assays were verified for concordance with Mendelian inheritance using PED-CHECK in 489 individuals from 40 CEPH families and assays were performed in triplicate to insure reliability. The assay technique was highly reliable,

with <0.2% of Mendelian inconsistent genotypes. To eliminate the chance of human data entry errors, all TaqMan output was processed electronically for downloading into analytical programs.

For GSTM1, a PCR-based test was performed to classify those subjects according to whether or not they had a deletion of the gene.

2.4. Statistical analysis

Data were analyzed using SAS software version 8.0. The genotype frequency of CYP1A1 showed no significant deviation from Hardy Weinberg equilibrium (HWE) among controls, according to Pearson's χ^2 test with 1 degree of freedom. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate unconditional logistic regression analyses to estimate the associations between lung cancer and CYP1A1 I462V and GSTM1 polymorphisms. Logistic regression gave similar ORs for heterozygous and null genotypes, except that the 95% CIs for null genotypes were wider due to the small number of subjects with the null genotype. Heterozygous and null genotypes were pooled in the later analysis. ORs for the combined genotypes of GSTM1 and CYP1A1 were calculated by taking the risk of the combined CYP1A1 Ile/Ile and GSTM1 (+) as a baseline.

Exposure variables examined in the analysis included age, education, marital status, income, cigarette smoking, family history of cancer, outdoor air pollution, and indoor air pollution from burning coals and cooking. The association between each exposure variable and lung cancer risk was assessed by univariate regression. Cigarette smoking was analyzed separately by ever smoking status, total years of smoking, numbers of cigarettes smoked per day, and total pack-years smoked. ORs obtained by using each individual smoking variable and combined variables resembled one another, so we selected only ever smoking in the final model. All continuous variables were entered into the model separately as continuous and as categorical variables. We included only categorical variables in the final model.

Multivariate logistic regression analyses were performed to compute ORs for CYP1A1, adjusted for age, ever smoking status, family history of cancer, and eye irritation during cooking. The interaction

between CYP1A1 and these risk factors was assessed by adding an interaction term to the regression model and also by comparing ORs stratified by smoking status and the CYP1A1 genotype.

2.5. Calculation of FPRP

Recently, Wacholder et al. proposed a measure called false-positive report probability (FPRP)-based, based on the prior probability of the hypothesis, the power of the study, as well as the *P* value, to assess the likelihood that a molecular epidemiological finding is a false positive [21]. We calculated FPRP for our data on CYP1A1 variants and lung cancer risk. Since CYP1A1 plays central roles in the activation of carcinogens involved in tobacco smoke [7,8] and the association between the genetic variants of these enzymes and lung cancer risk has been indicated in a number of studies [11–13], we assigned a relatively high prior probability range (0.01–0.1). FPRP values were calculated using the estimated prior probability range, the statistical power to detect an OR of 1.5, and observed ORs and 95% confident intervals, based on an FPRP calculation spreadsheet provided in that paper [21].

3. Results

As shown in Table 1, significantly more cases than controls in the genotyping study were cigarette smokers ($P < 0.001$, OR = 2.57, 95% CI, 1.63–4.05). The cases had significantly greater pack-years smoked, total years of smoking, and cigarettes smoked per day compared to controls. Table 1 also shows the risks associated with other factors using univariate logistic regression analysis. No significant case-control differences were seen in the distribution by age, education level, marriage status, and income. Significant increases in lung cancer risk were found in subjects with a positive family history for lung cancer (OR = 2.77, 95% CI, 1.22–6.27), more than two meals cooked per day (OR = 3.53, 95% CI, 1.52–8.20), and frequent eye irritation during cooking (OR = 2.31, 95% CI, 1.10–4.86). However, no significant effects were found in this subset analysis for other factors, including a history of lung disease or TB and indoor air pollution from use of coal-burning stoves.

There were no trends in risk with reproductive history (e.g. age at menarche or menopause), except for a two-fold increase in risk associated with high number (> 5) of lifetime pregnancies (OR = 2.05, 95% CI, 1.07–3.94), which is consistent with another study of lung cancer in Shenyang on a different study population [22].

Table 2 shows genotype frequencies and crude ORs for the CYP1A1 I462V and GSTM1 null genotypes, separately and combined, in patients and controls. A significant increase in the risk of lung cancer was found for carriers of the CYP1A1 I462V genotype (OR = 2.53; 95% CI, 1.62–3.97). The elevated risk associated with CYP1A1 I462V remained significant after adjustment for age, smoking, family history of cancer, and eye irritation during cooking (OR = 2.50, 95% CI, 1.55–4.03). Little evidence for interaction was found between these risk factors and CYP1A1 I462V. However, the gene effect was marginally stronger among non-smokers (OR = 3.67, 95% CI, 1.85–7.28) than among smokers (OR = 1.74, 95% CI, 0.85–3.54), although the test of multiplicative interaction was not significant ($P = 0.13$).

The GSTM1 null genotype was not significantly associated with lung cancer risk (OR = 1.18, 95% CI, 0.76–1.84), in either never smoking group (OR = 1.05, 95% CI, 0.56–2.00) or ever smoking group (OR = 1.61, 95% CI, 0.80–3.25), and no evidence of interaction was found between GSTM1 and CYP1A1. Individuals with a combined genotype of CYP1A1 I462V and GSTM1 null did not show significantly high risk of lung cancer (adjusted OR = 3.20, 95% CI, 1.65–6.21) compared to those with CYP1A1 I462V genotype alone (Table 2).

The FPRP values [21] for the adjusted OR for CYP1A1 I462V were 0.078 and 0.482 for prior probabilities of 0.1 and 0.01, respectively, for detecting an OR of 1.5.

4. Discussion

Lung cancer is the leading cause of cancer death in China. In the last decade the incidence and mortality rates of lung cancer in China have increased sharply and consistently [23]. Tobacco smoking is the major cause of lung cancer, responsible for over 50% of lung cancer deaths in China [23]. However, the incidence

Table 1
Distribution of subject characteristics in lung cancer patients and controls

Variables	Cases (n=200) n(%)	Controls (n=144) n(%)	$P(\chi^2)^a$	Crude ORs (95% CI)
Age			0.7313	
≤50	41(20.5)	27(18.8)		1.00
>50	159(79.5)	117(81.2)		0.91(0.53–1.56)
Education level			0.5916	
No formal school	99(49.5)	65(45.1)		1.00
Primary school +	101(50.5)	79(54.9)		0.84(0.55–1.29)
Marital status			0.4378	
Married	167(83.5)	126(87.5)		1.00
Other	33(16.5)	18(12.5)		1.38(0.75–2.57)
Monthly income			0.4693	
≤¥125	94(47.0)	72(50.0)		1.00
>¥125	106(53.0)	72(50.0)		1.13(0.73–1.73)
Ever smoked cigarettes			0.0009	
No	89(44.5)	90(62.5)		1.00
Yes	111(55.5)	54(37.5)		2.57(1.63–4.05)
Total years of smoking			0.0001	
0	89(44.5)	90(62.5)		1.00
0 < years ≤ 30	26(13.0)	26(18.0)		1.01(0.55–1.88)
30 < years ≤ 45	67(33.5)	23(16.0)		2.95(1.69–5.14)
> 45	18(9.0)	5(3.5)		3.64(1.30–10.23)
Cigarettes smoked per day			0.0016	
0	89(56.7)	90(69.8)		1.00
≤ 8	20(12.7)	20(15.5)		0.80(0.41–1.56)
> 8	48(30.6)	19(14.7)		2.01(1.13.62)
Total pack years smoked			0.0004	
0	89(56.7)	90(69.8)		1.00
≤ 10	16(10.2)	18(13.9)		0.71(0.34–1.45)
10 < pack years ≤ 20	18(11.5)	14(10.9)		1.02(0.49–2.15)
> 20	34(21.6)	7(5.4)		3.86(1.65–9.07)
Eye irritation during cooking			0.0252	
Rarely	120(62.2)	109(75.7)		1.00
Sometimes	45(23.3)	24(16.7)		1.70(0.97–2.98)
Frequently	28(14.5)	11(7.6)		2.31(1.10–4.86)
# of meals cooked per day			0.001	
≤ 1	86(43.9)	90(62.5)		1.00
1 < meals ≤ 2	83(42.3)	46(31.9)		1.89(1.19–3.01)
> 2	27(13.8)	8(5.6)		3.53(1.52–8.20)
Family history of cancer			0.0093	
No	172(86.0)	136(94.4)		1.00
Yes	28(14.0)	8(5.6)		2.77(1.22–6.27)
History of lung disease			0.1288	
No	141(70.5)	112(77.8)		1.00
Yes	59(29.5)	32(22.2)		1.47(0.89–2.41)
Previous TB			0.8889	
No	176(88.0)	126(87.5)		1.00
Yes	24(12.0)	18(12.5)		0.95(0.50–1.83)

(continued on next page)

Table 1 (continued)

Variables	Cases (<i>n</i> =200) <i>n</i> (%)	Controls (<i>n</i> =144) <i>n</i> (%)	<i>P</i> (χ^2) ^a	Crude ORs (95% CI)
Age at menarche			0.6693	
<16	76(38.0)	58(40.3)		1.00
≥16	124(62.0)	86(59.7)		1.10(0.71–1.71)
Age at menopause			0.9621	
<49	68(44.4)	51(44.7)		1.00
≥49	85(55.6)	63(55.3)		1.01(0.62–1.65)
Number of pregnancies			0.094	
≤2	23(11.5)	28(19.4)		1.00
2<pregnancies ≤5	91(45.5)	65(45.1)		1.70(0.90–3.22)
>5	86(43.0)	51(35.4)		2.05(1.07–3.94)

^a Pearson's χ^2 statistic for the test of equality of proportions between cases and controls.

of lung cancer among Chinese women is high even among non-smokers, due at least partly to cooking oil fumes from high-temperature wok cooking [2], and to indoor air pollution from coal-burning stoves in poorly ventilated homes [1,3]. To evaluate the role of genetic susceptibility to lung cancer, we examined the effects of the CYP1A1 I462V polymorphism and GSTM1 null genotype, which have been previously related to lung cancer risk [5,19,24,25].

Higher frequency of the valine allele in Japanese may explain the more consistent evidence of an association between CYP1A1 I462V and lung cancer in the Japanese population [5,11–13,26] than in Caucasian or African–American populations [27]. The frequency of the valine allele in the Chinese is intermediate between the frequencies in Japanese

and non-Asian populations [15]. Results are inconsistent in the few studies evaluating the role of CYP1A1 I462V polymorphism in lung cancer among the Chinese [14–16].

In our study population, the CYP1A1 I462V polymorphism was associated with a significantly increased risk of lung cancer, consistent with the findings in Japanese populations. In contrast to some of the other studies, we did not observe a significant effect of the GSTM1 null genotype on lung cancer risk, with or without stratification by smoking status, or an interactive effect with CYP1A1 I462V. However, the slightly increased risk for the GSTM1 null genotype fell into the range indicated by meta-analyses [24,28,29], so that a weak effect on lung cancer risk is possible.

Table 2

Genotype frequencies and crude ORs for CYP1A1 I462V and GSTM1 in lung cancer patients and controls

Variables	Cases (<i>n</i> =200) <i>n</i> (%)	Controls (<i>n</i> =144) <i>n</i> (%)	<i>P</i> (χ^2) ^a	Crude ORs (95% CI)
CYP1A1 I462V			0.0002	
Ile/Ile	90(45.7)	98(68.1)		1.00
Ile/Val	96(48.7)	39(27.1)		2.68(1.68–4.29)
Val/Val	11(5.6)	7(4.8)		1.71(0.64–4.61)
(Ile/Val + Val/Val)	107(54.3)	46(31.9)	<0.0001	2.53(1.62–3.97)
GSTM1			0.4601	
(+)	78(41.9)	64(46.0)		1.00
(–)	108(58.1)	75(54.0)		1.18(0.76–1.84)
CYP1A1/GSTM1			0.002	
Ile/Ile and (+)	29(15.7)	41(29.5)		1.00
(Ile/Val)/Val or (–)	102(55.1)	75(54.0)		1.86(1.08–3.18)
(Ile/Val)/Val and (–)	54(29.2)	23(16.5)		3.20(1.65–6.21)

^a χ^2 statistic with 2 degrees of freedom for the test of equality of proportions between cases and controls.

The risk associated with the CYP1A1 I462V genotype in our study was greater among non-smokers than ever smokers, in accord with evidence suggesting that the effect of this genotype is more pronounced at low levels of smoking [15,18,29]. From the available data, we could not determine whether the genetic susceptibility mechanisms are specific to carcinogenic substrates resulting from the use of coal-burning stoves in this study population.

We recognize that many reports of significant associations seem to be false positives. A major reason for these false-positive findings is the strategy of declaring statistical significance based on a *P* value alone [21]. Recently, Wacholder et al. [21] proposed a new FPRP-based approach that integrates the prior probability of the hypothesis, the power of the study, and the tolerance for a false-positive decision, as well as the *P* value, into a decision of whether a molecular epidemiological finding is noteworthy. We therefore calculated the FPRP [21] to assess the probability that our CYP1A1 finding is a false positive. For a realistic prior probability of 0.1, the FPRP value analysis suggests that there is only a 7.8% chance that the statistically significant finding of CYP1A1 I462V and lung cancer risk represents a false-positive association and thus suggests that there is strong evidence that the finding is a true positive. We also show that for a very conservative prior probability of 0.01 for CYP1A1 I462V, the FPRP value was below 50%, suggesting that there is a 48% probability of representing a false-positive association, is still quite low.

In summary, our population-based case-control study of lung cancer among women in a high-incidence population in northeast China revealed an elevated risk associated with the CYP1A1 I462V polymorphism, but an interaction with major environmental risk factors (smoking, indoor pollution from coal-burning stoves) could not be demonstrated.

References

- [1] Z.Y. Xu, W.J. Blot, H.P. Xiao, A. Wu, Y.P. Feng, B.J. Stone, et al., Smoking, air pollution, and the high rates of lung cancer in Shenyang, China, *J. Natl. Cancer Inst.* 81 (1989) 1800–1806.
- [2] Y.T. Gao, W.J. Blot, W. Zheng, A.G. Ershow, C.W. Hsu, L.I. Levin, et al., Lung cancer among Chinese women, *Int. J. Cancer* 40 (1987) 604–609.
- [3] Q. Lan, R.S. Chapman, D.M. Schreinemachers, L. Tian, X. He, Household stove improvement and risk of lung cancer in Xuanwei, China, *J. Natl. Cancer Inst.* 94 (2002) 826–835.
- [4] F.J. Gonzalez, The role of carcinogen-metabolizing enzyme polymorphisms in cancer susceptibility, *Reprod. Toxicol.* 11 (1997) 397–412.
- [5] H. Bartsch, U. Nair, A. Risch, M. Rojas, H. Wikman, K. Alexandrov, Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers, *Cancer Epidemiol. Biomarkers Prev.* 9 (2000) 3–28.
- [6] J. Seidegard, W.R. Vorachek, R.W. Pero, W.R. Pearson, Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion, *Proc. Natl. Acad. Sci. USA* 85 (1988) 7293–7297.
- [7] T. Shimada, C.H. Yun, H. Yamazaki, J.C. Gautier, P.H. Beaune, F.P. Guengerich, Characterization of human lung microsomal cytochrome P-450 1A1 and its role in the oxidation of chemical carcinogens, *Mol. Pharmacol.* 41 (1992) 856–864.
- [8] S.S. Hecht, Tobacco smoke carcinogens and lung cancer, *J. Natl. Cancer Inst.* 91 (1999) 1194–1210.
- [9] S. Hayashi, J. Watanabe, K. Nakachi, K. Kawajiri, Genetic linkage of lung cancer-associated MspI polymorphisms with amino acid replacement in the heme binding region of the human cytochrome P450IA1 gene, *J. Biochem. (Tokyo)* 110 (1991) 407–411.
- [10] P. Vineis, F. Veglia, S. Benhamou, D. Butkiewicz, I. Cascorbi, M.L. Clapper, et al., CYP1A1 T3801 C polymorphism and lung cancer: a pooled analysis of 2451 cases and 3358 controls, *Int. J. Cancer* 104 (2003) 650–657.
- [11] H. Sugimura, K. Wakai, K. Genka, K. Nagura, H. Igarashi, K. Nagayama, et al., Association of Ile462Val (Exon 7) polymorphism of cytochrome P450 IA1 with lung cancer in the Asian population: further evidence from a case-control study in Okinawa, *Cancer Epidemiol. Biomarkers Prev.* 7 (1998) 413–417.
- [12] S. Hayashi, J. Watanabe, K. Kawajiri, High susceptibility to lung cancer analyzed in terms of combined genotypes of P450IA1 and Mu-class glutathione S-transferase genes, *Jpn. J. Cancer Res.* 83 (1992) 866–870.
- [13] K. Nakachi, S. Hayashi, K. Kawajiri, K. Imai, Association of cigarette smoking and CYP1A1 polymorphisms with adenocarcinoma of the lung by grades of differentiation, *Carcinogenesis* 16 (1995) 2209–2213.
- [14] N. Song, W. Tan, D. Xing, D. Lin, CYP 1A1 polymorphism and risk of lung cancer in relation to tobacco smoking: a case-control study in China, *Carcinogenesis* 22 (2001) 11–16.
- [15] S.J. London, J.M. Yuan, G.A. Coetzee, Y.T. Gao, R.K. Ross, M.C. Yu, CYP1A1 I462V genetic polymorphism and lung cancer risk in a cohort of men in Shanghai, China, *Cancer Epidemiol. Biomarkers Prev.* 9 (2000) 987–991.
- [16] S. Chen, K. Xue, L. Xu, G. Ma, J. Wu, Polymorphisms of the CYP1A1 and GSTM1 genes in relation to individual susceptibility to lung carcinoma in Chinese population, *Mutat. Res.* 458 (2001) 41–47.

- [17] B. Mannervik, U.H. Danielson, Glutathione transferases-structure and catalytic activity, *CRC Crit Rev. Biochem.* 23 (1988) 283–337.
- [18] K. Nakachi, K. Imai, S. Hayashi, K. Kawajiri, Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population, *Cancer Res.* 53 (1993) 2994–2999.
- [19] S. Zhong, A.F. Howie, B. Ketterer, J. Taylor, J.D. Hayes, G.J. Beckett, et al., Glutathione S-transferase mu locus: use of genotyping and phenotyping assays to assess association with lung cancer susceptibility, *Carcinogenesis* 12 (1991) 1533–1537.
- [20] Z.Y. Xu, W.J. Blot, G. Li, J.F. Fraumeni Jr., D.Z. Zhao, B.J. Stone, et al., Environmental determinants of lung cancer in Shenyang, China, *IARC Sci. Publ.* 1991; 460–465.
- [21] S. Wacholder, S. Chanock, M. Garcia-Closas, L. El ghormli, N. Rothman, Assessing the probability that a positive report is false: an approach for molecular epidemiology studies, *J. Natl. Cancer Inst.* 96 (2004) 434–442.
- [22] B.S. Zhou, T.J. Wang, P. Guan, J.M. Wu, Indoor air pollution and pulmonary adenocarcinoma among females: a case-control study in Shenyang, China, *Oncol. Rep.* 7 (2000) 1253–1259.
- [23] Z.M. Chen, Z. Xu, R. Collins, W.X. Li, R. Peto, Early health effects of the emerging tobacco epidemic in China. A 16-year prospective study, *J. Am. Med. Assoc.* 278 (1997) 1500–1504.
- [24] J.E. McWilliams, B.J. Sanderson, E.L. Harris, K.E. Richert-Boe, W.D. Henner, Glutathione S-transferase M1 (GSTM1) deficiency and lung cancer risk, *Cancer Epidemiol. Biomarkers Prev.* 4 (1995) 589–594.
- [25] S. Benhamou, W.J. Lee, A.K. Alexandrie, P. Boffetta, C. Bouchardy, D. Butkiewicz, et al., Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk, *Carcinogenesis* 23 (2002) 1343–1350.
- [26] A.K. Alexandrie, M.I. Sundberg, J. Seidegard, G. Tornling, A. Rannug, Genetic susceptibility to lung cancer with special emphasis on CYP1A1 and GSTM1: a study on host factors in relation to age at onset, gender and histological cancer types, *Carcinogenesis* 15 (1994) 1785–1790.
- [27] L. Le Marchand, C. Guo, S. Benhamou, C. Bouchardy, I. Cascorbi, M.L. Clapper, et al., Pooled analysis of the CYP1A1 exon 7 polymorphism and lung cancer (United States), *Cancer Causes Control* 14 (2003) 339–346.
- [28] R.C. Strange, A.A. Fryer, The glutathione S-transferases: influence of polymorphism on cancer susceptibility in: P. Vineis, N. Malats, M. Lang, A. d'Errico, N. Caporaso, J. Cuzick, P. Boffetta (Eds.), *Metabolic Polymorphisms and Susceptibility to Cancer*, IARC, Lyon, France, 1999, pp. 231–249.
- [29] R.J. Hung, P. Boffetta, J. Brockmoller, D. Butkiewicz, I. Cascorbi, M.L. Clapper, S. Garte, et al., CYP1A1 and GSTM1 genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis, *Carcinogenesis* 2003; 2475–2882.