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The effect of *CYP1A1* polymorphisms on the risk of lung cancer: a global meta-analysis based on 71 case–control studies

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The cytochrome P450 1A1 (*CYP1A1*) is a phase I enzyme involved in many oxidative reactions that has attracted considerable attention as a candidate gene for lung cancer susceptibility based on its function as a key factor required for bioactivation of carcinogenic polycyclic aromatic hydrocarbons and catechol oestrogen formation. In the past decade, the relationship between *CYP1A1* and lung cancer has been reported in various ethnic groups; however, these studies have yielded contradictory results. To investigate this inconsistency, we performed a meta-analysis of 71 studies involving a total of 30 368 subjects for the MspI and Ile-Val polymorphism of the *CYP1A1* gene to evaluate the effect of *CYP1A1* on genetic susceptibility for lung cancer. In a combined analysis, the summary per-allele odds ratios for lung cancer of the MspI and Ile-Val polymorphism were 1.19 [95% confidence interval (CI): 1.11–1.28] and 1.20 (95% CI: 1.08–1.33), respectively. Significant results were also observed using dominant or recessive genetic model. In the subgroup analysis by ethnicity, significantly increased risks were found for the MspI and Ile-Val polymorphism among East Asians in almost all genetic models. However, only marginal significant associations were detected for the MspI polymorphism among Caucasians and other population, while no significant associations were observed for the Ile-Val polymorphism in Caucasians and other population. This meta-analysis demonstrated that the MspI and Ile-Val polymorphism of *CYP1A1* is a risk factor associated with increased lung cancer susceptibility, but these associations vary in different ethnic populations.

Introduction

Lung cancer is the most common malignancy and the leading cause of cancer death world wide, with an estimated 5-year survival rate of 15% (1). Despite much investigation, the causes are not yet fully understood. Epidemiological evidence suggests that exposure to tobacco-associated carcinogens is clearly implicated in its aetiology (2). However, it has also been reported that only <20% of smokers develop lung cancer, suggesting that genetic variations and other environmental factors also play important roles in determining individual differences in lung cancer susceptibility (3,4).

The cytochrome p450 (CYP) enzymes play an important role in the metabolism of many endogenous substrates such as steroids and eicosanoids and exogenous carcinogens such as polycyclic aromatic hydrocarbons (PAHs), aromatic and heterocyclic amines that can then covalently bind to DNA forming DNA adducts, thereby initiating the carcinogenic process (5). Within the CYP system, cytochrome p450 1A1 (*CYP1A1*) is key to the metabolic activation of PAHs found in tobacco smoke and is mainly expressed in extrahepatic tissues, including the lung (6). Several important single nucleotide polymorphisms have been identified in the *CYP1A1* gene. Among them, two genetically liked polymorphisms in *CYP1A1*, the 3801T > C substitution (rs4646903) creating a MspI restriction site in the 3′ non-coding region and the 2455A > G substitution (rs1048943) resulting in an amino acid change (Ile462Val), have been wildly studied for their association with lung cancer susceptibility.

Over the past few years, considerable efforts have been devoted to exploring the relationships between the *CYP1A1* polymorphisms and lung cancer risk among various populations. However, existing studies have yielded inconsistent results. These disparate findings may be due partly to insufficient power, false-positive results and publication biases. The interpretation of these studies has been further complicated by the use of different populations or different control source. To help clarify the inconsistent findings, we therefore conducted a comprehensive meta-analysis to quantify the overall risk of *CYP1A1* polymorphisms on developing lung cancer.

Materials and methods

Search strategy and selection criteria

Eligible literatures published before the end of September 2010 were identified by a search of PUBMED, EMBASE, Web of science and China National Knowledge Infrastructure databases using combinations of the following keywords: 'cytochrome p450 1A1', 'cyp1a1', 'polymorphism' or 'variant' and 'lung cancer' or 'lung carcinoma' without restriction on language. All the searched studies were retrieved, and their references including relevant reviews were checked as well for other relevant publications.

Eligible studies had to meet all the following criteria: (i) original papers containing independent data, (ii) identification of lung cancer cases was confirmed histologically or pathologically, (iii) case–control or cohort studies and (iv) genotype distribution information in cases and controls or odds ratio (OR) with its 95% confidence interval (CI) and *P*-value. The major reasons for exclusion of studies were (i) overlapping data and (ii) case-only studies, family-based studies and review articles.

Data extraction

The following information was independently extracted from each report by two participants in the meta-analysis: the first author, publication year, ethnicity of the study population, number of cases and controls, gender, age of cases and controls, cigarette smoking status, source of control, genotyping method and

number of genotypes in cases and controls. Disagreement was resolved by discussion between authors. Where essential information was not presented in articles, every effort was made to contact the authors.

Statistical analysis

The strength of association between MspI and Ile-Val polymorphisms of *CYP1A1* and lung cancer risk was assessed by OR with the corresponding 95% CI. We first used the chi-square test to check if there was significant deviation from Hardy–Weinberg equilibrium (HWE) among the control subjects in each study. If controls of studies were found not to be in HWE, sensitivity analyses were performed with and without these studies to test the robustness of the findings. The per-allele OR of the risk allele was compared between cases and controls. Then we examined the association between risk genotype of these polymorphisms and the lung cancer susceptibility using dominant and recessive genetic models.

Heterogeneity across individual studies was calculated using the Cochran chi-square Q test followed by subsidiary analysis or by random-effects regression models with restricted maximum likelihood estimation (7–9). Random-effects and fixed-effect summary measures were calculated as inverse variance-weighted average of the log OR. The results of random-effects summary were reported in the text because it takes into account the variation between studies. In addition, we investigated potential sources of identified heterogeneity among studies by stratification according to the number of cancer cases (<300 and ≥ 300), ethnic group, source of control (population or hospital), status of HWE (yes or no) and pathological type [lung squamous carcinoma (SCC), adenocarcinoma (AC), small cell lung cancer (SCLC) and large cell lung cancer (LCLC)]. Ethnic group was defined as East Asians, Caucasians (i.e. people of European origin) and others (e.g. Indian and African–American). The Z test was used to determine the significance of the pooled OR. Gender distribution in cases and controls, genotyping method and mean age of cases and controls were analysed as covariates in meta-regression.

We assessed publication bias by using an ancillary procedure attributed to Egger *et al.* (10), which uses a linear regression approach to measure funnel plot asymmetry on the natural logarithm of the OR. The larger the deviation from the funnel curve of each study the more pronounced the asymmetry. The results from small studies tend to scatter widely at the bottom of the graph, with the spread narrowing among larger studies. The significance of the intercept is evaluated using the t test. Sensitivity analysis was performed by removing each individual study in turn from the total and re-analysing the remainder. This procedure was used to ensure that no individual study was entirely responsible for the combined results. All statistical analyses were carried out with the Stata software version 10.0 (Stata Corporation, College Station, TX, USA). The type I error rate was set at 0.05. All the P-values were for two-sided analysis.

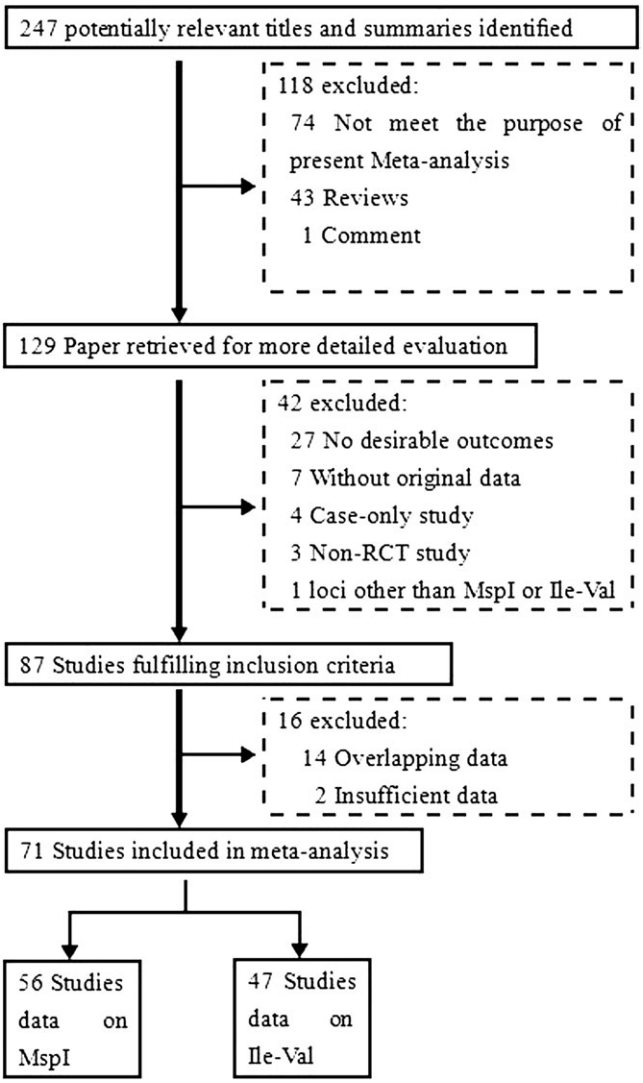

Fig. 1. Flow chart of literature search for studies examining *CYP1A1* gene polymorphism and risk of lung cancer.

Results

Characteristics of the included studies

The combined search yielded 247 references. Study selection process was shown in Figure 1. A total of 71 studies were finally included with 12 815 patients and 17 553 controls (11–81). The detailed characteristics of the studies included in this meta-analysis are shown in Table I. For the MspI polymorphism, 56 studies were available, including a total of 9688 cases and 12 670 controls. For the Ile-Val polymorphism, 47 studies involved a total of 8920 cases and 12 540 controls. These two polymorphisms were found to occur in frequencies consistent with HWE in the control populations of the vast majority of the published studies. Of the cases, 32% were East Asians, 44% were Caucasians and 24% were of other ethnic origins.

Meta-analysis results

Association of MspI variant with lung cancer. Using random-effect model, the per-allele overall OR of the C variant for lung cancer was 1.19 [95% CI: 1.11–1.28; $P(Z) < 10^{-5}$; $P(Q) < 10^{-4}$], with corresponding results under dominant and recessive genetic models of 1.22 [95% CI: 1.11–1.34; $P(Z) < 10^{-4}$; $P(Q) < 10^{-5}$; Figure 2] and 1.35 [95% CI: 1.18–1.54; $P(Z) < 10^{-4}$; $P(Q) = 0.03$], respectively.

When studies were stratified for ethnicity, significant risks were found among East Asians in all genetic models (C allele: OR = 1.19, 95% CI: 1.07–1.32; dominant model: OR = 1.24, 95% CI: 1.07–1.44; recessive model: OR = 1.36, 95% CI: 1.13–1.64). Similar results were also found in the Caucasians and other populations with a per-allele OR of 1.15 (95% CI: 1.01–1.32) and 1.23 (95% CI: 1.05–1.43), respectively. Subsidiary analyses of control source yielded a per-allele OR for hospital-based controls of 1.22 (95% CI: 1.09–1.67) and for population-based controls of 1.17 (95% CI: 1.06–1.28). However, in the stratified analysis according to sample size, no significant association was detected among five large studies. In the subgroup analyses by pathological type, significant associations were found for lung SCC in all genetic modes. However, we failed to detect any association between lung AC, SCLC or LCLC and the polymorphism for all genetic models (Table II).

In meta-regression analysis, mean age of cases ($P = 0.96$) and controls ($P = 0.73$), genotyping method ($P = 0.89$) and gender distribution in controls ($P = 0.10$) did not significantly explain such heterogeneity. By contrast, the gender distribution

Table I. Studies investigating the association between the *CYP1A1* polymorphisms and lung cancer risk

Reference	Year	Ethnicity	No. of cases/controls	Age of cases/controls	Gender distribution in cases/controls (male %)	Source of control	Genotyping method
Kawajiri (11)	1990	Japanese	68/104	NA/NA	NA/NA	Population	RFLP
Tefre (12)	1991	Norwegain	221/212	63.0/NA	79.6/89.7	Population	RFLP
Hirvonen (13)	1992	Finnish	87/121	63.0/52.0	80.5/87.6	Population	RFLP
Nakachi (14)	1993	Japanese	85/170	65.2/65.2	NA/NA	Population	RFLP
Shields (15)	1993	American	56/48	65.1/62.1	96.4/93.8	Hospital	RFLP
Drakoulis (16)	1994	German	142/171	65.0/59.0	80.9/57.9	Hospital	RFLP
Sugimura (17)	1994	Brazilian	110/112	61.4/61.9	80.0/80.4	Hospital	RFLP
Kihara (18)	1995	Japanese	97/258	NA/NA	86.4/77.9	Population	RFLP
Hamada (19)	1995	Brazilian	99/108	62.9/61.8	76.7/81.1	Hospital	RFLP
Jacquet (20)	1996	Belgian	44/81	62.0/NA	NA/NA	Population	RFLP
Ishibe (21)	1997	Mexican– and African–Americans	171/295	62.1/61.9	NA/NA	Hospital	RFLP
García-Closas (22)	1997	American	416/446	67.0/64.0	53.6/46.9	Population	RFLP
Bouchardy (23)	1997	French	150/171	58.4/55.0	NA/NA	Hospital	RFLP
Taioli (24)	1998	African–Americans	289/190	58.9/41.1	76.2/51.5	Population	RFLP
Hong (25)	1998	Korean	85/63	NA/NA	NA/NA	Hospital	RFLP
Marchand (26)	1998	Japanese, American	339/454	64.5/65.1	61.0/65.1	Population	RFLP
Sugimura (27)	1998	Japanese	247/185	67.8/62.1	100/100	Hospital	RFLP
Persson (28)	1999	Chinese	76/119	NA/NA	55.3/NA	Population	RFLP
Hu (29)	1999	Chinese	59/132	56.0/55.1	72.9/64.4	Population, Hospital	RFLP
Dresler (30)	2000	American	158/149	65.3/60.6	52.0/36.0	Population	RFLP
London (31)	2000	Chinese	214/669	63.0/63.0	100/100	Population	RFLP
Lin (32)	2000	Chinese	132/259	63.0/58.0	69.7/61.4	Population	RFLP
Dolzan (33)	2000	Slovenian	195/100	NA/NA	NA/NA	Population	RFLP, allele-specific PCR
Quiñones (34)	2001	Chilean	60/140	62.8/50.3	83.3/60.6	Population	RFLP
Chen (35)	2001	Chinese	106/106	56.9/53.6	82.1/82.1	Population	Allele-specific PCR
Song (36)	2001	Chinese	217/404	57.8/58.3	80.2/83.7	Population	RFLP
Gsur (37)	2001	Australian	134/134	63.9/64.1	100/100	Hospital	RFLP
Ratnasinghe (38)	2001	Finn	282/324	60.0/59.0	100/100	Population	RFLP
Zhang (39)	2002	Chinese	65/60	59.4/55.6	86.2/90.0	Hospital	RFLP
Zhou (40)	2002	Chinese	92/98	57.5/55.6	70.7/69.4	Hospital	RFLP
Oztürk (41)	2003	Turkish	55/65	57.8/56.3	72.1/56.9	Population	RFLP
Kiyohara (42)	2003	Japanese	158/259	NA/NA	0/0	Hospital	RFLP
Taioli (43)	2003	Italian	110/707	34.8/40.7	66.7/68.7	Population, hospital	RFLP
Wang (44)	2003	Chinese	162/181	55.7/54.8	64.6/66.9	Population	RFLP
Dialyna (45)	2003	Greek	122/178	64.6/58.8	86.0/83.1	Population	RFLP
Li (46)	2004	Chinese	217/200	NA/NA	NA/NA	Hospital	RFLP
Dong (47)	2004	Chinese	82/91	NA/NA	NA/NA	Hospital	RFLP, allele-specific PCR
Sobti (48)	2004	Indian	100/76	55.5/50.9	95.0/96.1	Population	RFLP
Liang (49)	2004	Chinese	152/152	60.9/60.5	70.4/70.4	Hospital	RFLP
Yang (50)	2004	Chinese	197/144	56.0/56.0	0/0	Population	TaqMan
Alexandrie (51)	2004	Swedes	524/530	66.0/44.0	65.6/77.9	Population	RFLP, allele-specific PCR
Demir (52)	2005	Turkish	32/37	55.0/34.0	93.5/64.9	Population	RFLP
Wrensch (53)	2005	Latinos, African–Americans	370/944	64.0/63.5	47.1/47.8	Population	RFLP
Li (54)	2005	Chinese	103/138	58.9/58.9	77.5/69.8	Population	RFLP
Ng (55)	2005	Chinese	126/162	62.0/63.4	0/0	Hospital	RFLP
Adonis (56)	2005	Chilean	57/103	63.2/53.3	70.2/54.4	Population	RFLP
Sreeja (57)	2005	Indian	146/146	58.2/56.1	91.1/87.7	Hospital	RFLP
Wenzlaff (58)	2005	American	159/179	63.2/54.9	41.3/49.2	Population	RFLP
Belogubova (59)	2006	Russian	141/450	60.6/59.5	87.9/48.4	Population, hospital	RFLP
Li (60)	2006	Chinese	150/152	57.1/54.8	76.7/77.0	Population	Allele-specific PCR
Chang (61)	2006	Chinese	163/163	NA/NA	56.4/56.4	Hospital	RFLP
Wang (62)	2006	Chinese	91/91	NA/NA	65.9/65.9	Hospital	RFLP
Qian (63)	2006	Chinese	108/108	59.4/57.6	61.1/61.1	Population	RFLP
Yang (64)	2007	Korean	314/349	55.4/48.3	67.6/61.8	Population	RFLP
Gu (65)	2007	Chinese	279/684	NA/NA	NA/NA	Population	RFLP
Cote (66)	2007	American	354/440	42.5/41.4	49.6/44.3	Population	RFLP
Pisani (67)	2007	Thai	168/287	NA/NA	66.4/61.1	Population, hospital	RFLP
Yoon (68)	2008	Korean	213/213	57.0/57.0	0/0	Population	RFLP
Gallegos-Arreola (69)	2008	Mexican	222/248	60.7/46.2	60.8/53.2	Population	RFLP
Shah (70)	2008	Indian	200/200	56.0/43.0	100/100	Population	RFLP
Xia (71)	2008	Chinese	58/116	57.0/57.0	89.7/89.7	Hospital	RFLP
Liu (72)	2008	Chinese	110/125	58.1/59.2	63.6/65.6	Population	Oligonucleotide chip
Cote (73)	2009	American	502/523	59.7/59.0	0/0	Population	RFLP, TaqMan
Honma (74)	2009	Brazilian	200/264	64.0/NA	72.0/60.6	Population	RFLP

Table 1. *Continued*

Reference	Year	Ethnicity	No. of cases/controls	Age of cases/controls	Gender distribution in cases/controls (male %)	Source of control	Genotyping method
Kumar (75)	2009	Indian	93/253	42.6/39.8	86.0/80.2	Population	RFLP
Klinchid (76)	2009	Thai	85/82	59.8/57.8	64.0/46.0	Population	RFLP
Timofeeva (77)	2009	German	619/1264	45.1/45.0	63.6/62.9	Population	Mass array
Shaffi (78)	2009	Indian	109/163	52.7/53.2	79.8/41.7	Hospital	RFLP
San Jose (79)	2010	Spanish	104/265	66.0/63.9	NA/NA	Hospital	RFLP
Jin (80)	2010	Chinese	124/154	59.3/54.5	NA/NA	Hospital	RFLP
Wright (81)	2010	Australian	1040/784	65.7/63.1	68.0/68.0	Population, hospital	RFLP

NA, not available; RFLP, restriction fragment length polymorphism; PCR, polymerase chain reaction.

in cases ($P = 0.015$) was significantly correlated with the magnitude of the genetic effect, explaining 36% of the heterogeneity.

Association of Ile-Val variant with lung cancer. Overall, the per-allele OR of the 462Val variant for lung cancer was 1.20 [95% CI: 1.08–1.33; $P(Z) = 0.0007$; $P(Q) < 10^{-5}$], with corresponding results under dominant and recessive genetic models of 1.21 [95% CI: 1.05–1.38; $P(Z) = 0.007$; $P(Q) < 10^{-5}$] and 1.57 [95% CI: 1.30–1.90; $P(Z) < 10^{-5}$; $P(Q) = 0.15$], respectively (Table III).

In the stratified analysis by ethnicity, significant associations were detected among East Asians in all genetic models (G allele: OR = 1.20, 95% CI: 1.06–1.35; recessive model: OR = 1.54, 95% CI: 1.24–1.91). Unfortunately, we failed to detect any association to cancer risk for Caucasians and other populations in all genetic models (Figure 3). Subsidiary analyses of control source yielded a per-allele OR for hospital-based controls of 1.30 (95% CI: 1.06–1.59) and for population-based controls of 1.14 (95% CI: 1.01–1.29). In sample size subgroup, this association became nonsignificant when the meta-analysis was restricted to larger studies.

Significant heterogeneity was present among the 47 studies of the Ile-Val polymorphism [$P(Q) < 10^{-5}$]. However, mean age of cases ($P = 0.76$) and controls ($P = 0.52$), genotyping method ($P = 0.17$) and gender component of cases ($P = 0.05$) and controls ($P = 0.91$) only explained little heterogeneity.

Gene–environment interaction. The data on genotypes of the MspI and Ile-Val polymorphism among cases stratified by smoking status were available in 18 (including 2451 cancer cases) and 11 (including 1837 cancer cases) studies, respectively. Using dominant genetic model, smokers with the risk allele of MspI or Ile-Val variant had no significantly increased lung cancer risk compared to non-smoker cancer cases with an OR of 1.41 [95% CI: 0.77–2.02; $P(Q) < 10^{-5}$] and 1.08 [95% CI: 0.67–1.74; $P(Q) = 0.0004$], respectively.

Sensitivity analyses and publication bias

Sensitivity analysis indicated that no single study influenced the pooled OR qualitatively, suggesting that the results of this meta-analysis are stable (data not shown).

The shape of the funnel plots was symmetrical (Figures 4 and 5). The statistical results still did not show publication bias in these studies for MspI (Begg test, $P = 0.25$; Egger test, $P = 0.29$) and Ile-Val polymorphism (Begg test, $P = 0.32$; Egger test, $P = 0.18$).

Discussion

Large sample and unbiased epidemiological studies of predisposition gene polymorphisms could provide insight into the *in vivo* relationship between candidate genes and diseases. This is the most comprehensive meta-analysis that examined the *CYP1A1* polymorphisms and the relationship to susceptibility for lung cancer. Its strength was based on the accumulation of published data giving greater information to detect significant differences. In total, the meta-analysis involved 71 studies for lung cancer, which provided 12 815 cases and 17 553 controls.

Our results demonstrated that the MspI and Ile-Val polymorphism of *CYP1A1* is a risk factor for developing lung cancer. In the stratified analysis by ethnicity, significant associations were found in East Asians for the two polymorphisms in almost all genetic models. However, only marginal significant associations were detected among Caucasians and other population for MspI polymorphism of *CYP1A1*, while no associations were found in Caucasians and other population for Ile-Val variant. In fact, the distribution of the less common Val allele varies extensively between different races, with a prevalence of ~25% among East Asians, ~5% among Caucasians and ~15% among other population. Thus, failing to identify any significant association in Caucasians and other populations could be due to substantially lower statistical power caused by the relatively lower prevalence of Val allele of *CYP1A1*. Therefore, additional studies are warranted to further validate ethnic difference in the effect of this functional polymorphism on lung cancer risk. In addition, studies using different source of controls also get consistent positive results.

When subgroup analyses by pathological types were considered, the C allele of MspI polymorphism has an increased risk factor in lung SCC subgroup but not in lung AC, SCLC or LCLC subgroup. Our results support the hypothesis by Marchand *et al*. (26) that genetic susceptibility to PAHs predominantly causes squamous cell carcinoma. The reason for the observed tumour-specific difference in the risk conferred by the *CYP1A1* MspI polymorphism is unknown. However, different carcinogenic processes may be involved in the genesis of various tumour types because of the presence of functionally different *CYP1A1* MspI polymorphism. Hence, future studies should use homogeneous cancer patients.

Compared with the previous meta-analysis (82,83), the present study is much larger, with almost four times as many cases as the earlier meta-analysis. In addition, we also investigated the interaction between *CYP1A1* gene polymorphisms, smoking status and lung cancer susceptibility. Furthermore, we explored

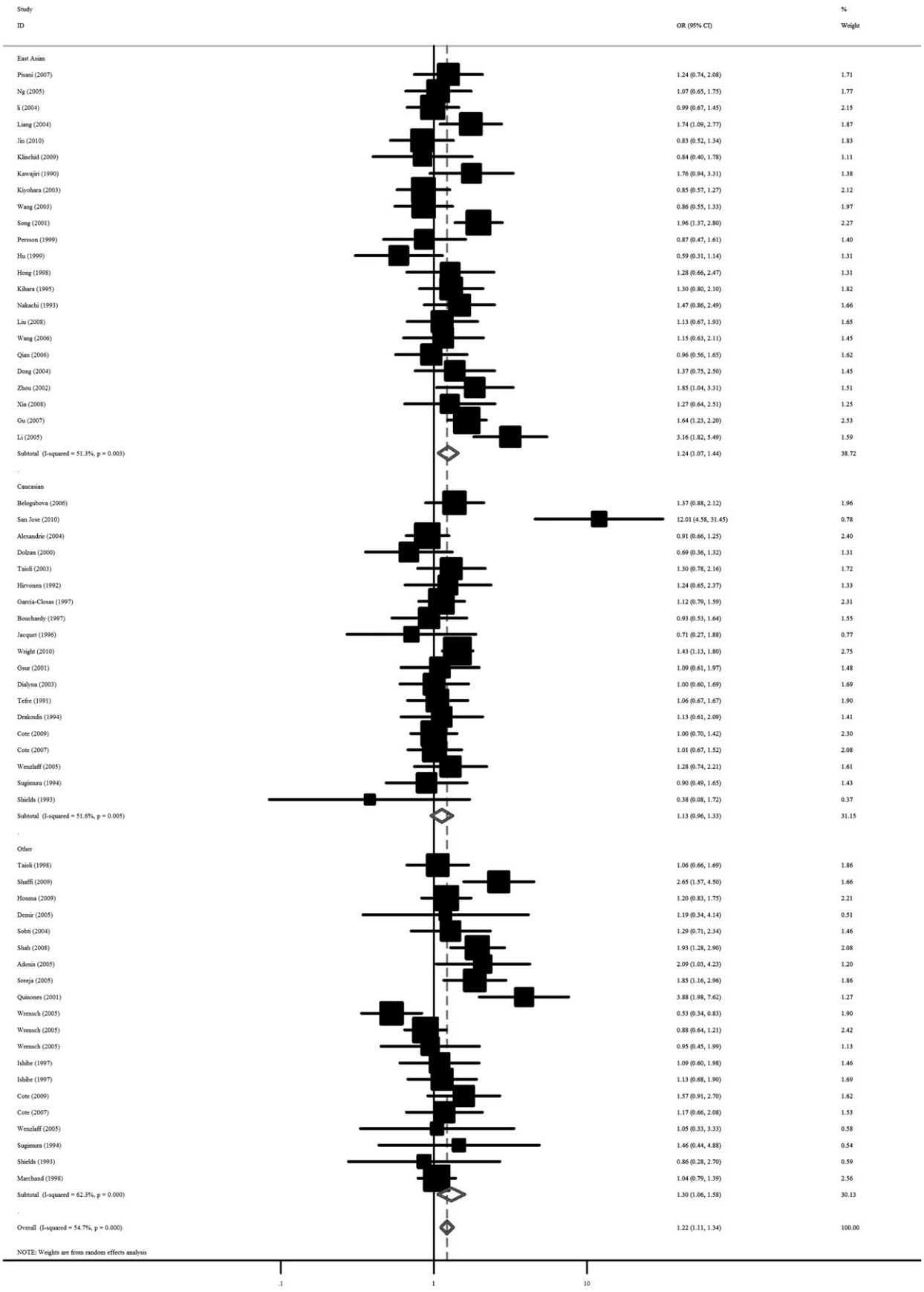

Fig. 2. Forest plot (random-effects model) of lung cancer risk associated with *CYP1A1* MspI polymorphism using dominant genetic model.

Table II. Main results of pooled ORs with CI for association of the MspI polymorphism and lung cancer risk in the meta-analysis

Subgroup analysis	No. of cases/controls	C allele versus T allele			Dominant model			Recessive model		
		OR (95% CI)	*P*(*Z*)	*P*(*Q*)	OR (95% CI)	*P*(*Z*)	*P*(*Q*)	OR (95% CI)	*P*(*Z*)	*P*(*Q*)
Total	9688/12 670	1.19 (1.11–1.28)	$<10^{-5}$	$<10^{-4}$	1.22 (1.11–1.34)	$<10^{-4}$	$<10^{-5}$	1.35 (1.18–1.54)	$<10^{-4}$	0.03
Ethnicity										
East Asians	3095/4569	1.19 (1.07–1.32)	0.001	0.01	1.24 (1.07–1.44)	0.005	0.003	1.36 (1.13–1.64)	0.001	0.009
Caucasians	4237/4865	1.15 (1.01–1.32)	0.04	0.04	1.13 (0.96–1.33)	0.15	0.005	1.58 (1.08–2.30)	0.02	0.78
Others	2356/3236	1.23 (1.05–1.43)	0.01	0.0002	1.30 (1.06–1.58)	0.01	0.0001	1.25 (0.97–1.62)	0.09	0.11
Control source										
Hospital	6087/8460	1.22 (1.09–1.37)	0.0008	0.003	1.26 (1.08–1.48)	0.004	0.001	1.41 (1.19–1.67)	$<10^{-4}$	0.37
Population	3801/4210	1.17 (1.06–1.28)	0.0009	0.001	1.18 (1.05–1.34)	0.007	$<10^{-4}$	1.33 (1.10–1.61)	0.003	0.02
Sample size										
Small	6984/10 057	1.20 (1.10–1.30)	$<10^{-4}$	$<10^{-4}$	1.24 (1.11–1.38)	0.0001	$<10^{-5}$	1.34 (1.16–1.55)	$<10^{-4}$	0.02
Big	2704/2613	1.16 (0.99–1.37)	0.07	0.20	1.11 (0.94–1.32)	0.22	0.17	1.32 (0.92–1.89)	0.13	0.55
HWE										
Yes	8690/11 309	1.19 (1.10–1.28)	$<10^{-4}$	$<10^{-4}$	1.22 (1.10–1.35)	$<10^{-4}$	$<10^{-5}$	1.34 (1.15–1.55)	0.0002	0.07
No	998/1361	1.21 (0.96–1.52)	0.11	0.02	1.23 (0.85–1.80)	0.28	0.002	1.25 (0.94–1.65)	0.13	0.24
Pathological type										
SCC	1483/4867	1.59 (1.25–2.01)	0.0001	$<10^{-5}$	1.61 (1.30–2.01)	$<10^{-4}$	0.0001	1.80 (1.22–2.65)	0.003	0.05
AC	912/4296	1.02 (0.87–1.19)	0.81	0.57	0.98 (0.83–1.16)	0.85	0.58	1.09 (0.78–1.52)	0.62	0.95
SCLC	421/3689	1.07 (0.86–1.34)	0.52	0.88	0.88 (0.69–1.11)	0.26	0.53	1.65 (1.02–2.68)	0.04	0.60
LCLC	59/864	1.34 (0.79–2.29)	0.28	0.81	1.36 (0.72–2.58)	0.34	0.51	2.69 (0.72–10.04)	0.14	0.87

Table III. Main results of pooled ORs with CI for association of the Ile-Val polymorphism and lung cancer risk in the meta-analysis

Subgroup analysis	No. of cases/controls	G allele versus A allele			Dominant model			Recessive model		
		OR (95% CI)	*P*(*Z*)	*P*(*Q*)	OR (95% CI)	*P*(*Z*)	*P*(*Q*)	OR (95% CI)	*P*(*Z*)	*P*(*Q*)
Total	8920/12 540	1.20 (1.08–1.33)	0.0007	$<10^{-5}$	1.21 (1.05–1.38)	0.007	$<10^{-5}$	1.57 (1.30–1.90)	$<10^{-5}$	0.15
Ethnicity										
East Asians	2780/3863	1.20 (1.06–1.35)	0.003	0.003	1.20 (0.99–1.47)	0.06	$<10^{-5}$	1.54 (1.24–1.91)	$<10^{-4}$	0.43
Caucasians	4093/5312	1.19 (0.92–1.54)	0.17	0.0005	1.16 (0.88–1.53)	0.29	0.0002	1.52 (0.80–2.88)	0.20	0.76
Others	2047/3365	1.19 (0.93–1.51)	0.16	$<10^{-4}$	1.26 (0.96–1.65)	0.10	0.0002	1.50 (0.91–2.48)	0.11	0.01
Control source										
Hospital	6113/9623	1.30 (1.06–1.59)	0.01	0.0003	1.38 (1.07–1.77)	0.01	0.0006	1.71 (1.18–2.48)	0.004	0.18
Population	2866/2917	1.14 (1.01–1.29)	0.03	$<10^{-4}$	1.16 (0.99–1.36)	0.06	$<10^{-5}$	1.50 (1.20–1.88)	0.0003	0.24
Sample size										
Small	6223/9288	1.21 (1.08–1.35)	0.0007	$<10^{-5}$	1.22 (1.05–1.41)	0.01	$<10^{-5}$	1.69 (1.38–2.06)	$<10^{-5}$	0.23
Big	2697/3252	1.10 (0.80–1.52)	0.56	0.002	1.14 (0.81–1.59)	0.45	0.003	0.91 (0.56–1.49)	0.71	0.56
HWE										
Yes	5987/8467	1.20 (1.05–1.36)	0.007	$<10^{-5}$	1.20 (1.03–1.39)	0.02	$<10^{-5}$	1.53 (1.17–1.99)	0.002	0.05
No	2933/4073	1.19 (0.99–1.42)	0.06	0.005	1.16 (0.83–1.61)	0.38	$<10^{-5}$	1.68 (1.25–2.25)	0.0006	0.79
Pathological type										
SCC	1286/3294	1.20 (0.96–1.50)	0.11	0.10	1.32 (0.97–1.81)	0.08	0.001	1.66 (0.95–2.92)	0.08	0.18
AC	918/3474	0.91 (0.74–1.13)	0.39	0.21	0.92 (0.70–1.20)	0.52	0.10	1.67 (0.69–4.02)	0.25	0.005
SCLC	331/2181	1.12 (0.67–1.86)	0.66	0.002	0.77 (0.43–1.37)	0.37	0.03	3.21 (1.62–6.34)	0.0008	0.32
LCLC	60/649	1.25 (0.37–4.31)	0.72	0.23	1.23 (0.29–5.25)	0.78	0.22	NA	NA	NA

NA, not available.

potential sources of heterogeneity across studies. Besides, our results suggest an overestimation of the true genetic association by small studies, consistent with the phenomenon known as 'winner's curse' (84,85).

A number of factors predict lung cancer; however, detailed pathogenesis mechanisms of lung cancer remain a matter of speculation. *CYP1A1* is a key phase I enzyme that converts many lung carcinogens into DNA-binding metabolites with carcinogenic potential (5). Evidence from *in vitro* expression studies indicates that the C allele of MspI polymorphism of *CYP1A1* could affect the transcriptional control elements involved in enzyme inducibility (86,87). The second polymorphism is an A → G transition in exon7 of *CYP1A1* that results in substitution of isoleucine to valine in the heme-binding region, which increases microsomal enzyme activity (6,88). Thus, the risk allele may therefore have more ability to metabolise mutagens and pro-carcinogens, hence more liable to metabolically activate mutagens and carcinogens.

In interpreting the results, some limitations of this meta-analysis should be addressed. First, in the subgroup analyses, different ethnicities were pooled in other population, which may bring in some heterogeneity. As studies among the Indians and Africans are currently limited, further studies including a wider spectrum of subjects should be carried to investigate the role of these variants in different populations. Second, the two subgroup meta-analyses considering interactions between *CYP1A1* polymorphisms and cigarette smoking, as well as between different pathological types of lung cancer were performed on the basis of a fraction of all the possible data to be pooled, so selection bias may have occurred and our results may be overinflated. Nevertheless, the total number of subjects included in this part of the analysis comprises the largest

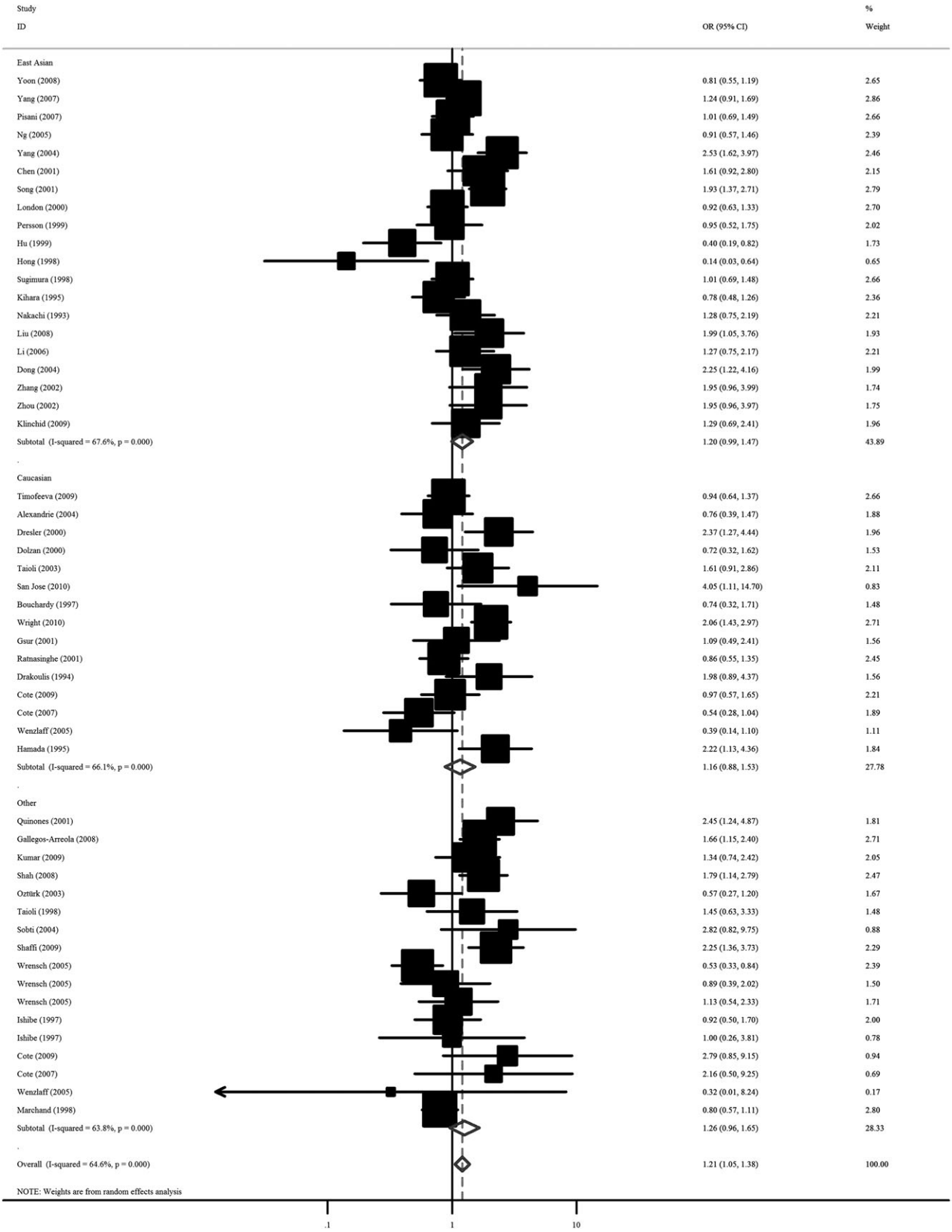

Fig. 3. Forest plot (random-effects model) of lung cancer risk associated with *CYP1A1* Ile-Val polymorphism using dominant genetic model.

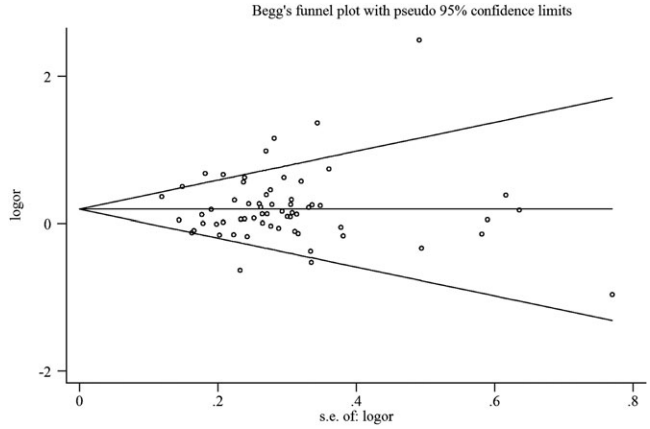

Fig. 4. Begg's funnel plot of *CYP1A1* MspI polymorphism and lung cancer risk; Egger's test was also performed to investigate the symmetry of the funnel plot ($P = 0.29$).

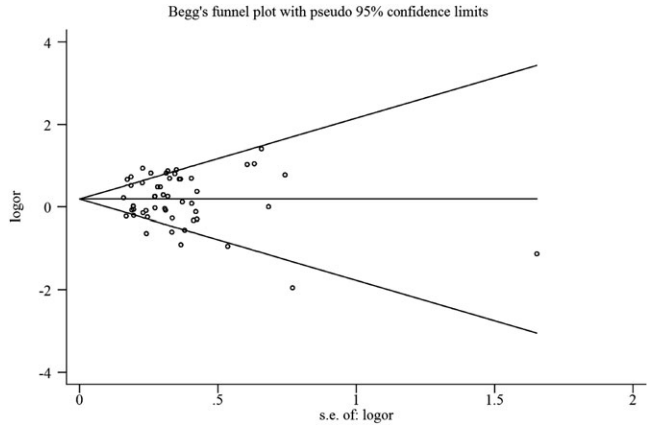

Fig. 5. Begg's funnel plot of *CYP1A1* Ile-Val polymorphism and lung cancer risk; Egger's test was also performed to investigate the symmetry of the funnel plot ($P = 0.18$).

sample size so far. Third, only published studies were included in this meta-analysis. Therefore, publication bias may have occurred, even though the use of a statistical test did not show it. In spite of these, our present meta-analysis also had some advantages. First, substantial number of cases and controls were pooled from different studies, which greatly increased statistical power of the analysis. Second, no publication biases were detected, indicating that the whole pooled results may be unbiased.

To conclude, this meta-analysis suggests that the MspI and Ile-Val polymorphism of *CYP1A1* is associated with lung cancer susceptibility. For future association studies, strict selection of patients, well-matched controls and larger sample size will be required. More studies should also be carried out to examine the impact of *CYP1A1* on lung cancer. Moreover, gene–gene and gene–environment interactions should also be considered in future studies.

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References

1. Walser, T., Cui, X., Yanagawa, J., Lee, J. M., Heinrich, L. E., Lee, G., Sharma, S. and Dubinett, S. M. (2008) Smoking and lung cancer. *Proc. Am. Thorac. Soc.*, **5**, 811–815.
2. Vineis, P., Alavanja, M., Buffler, P. *et al.* (2004) Tobacco and cancer: recent epidemiological evidence. *J. Natl. Cancer. Inst.*, **96**, 99–106.
3. Osann, K. E. (1998) Epidemiology of lung cancer. *Curr. Opin. Pulm. Med.*, **4**, 198–204.
4. Hecht, S. S. (2002) Cigarette smoking and lung cancer: chemical mechanisms and approaches to prevention. *Lancet Oncol.*, **3**, 461–469.
5. Nerurkar, P. V., Okinaka, L., Aoki, C., Seifried, A., Lum-Jones, A., Wilkens, L. R. and Le Marchand, L. (2000) CYP1A1, GSTM1, and GSTP1 genetic polymorphisms and urinary 1-hydroxypyrene excretion in non-occupationally exposed individuals. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 1119–1122.
6. Kiyohara, C., Nakanishi, Y., Inutsuka, S., Takayama, K., Hara, N., Tanaka, K., Kono, S. and Hirohata, T. (1998) The relationship between CYP1A1 and aryl hydrocarbon hydroxylase activity and lung cancer in a Japanese population. *Pharmacogenetics*, **8**, 315–323.
7. Cochran, W. G. (1954) The combination of estimates from different experiments. *Biometrics*, **10**, 101–129.
8. DerSimonian, R. and Laird, N. (1896) Meta-analysis in clinical trials. *Control Clin. Trials.*, **7**, 177–188.
9. Thompson, S. G. and Sharp, S. J. (1999) Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat. Med.*, **18**, 2693–2708.
10. Egger, M., Davey Smith, G., Schneider, M. and Minder, C. (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629–634.
11. Kawajiri, K., Nakachi, K., Imai, K., Yoshii, A., Shinoda, N. and Watanabe, J. (1990) Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P450IA1 gene. *FEBS Lett.*, **263**, 131–133.
12. Tefre, T., Ryberg, D., Haugen, A., Nebert, D. W., Skaug, V., Brøgger, A. and Børresen, A. L. (1991) Human CYP1A1 (cytochrome P1 450) gene: lack of association between the Msp I restriction fragment length polymorphism and incidence of lung cancer in a Norwegian population. *Pharmacogenetics*, **1**, 20–25.
13. Hirvonen, A., Husgafvel-Pursiainen, K., Karjalainen, A., Anttila, S. and Vainio, H. (1992) Point-mutational MspI and Ile-Val polymorphisms closely linked in the CYP1A1 gene: lack of association with susceptibility to lung cancer in a Finnish study population. *Cancer Epidemiol. Biomarkers Prev.*, **1**, 485–489.
14. Nakachi, K., Imai, K., Hayashi, S. and Kawajiri, K. (1993) 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**, 2994–2999.
15. Shields, P. G., Caporaso, N. E., Falk, R. T., Sugimura, H., Trivers, G. E., Trump, B. F., Hoover, R. N., Weston, A. and Harris, C. C. (1993) Lung cancer, race, and a CYP1A1 genetic polymorphism. *Cancer Epidemiol. Biomarkers Prev.*, **2**, 481–485.
16. Drakoulis, N., Cascorbi, I., Brockmöller, J., Gross, C. R. and Roots, I. (1994) Polymorphisms in the human CYP1A1 gene as susceptibility factors for lung cancer: exon-7 mutation (4889 A to G), and a T to C mutation in the 3′-flanking region. *Clin. Investig.*, **72**, 240–248.
17. Sugimura, H., Wakai, K., Genka, K. *et al.* (1998) 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**, 413–417.
18. Kihara, M., Kihara, M. and Noda, K. (1995) Risk of smoking for squamous and small cell carcinomas of the lung modulated by combinations of CYP1A1 and GSTM1 gene polymorphisms in a Japanese population. *Carcinogenesis*, **16**, 2331–2336.
19. Hamada, G. S., Sugimura, H., Suzuki, I. *et al.* (1995) The heme-binding region polymorphism of cytochrome P450IA1 (CypIA1), rather than the RsaI polymorphism of IIE1 (CypIIE1), is associated with lung cancer in Rio de Janeiro. *Cancer Epidemiol. Biomarkers Prev.*, **4**, 63–67.
20. Jacquet, M., Lambert, V., Baudoux, E., Muller, M., Kremers, P. and Gielen, J. (1996) Correlation between P450 CYP1A1 inducibility, MspI genotype and lung cancer incidence. *Eur. J. Cancer.*, **32A**, 1701–1706.
21. Ishibe, N., Wiencke, J. K., Zuo, Z. F., McMillan, A., Spitz, M. and Kelsey, K. T. (1997) Susceptibility to lung cancer in light smokers associated with CYP1A1 polymorphisms in Mexican- and African-Americans. *Cancer Epidemiol. Biomarkers Prev.*, **6**, 1075–1080.

22. Garcia-Closas, M., Kelsey, K. T., Wiencke, J. K., Xu, X., Wain, J. C. and Christiani, D. C. (1997) A case-control study of cytochrome P450 1A1, glutathione S-transferase M1, cigarette smoking and lung cancer susceptibility (Massachusetts, United States). *Cancer Causes Control*, **8**, 544–553.
23. Bouchardy, C., Wikman, H., Benhamou, S., Arihirvonen Dayer, P. and Husgafvel-Pursiainen, K., (1997) CYP1A1 genetic polymorphisms, tobacco smoking and lung cancer risk in a French Caucasian population. *Biomarkers*, **2**, 131–134.
24. Taioli, E., Ford, J., Trachman, J., Li, Y., Demopoulos, R. and Garte, S. (1998) Lung cancer risk and CYP1A1 genotype in African Americans. *Carcinogenesis*, **19**, 813–817.
25. Hong, Y. S., Chang, J. H., Kwon, O. J., Ham, Y. A. and Choi, J. H. (1998) Polymorphism of the CYP1A1 and glutathione-S-transferase gene in Korean lung cancer patients. *Exp. Mol. Med*., **30**, 192–198.
26. Le Marchand, L., Sivaraman, L., Pierce, L., Seifried, A., Lum, A., Wilkens, L. R. and Lau, A. F. (1998) Associations of CYP1A1, GSTM1, and CYP2E1 polymorphisms with lung cancer suggest cell type specificities to tobacco carcinogens. *Cancer Res*., **58**, 4858–4863.
27. Sugimura, H., Suzuki, I., Hamada, G. S. *et al*. (1994) Cytochrome P-450 lA1 genotype in lung cancer patients and controls in Rio de Janeiro, Brazil. *Cancer Epidemiol. Biomarkers Prev*., **3**, 145–148.
28. Persson, I., Johansson, I., Lou, Y. C., Yue, Q. Y., Duan, L. S., Bertilsson, L. and Ingelman-Sundberg, M. (1999) Genetic polymorphism of xenobiotic metabolizing enzymes among Chinese lung cancer patients. *Int. J. Cancer*., **81**, 325–329.
29. Hu, Y. and Zhang, Q. (1999) Genetic polymorphisms of CYP1A1 and susceptibility of lung cancer [in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, **16**, 26–28.
30. Dresler, C. M., Fratelli, C., Babb, J., Everley, L., Evans, A. A. and Clapper, M. L. (2000) Gender differences in genetic susceptibility for lung cancer. *Lung Cancer*, **30**, 153–160.
31. London, S. J., Yuan, J. M., Coetzee, G. A., Gao, Y. T., Ross, R. K. and Yu, M. C. (2000) CYP1A1 I462V genetic polymorphism and lung cancer risk in a cohort of men in Shanghai, China. *Cancer Epidemiol. Biomarkers Prev*., **9**, 987–991.
32. Lin, P., Wang, S. L., Wang, H. J., Chen, K. W., Lee, H. S., Tsai, K. J., Chen, C. Y. and Lee, H. (2000) Association of CYP1A1 and microsomal epoxide hydrolase polymorphisms with lung squamous cell carcinoma. *Br. J. Cancer*., **82**, 852–857.
33. Dolzan, V., Rudolf, Z. and Breskvar, K. (2000) Genetic polymorphism of xenobiotic metabolising enzymes in Slovenian lung cancer patients. *Pflugers Arch*., **439** (Suppl.), R29–R30.
34. Quiñones, L., Lucas, D., Godoy, J. *et al*. (2001) CYP1A1, CYP2E1 and GSTM1 genetic polymorphisms. The effect of single and combined genotypes on lung cancer susceptibility in Chilean people. *Cancer Lett*., **174**, 35–44.
35. Chen, S., Xue, K., Xu, L., Ma, G. and Wu, J. (2001) Polymorphisms of the CYP1A1 and GSTM1 genes in relation to individual susceptibility to lung carcinoma in Chinese population. *Mutat. Res*., **458**, 41–47.
36. Song, N., Tan, W., Xing, D. and Lin, D. (2001) CYP 1A1 polymorphism and risk of lung cancer in relation to tobacco smoking: a case-control study in China. *Carcinogenesis*, **22**, 11–16.
37. Gsur, A., Haidinger, G., Hollaus, P. *et al*. (2001) Genetic polymorphisms of CYP1A1 and GSTM1 and lung cancer risk. *Anticancer Res*., **21**, 2237–2242.
38. Ratnasinghe, D., Tangrea, J. A., Stewart, C., Bhat, N. K., Virtamo, J., Albanes, D. and Taylor, P. R. (2001) Influence of antioxidants and the CYP1A1 isoleucine to valine polymorphism on the smoking—lung cancer association. *Anticancer Res*., **21**, 1295–1299.
39. Zhang, L. Z., Wang, X., Hao, X. Z., Shi, Y. X. and Liu, Z. H. (2002) Relationship between susceptibility to lung cancer and genetic polymorphism in CYP1A1, GSTM1 [in Chinese]. *Chin. J. Clin. Oncol*., **29**, 536–540.
40. Zhou, X. W., Shi, Y. and Zhou, Y. K. (2002) The relationship between CYP1A1 genetic polymorphism and susceptibility to lung cancer [in Chinese]. *J. Environ. Occup. Med*., **19**, 355–357.
41. Oztürk, O., Isbir, T., Yaylim, I., Kocatürk, C. I. and Gürses, A. (2003) GST M1 and CYP1A1 gene polymorphism and daily fruit consumption in Turkish patients with non-small cell lung carcinomas. *In Vivo*, **17**, 625–632.
42. Kiyohara, C., Wakai, K., Mikami, H., Sido, K., Ando, M. and Ohno, Y. (2003) Risk modification by CYP1A1 and GSTM1 polymorphisms in the association of environmental tobacco smoke and lung cancer: a case-control study in Japanese nonsmoking women. *Int. J. Cancer*., **107**, 139–144.
43. Taioli, E., Gaspari, L., Benhamou, S. *et al*. (2003) Polymorphisms in CYP1A1, GSTM1, GSTT1 and lung cancer below the age of 45 years. *Int. J. Epidemiol*., **32**, 60–63.
44. Wang, J., Deng, Y., Li, L. *et al*. (2003) Association of GSTM1, CYP1A1 and CYP2E1 genetic polymorphisms with susceptibility to lung adenocarcinoma: a case-control study in Chinese population. *Cancer Sci*., **94**, 448–452.
45. Dialyna, I. A., Miyakis, S., Georgatou, N. and Spandidos, D. A. (2003) Genetic polymorphisms of CYP1A1, GSTM1 and GSTT1 genes and lung cancer risk. *Oncol. Rep*., **10**, 1829–1835.
46. Li, W. Y., Lai, B. T. and Zhan, X. P. (2004) The relationship between genetic polymorphism of metabolizing enzymes and the genetic susceptibility to lung cancer [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*, **25**, 1042–1045.
47. Dong, C. T., Yang, Q., Jiang, B. and Dong, Q. N. (2004) Study on the relationship between polymorphisms of CYP1A1 gene and susceptibility of lung cancer in Sichuan population [in Chinese]. *Chin. J. Lung Cancer*, **7**, 38–42.
48. Sobti, R. C., Sharma, S., Joshi, A., Jindal, S. K. and Janmeja, A. (2004) Genetic polymorphism of the CYP1A1, CYP2E1, GSTM1 and GSTT1 genes and lung cancer susceptibility in a North Indian population. *Mol. Cell. Biochem*., **266**, 1–9.
49. Liang, G. Y., Pu, Y. P. and Yin, L. H. (2004) Studies of the genes related to lung cancer susceptibility in Nanjing Han population, China [in Chinese]. *Yi Chuan*, **26**, 584–588.
50. Yang, X. R., Wacholder, S., Xu, Z. *et al*. (2004) CYP1A1 and GSTM1 polymorphisms in relation to lung cancer risk in Chinese women. *Cancer Lett*., **214**, 197–204.
51. Alexandrie, A. K., Nyberg, F., Warholm, M. and Rannug, A. (2004) Influence of CYP1A1, GSTM1, GSTT1, and NQO1 genotypes and cumulative smoking dose on lung cancer risk in a Swedish population. *Cancer Epidemiol. Biomarkers Prev*., **13**, 908–914.
52. Demir, A., Altin, S., Demir, I., Köksal, V., Cetinçelik, U. and Dinçer, I. (2005) The role of CYP1A1 Msp1 gene polymorphisms on lung cancer development in Turkey. *Tuberk. Toraks*., **53**, 5–9.
53. Wrensch, M. R., Miike, R., Sison, J. D., Kelsey, K. T., Liu, M., McMillan, A., Quesenberry, C. and Wiencke, J. K. (2005) CYP1A1 variants and smoking-related lung cancer in San Francisco Bay area Latinos and African Americans. *Int. J. Cancer*., **113**, 141–147.
54. Li, Y., Tang, X. Y. and Ma, X. T. (2005) Cytochrome P24501A1 polymorphisms and susceptibility to lung cancer: a case-control study on Chinese population in Henan [in Chinese]. *Henan Med. Res*., **14**, 227–229.
55. Ng, D. P., Tan, K. W., Zhao, B. and Seow, A. (2005) CYP1A1 polymorphisms and risk of lung cancer in non-smoking Chinese women: influence of environmental tobacco smoke exposure and GSTM1/T1 genetic variation. *Cancer Causes Control*, **16**, 399–405.
56. Adonis, M., Martínez, V., Marín, P. and Gil, L. (2005) CYP1A1 and GSTM1 genetic polymorphisms in lung cancer populations exposed to arsenic in drinking water. *Xenobiotica*, **35**, 519–530.
57. Sreeja, L., Syamala, V., Hariharan, S., Madhavan, J., Devan, S. C. and Ankathil, R. (2005) Possible risk modification by CYP1A1, GSTM1 and GSTT1 gene polymorphisms in lung cancer susceptibility in a South Indian population. *J. Hum. Genet*., **50**, 618–627.
58. Wenzlaff, A. S., Cote, M. L., Bock, C. H., Land, S. J., Santer, S. K., Schwartz, D. R. and Schwartz, A. G. (2005) CYP1A1 and CYP1B1 polymorphisms and risk of lung cancer among never smokers: a population-based study. *Carcinogenesis*, **26**, 2207–2212.
59. Belogubova, E. V., Ulibina, Y. M., Suvorova, I. K. *et al*. (2006) Combined CYP1A1/GSTM1 at-risk genotypes are overrepresented in squamous cell lung carcinoma patients but underrepresented in elderly tumor-free subjects. *J. Cancer Res. Clin. Oncol*., **132**, 327–331.
60. Li, D. R., Zhou, Q. H., Guo, Z. L., Yuan, T. Z., Zhu, W., Wang, Y. P. and Chen, X. H. (2006) Relationship between genetic polymorphism of GYP1A1 and lung cancer genetic susceptibility [in Chinese]. *Chin. J. Cancer Prev. Treat*., **13**, 1765–1768.
61. Chang, F. H., Hu, T. M. and Wang, G. (2006) Relationship between CYPIAI and GSTMI genetic polymorphisms and lung cancer susceptibility in population of Inner Mongoli [in Chinese]. *Chin. J. Lung Cancer*, **9**, 413–417.
62. Wang, D. Q., Chen, S. D., Wang, B. G., Cai, X. L. and Xian, X. Z. (2006) A case control study on relationship between lung cancer and genetic polymorphism of CYP1A1, CYP2E1 and GSTM1 in Han nationality, in Guangzhou Area [in Chinese]. *Bull. Chin. Cancer*., **15**, 579–582.
63. Qian, B. Y., Han, H. W., Gu, F. *et al*. (2006) Case-control study genetic polymorphism in CYP1A1 and GSTM1 and smoking and susceptibility to lung cancer [in Chinese]. *Chin. J. Clin. Oncol*., **33**, 500–502.
64. Yang, M., Choi, Y., Hwangbo, B. and Lee, J. S. (2007) Combined effects of genetic polymorphisms in six selected genes on lung cancer susceptibility. *Lung Cancer*, **57**, 135–142.

65. Gu, Y. F., Zhang, Z. D., Zhang, S. C., Zheng, S. H., Jia, H. Y. and Gu, S. X. (2007) Combined effects of genetic polymorphisms in cytochrome P450s and GSTM1 on lung cancer susceptibility [in Chinese]. *Natl. Med. J. China*., **87**, 3064–3068.
66. Cote, M. L., Wenzlaff, A. S., Bock, C. H., Land, S. J., Santer, S. K., Schwartz, D. R. and Schwartz, A. G. (2007) Combinations of cytochrome P-450 genotypes and risk of early-onset lung cancer in Caucasians and African Americans: a population-based study. *Lung Cancer*, **55**, 255–262.
67. Pisani, P., Srivatanakul, P., Randerson-Moor, J., Vipasrinimit, S., Lalitwongsa, S., Unpunyo, P., Bashir, S. and Bishop, D. T. (2006) GSTM1 and CYP1A1 polymorphisms, tobacco, air pollution, and lung cancer: a study in rural Thailand. *Cancer Epidemiol. Biomarkers Prev*., **15**, 667–674.
68. Yoon, K. A., Kim, J. H., Gil, H. J., Hwang, H., Hwangbo, B. and Lee, J. S. (2008) CYP1B1, CYP1A1, MPO, and GSTP1 polymorphisms and lung cancer risk in never-smoking Korean women. *Lung Cancer*, **60**, 40–46.
69. Gallegos-Arreola, M. P., Figuera-Villanueva, L. E., Troyo-Sanroman, R., Morgán-Villela, G., Puebla-Pérez, A. M., Flores-Marquez, M. R. and Zúniga-González, G. M. (2008) CYP1A1 *2B and *4 polymorphisms are associated with lung cancer susceptibility in Mexican patients. *Int. J. Biol. Markers*., **23**, 24–30.
70. Shah, P. P., Singh, A. P., Singh, M., Mathur, N., Pant, M. C., Mishra, B. N. and Parmar, D. (2008) Interaction of cytochrome P4501A1 genotypes with other risk factors and susceptibility to lung cancer. *Mutat. Res*., **639**, 1–10.
71. Xia, Y., Sun, Q. F., Shang, B. *et al.* (2008) Polymorphisms of the cytochrome P450 and glutathion s-transferase genes associated with lung cancer susceptibility for the residents in high radon-exposed area [in Chinese]. *Chin. J. Radiol. Med. Prot*., **28**, 327–332.
72. Liu, Q., Liu, J., Song, B. and Wang, Z. H. (2008) Relationship between susceptibility to lung cancer and genetic polymorphism [in Chinese]. *Shandong Med. J*., **48**, 32–34.
73. Cote, M. L., Yoo, W., Wenzlaff, A. S., Prysak, G. M., Santer, S. K., Claeys, G. B., Van Dyke, A. L., Land, S. J. and Schwartz, A. G. (2009) Tobacco and estrogen metabolic polymorphisms and risk of non-small cell lung cancer in women. *Carcinogenesis*, **30**, 626–635.
74. Honma, H. N., De Capitani, E. M., Barbeiro Ade, S., Costa, D. B., Morcillo, A. and Zambon, L. (2009) Polymorphism of the CYP1A1*2A gene and susceptibility to lung cancer in a Brazilian population. *J. Bras. Pneumol*., **35**, 767–772.
75. Kumar, M., Agarwal, S. K. and Goel, S. K. (2009) Lung cancer risk in North Indian population: role of genetic polymorphisms and smoking. *Mol. Cell. Biochem*., **322**, 73–79.
76. Klinchid, J., Chewaskulyoung, B., Saeteng, S., Lertprasertsuke, N., Kasinrerk, W. and Cressey, R. (2009) Effect of combined genetic polymorphisms on lung cancer risk in northern Thai women. *Cancer Genet. Cytogenet*., **195**, 143–149.
77. Timofeeva, M. N., Kropp, S., Sauter, W., Beckmann, L. *et al.* (2009) CYP450 polymorphisms as risk factors for early-onset lung cancer: gender-specific differences. *Carcinogenesis*, **30**, 1161–1169.
78. Shaffi, S. M., Shah, M. A., Bhat, I. A., Koul, P., Ahmad, S. N. and Siddiqi, M. A. (2009) CYP1A1 polymorphisms and risk of lung cancer in the ethnic Kashmiri population. *Asian Pac. J. Cancer Prev*., **10**, 651–656.
79. San Jose, C., Cabanillas, A., Benitez, J., Carrillo, J. A., Jimenez, M. and Gervasini, G. (2010) CYP1A1 gene polymorphisms increase lung cancer risk in a high-incidence region of Spain: a case control study. *BMC Cancer*, **10**, 463.
80. Jin, Y., Xu, H., Zhang, C., Kong, Y., Hou, Y., Xu, Y. and Xue, S. (2010) Combined effects of cigarette smoking, gene polymorphisms and methylations of tumor suppressor genes on non small cell lung cancer: a hospital-based case-control study in China. *BMC Cancer*, **10**, 422.
81. Wright, C. M., Larsen, J. E., Colosimo, M. L., Barr, J. J., Chen, L., McLachlan, R. E., Yang, I. A., Bowman, R. V. and Fong, K. M. (2010) Genetic association study of CYP1A1 polymorphisms identifies risk haplotypes in nonsmall cell lung cancer. *Eur. Respir. J*., **35**, 152–159.
82. Shi, X., Zhou, S., Wang, Z., Zhou, Z. and Wang, Z. (2008) CYP1A1 and GSTM1 polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. *Lung Cancer*, **59**, 155–163.
83. Houlston, R. S. (2000) CYP1A1 polymorphisms and lung cancer risk: a meta-analysis. *Pharmacogenetics*, **10**, 105–114.
84. Lohmueller, K. E., Pearce, C. L., Pike, M., Lander, E. S. and Hirschhorn, J. N. (2003) Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat. Genet*., **33**, 177–182.
85. Morgan, T. M., Coffey, C. S. and Krumholz, H. M. (2003) Overestimation of genetic risks owing to small sample sizes in cardiovascular studies. *Clin. Genet*., **64**, 7–17.
86. Petersen, D. D., McKinney, C. E., Iyeka, K., Smith, H. H., Bale, A. E., McBride, O. W. and Nerbert, D. W. (1991) Human CYP1A1 gene: co-segregation of the enzyme inducibility phenotype and an RFLP. *Am. J. Hum. Genet*., **48**, 720–725.
87. Landi, M. T., Bertazzi, P. A., Shields, P. G., Clark, G., Lucier, G. W., Garte, S. J., Cosma, G. and Caporaso, N. (1994) Association between CYP1A1 genotype, mRNA expression and enzymatic activity in humans. *Pharmacogenetics*, **4**, 242–246.
88. Crofts, F., Taioli, E., Trachmann, J., Cosma, G. N., Currie, D., Toniolo, P. and Garte, S. J. (1993) Functional significance of different human CYP1A1 genotypes. *Carcinogenesis*, **15**, 2961–2963.