BIOMARKERS, 2002, VOL. 7, NO. 3, 230–241

REVIEW

Microsomal epoxide hydrolase polymorphisms and lung cancer risk: a quantitative review

WON JIN LEE[1], PAUL BRENNAN[1]*, PAOLO BOFFETTA[1], STEPHANIE J. LONDON[2], SIMONE BENHAMOU[3], AGNETA RANNUG[4], JORDI TO-FIGUERAS[5], MAGNUS INGELMAN-SUNDBERG[6], PETER SHIELDS[7], LAURA GASPARI[8] and EMANUELA TAIOLI[8]

[1] International Agency for Research on Cancer, Lyon, France
[2] National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
[3] INSERM U521, Institute Gustave Roussy, Villejuif, France
[4] National Institute of Occupational Health, Solna, Sweden
[5] Hospital Clinic Provincial, Barcelona, Spain
[6] Karolinska Institutet, Stockholm, Sweden
[7] Georgetown University Medical Center, Washington, DC, USA
[8] Ospedale Maggiore IRCCS, Milan, Italy

Received 31 August 2001, revised form accepted 18 December 2001

To investigate the role of microsomal epoxide hydrolase (mEH) polymorphisms in the aetiology of lung cancer and to assess the interaction between mEH polymorphisms and smoking, we performed a meta-analysis of seven published studies, which included 2078 cases and 3081 controls, and a pooled analysis of eight studies (four published and four unpublished at that time) with a total of 986 cases and 1633 controls. The combined meta-analysis odds ratios (ORs) were 0.98 (95% confidence interval [CI] = 0.72–1.35) for polymorphism at amino acid 113 in exon 3 (His/His versus Tyr/Tyr genotype) and 1.00 (95% CI = 0.71–1.41) for polymorphism at amino acid 139 in exon 4 (Arg/Arg versus His/His genotype). In the pooled analysis, we observed a significant decrease in lung cancer risk (OR = 0.70, 95% CI = 0.51–0.96) for exon 3 His/His genotype after adjustment for age, sex, smoking and centre. The protective effect of exon 3 polymorphism seems stronger for adenocarcinoma of the lung than for other histological types. The OR for high predicted mEH activity, compared with low activity, was 1.54 (95% CI = 0.77–3.07) in the meta analysis and 1.18 (95% CI = 0.92–1.52) in the pooled analysis. We did not find a consistent modification of the carcinogenic effect of smoking according to mEH polymorphism, although the risk of lung cancer decreased among never smokers with high mEH activity and among heavy smokers with the exon 3 His/His genotype. In conclusion, this study suggests a possible effect of mEH polymorphisms at exon 3 in modulating lung cancer. If present, this effect may vary among different populations, possibly because of interaction with genetic or environmental factors.

Keywords: microsomal epoxide hydrolase, polymorphism, lung cancer, smoking.

Introduction

The enzyme microsomal epoxide hydrolase (mEH) is known to play a dual role in the bioactivation and detoxication of procarcinogens. mEH catalyses the

* Corresponding author: Paul Brennan, Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69008 Lyon, France. Tel: (+33) 4 72738391; Fax: (+33) 4 72738320; e-mail: brennan@iarc.fr

Biomarkers ISSN 1354–750X print/ISSN 1366–5804 online © 2002 Taylor &
http://www.tandf.co.uk/journals
DOI: 10.1080/13547500210121882

hydrolysis of reactive aliphatic and arene epoxides; this reaction is generally considered to be a detoxification reaction (Oesch 1973). mEH also intervenes in the metabolic activation of the polycyclic aromatic hydrocarbons (PAHs), one group of carcinogens present in tobacco smoke, thereby triggering the formation of highly reactive metabolites (Lu and Miwa 1980). The mEH gene is composed of nine exons, and two genetic polymorphisms have been identified: one at amino acid 113 in exon 3, resulting in a tyrosine (Tyr) to histidine (His) change and in reduced enzyme activity, the other at amino acid 139 in exon 4, which changes histidine to arginine (Arg), and increases enzyme activity by modifying protein stability (Hassett *et al.* 1994). Since mEH is strongly expressed in bronchial epithelial cells and is presumably involved in metabolism of tobacco carcinogens such as PAHs, an association between mEH and susceptibility to lung cancer has been hypothesized. However, most of the published relevant studies are small and their results appear to be conflicting. Benhamou *et al.* (1998) and Persson *et al.* (1999) reported that the combination of both mEH polymorphisms resulting in decreased enzyme activity was associated with a decreased risk of lung cancer. In contrast, London *et al.* (2000) failed to find an association between lung cancer and predicted activity in Caucasians, while a decreased risk associated with predicted low activity was found among African-Americans. Lin *et al.* (2000) also found a significant risk excess for squamous cell carcinoma (but not other histological types of lung cancer) with high mEH activity. Smith and Harrison (1997), Yoshikawa *et al.* (2000) and Zhou *et al* (2001) suggested no association between lung cancer and mEH polymorphisms.

In most of these studies, the sample size was relatively small and the power to detect a moderate increase or decrease in risk was limited. Thus, a combined analysis of all relevant studies should be useful to properly evaluate the putative association between mEH polymorphism and lung cancer and to analyse the interaction between mEH polymorphism and smoking in causing lung cancer.

We therefore performed both a meta-analysis of published studies and a pooled analysis of the raw data from selected published and unpublished studies to obtain summary measures of the effect of mEH polymorphisms in the aetiology of lung cancer. In addition, we assessed the interaction between mEH polymorphism and tobacco smoking in the subset of the data where this information was available.

Materials and methods

Data collection

We included data submitted to the database of the International Collaborative Study on Genetic Susceptibility to Environmental Carcinogens (GSEC) containing original data of published and unpublished studies (Taioli 1999), together with other studies published before July 2001 found by searching in MEDLINE using a combination of key words such as 'epoxide hydrolase' and 'lung cancer', without restriction on language; we also used the reference lists of other publications. We conducted two complementary analysis of these data. First, we performed a meta-analysis of the results of published studies, whether or not they were included in the GSEC database. Second, we performed a pooled re-analysis of raw (i.e. individual-based) data submitted to the GSEC database, whether or not it had been published.

From the GSEC data set we identified six studies, of which three were published (Benhamou *et al.* 1998, Persson *et al.* 1999, London *et al.* 2000) and three unpublished at that time (Rannug, unpublished data, Shields, unpublished data, To-Figueras *et al.* 2001). From the literature search we identified eight published papers (Smith and Harrison 1997, Benhamou *et al.* 1998, Pastorelli *et al.* 1998, Persson *et al.* 1999, Lin *et al.* 2000, London *et al.* 2000, Yoshikawa *et al.* 2000, Zhou *et al.* 2001). We excluded one case control study because it did not show information on genotype but only on crude activity levels

(Lin *et al.* 2000). We also excluded one case-only study from the meta-analysis (Pastorelli *et al.* 1998). Two of the studies were stratified according to two ethnic groups, and we treated the data from each ethnic group as a separate study (London *et al.* 2000, Shields, unpublished data). Therefore, the number of individual studies retained in the analysis was seven for the meta-analysis and eight for the pooled analysis (table 1).

Based on the assumption that the exon 3 Tyr and exon 4 His alleles confer 'normal' activity, while the His allele at exon 3 confers 'low' activity and the Arg allele at exon 4 confers 'high' activity, we classified predicted mEH activity as low, intermediate or high based on the presence or absence of the two polymorphisms (table 2).

Statistical analyses

Odds ratios (ORs) and 95% confidence intervals (CIs) of lung cancer for mEH polymorphism and predicted mEH activity were estimated for each study. The reference groups were individuals with the Tyr/Tyr genotype for exon 3 polymorphism, the His/His genotype for exon 4 polymorphism and low predicted mEH activity. Meta-analyses techniques that weighted the logarithm of the OR for each study by a function of its variance were used to calculate summary risk estimates. Meta-ORs based on random effects models (DerSimonian and Laird 1986) were calculated for all available studies and for studies including Caucasians. We also assessed potential publication bias by using Egger's test (Egger *et al.* 1997).

Data from 986 lung cancer patients and 1633 controls included in the GSEC database were used to conduct a pooled analysis based on individual records. In particular, we aimed to assess the interaction between mEH polymorphisms and smoking. To this end, individuals were categorized as never smokers, light smokers (1–34 pack-years of cumulative consumption) or heavy smokers (35 or more pack-years). We performed the pooled analysis using unconditional logistic regression models that included terms for age (in tertiles), sex and study centre. In the interaction analysis, never smokers with either Tyr/Tyr polymorphism at exon 3, His/His polymorphism at exon 4 or low predicted activity were used as the reference category. The analysis was performed for the entire data, and again after stratification according to the type of control population (healthy or hospital) and histological type of lung cancer. One study (To-Figueras *et al.* 2001) included both healthy and hospital controls and was excluded from this analysis. All statistical analyses were performed using STATA software (version 6.0).

Results

Table 3 shows the study-specific ORs for the risk of lung cancer associated with mEH at exon 3 and exon 4. These results do not support a consistent pattern for either polymorphism or lung cancer risk. Out of the 44 ORs reported in table 3, only three (Benhamou *et al.* 1998, Persson *et al.* 1999, To-Figueras *et al.* 2001) showed any statistically significant increase or decrease from the reference group, and in all three this was for the effect of heterozygote status, arguing against a causal relationship.

Among the control group, the average distribution of each genotype was 48.9% for Tyr/Tyr, 37.7% for Tyr/His and 13.4% for His/His at exon 3, and 65.3% for His/His, 30.7% for His/Arg and 4.0% for Arg/Arg at exon 4. Asians showed higher proportions of the His/His type at exon 3.

The results of the meta-analysis (table 4) did not indicate an association between lung cancer and polymorphism at exon 3 for either the Tyr/His genotype (OR = 0.93, 95% CI = 0.72–1.21) or the His/His genotype (OR = 0.98, 95% CI = 0.72–1.35). The results for exon 4 also did not indicate an association for either the His/Arg genotype (OR = 1.15, 95% CI = 0.99–1.32) or the Arg/Arg genotype (OR = 1.00, 95% CI = 0.71–1.41). Similarly, predicted mEH activity level was not associated with an increased risk of lung cancer (table 4). The OR in the intermediate activity group was 1.21 (95% CI = 0.93–1.58) and that in the high activity group was 1.54 (95% CI = 0.77–3.07). Similar results were also observed when the analysis was restricted to Caucasians. In none of the meta-analysis we conducted was there evidence of publication bias. Heterogeneity was

Table 1. Summary of case-control studies of mEH and lung cancer included in the meta-analysis and the pooled analysis.

				Cases[a]							Controls[a]							Included in publication (cases/controls)[b]
					Age (years)		Smokers		Pack-years				Age (years)		Smokers		Pack-years		
Study	Analysis	Ethnic group	Country	No.	Mean	SD	No.	%	Mean	SD	No.	Source	Mean	SD	No.	%	Mean	SD	
Benhamou *et al.* 1998	M, P	Caucasian	France	150	58.4	9.9	150	100	48.3	25.8	172	Hospital	54.9	11.1	172	100	37.8	26.6	150/172
London *et al.* 2000	M, P	Caucasian	USA	184	64.1	10.0	178	96.7	55.9	35.4	460	Healthy	62.3	8.6	299	65.0	37.6	32.6	182/458
London *et al.* 2000	M, P	African/ American	USA	156	63.0	8.7	150	96.2	41.8	30.9	244	Healthy	63.0	7.8	169	69.3	30.0	26.5	155/242
Persson *et al.* 1999	M, P	Asian	China (cases), Sweden (controls)	74	53.8	11.7	48	64.9	41.4	29.7	122	Healthy	35.8	9.6	23	18.9	—	—	74/122
Rannug, unpublished	P	Caucasian	Sweden	199	63.6	9.8	192	96.5	31.2	19.1	423	Healthy	45.2	13.7	275	65.0	12.6	11.4	—
Shields, unpublished	P	Caucasian	USA	25	63.9	6.3	24	96.0	66.2	29.8	21	Hospital	62.6	4.2	19	90.5	86.8	48.2	—
Shields, unpublished	P	African/ American	USA	24	65.3	8.3	24	100	50.9	31.5	21	Hospital	60.6	10.7	20	95.2	52.5	37.6	—
Smith and Harrison 1997	M	Caucasian	UK	—	—	—	—	—	—	—	—	Healthy	—	—	—	—	—	—	50/203
To-Figueras *et al.* 2001	P	Caucasian	Spain	174	59.8	10.9	169	97.1	57.1	26.1	170	Healthy and hospital	51.9	10.2	170	100	50.0	28.2	—
Yoshikawa *et al.* 2000	M	Asian	Japan	—	—	—	—	—	—	—	—	Hospital	—	—	—	—	—	—	71/107
Zhou *et al.* 2001	M	Causasian	USA	—	—	—	—	—	—	—	—	Healhy	—	—	—	—	—	—	874/1142

M, meta-analysis; P, pooled analysis.
[a] As in GSEC database for studies included in the pooled analysis.
[b] As in original articles.

Table 2. Predicted activity of mEH.

	Exon 3		
Exon 4	Tyr/Tyr	Tyr/His	His/His
His/His	Intermediate	Low	Low
His/Arg	High	Intermediate	Low
Arg/Arg	High	High	Intermediate

high for predicted high activity ($P = 0.01$) and exon 3 Tyr/His genotype ($P = 0.03$) and increased when the analysis was restricted to Caucasians.

The pooled analysis was based on 986 cases and 1633 controls, of whom 422 cases and 635 controls were from unpublished studies. Results classified according to exon 3 and exon 4 polymorphisms and predicted activity are reported in table 5. The OR for the His/His genotype at exon 3 was significantly decreased (OR = 0.70, 95% CI = 0.51–0.96), while no effect of exon 4 polymorphism or predicted activity was apparent. When the analysis was restricted to Caucasians, there was no association between lung cancer and the polymorphism at exon 3, exon 4 or predicted mEH activity. When we stratified the analysis according to the type of controls (hospital patients or healthy individuals), the results of studies with healthy controls were similar to those found in the analysis of the total dataset, while the pooled analysis of studies with hospital-based controls resulted in decreased ORs associated with exon 3 polymorphism and increased ORs associated with exon 4 polymorphism and predicted activity.

We examined each of the three major histological types of lung cancer by using GSEC data to assess the effect of mEH polymorphisms on the risk of developing particular types. The analyses included 268 adenocarcinoma cases, 336 squamous cell carcinoma cases and 146 small cell carcinoma cases (table 6). The decreased OR for the His/His genotype at exon 3 was present for adenocarcinoma and squamous cell carcinoma, although it was statistically significant only in the former group. A non-significant increased OR for predicted high mEH activity was apparent for adenocarcinoma, but not for the other histological types of lung cancer.

Analysis of the interaction between mEH polymorphisms and tobacco smoking (table 7) did not suggest a clear modification of the carcinogenic effect of smoking according to either mEH polymorphism or predicted enzymatic activity. There was, however, a suggestion of a decrease in the OR for exon 3 polymorphism among heavy smokers and for predicted high mEH activity among non-smokers, although the small number of cases hampered the interpretation of these results.

Discussion

The results of our meta-analysis indicate no significant association between lung cancer risk and either mEH exon 3 or exon 4 polymorphism. On the other hand, the results of the analysis of the individual data provided to the GSEC database suggest a protective effect from the exon 3 His/His genotype compared with the Tyr/Tyr genotype. This finding, which could be explained by a predominant activating role of mEH in metabolism of lung carcinogens, is at

Table 3. Study-specific ORs of lung cancer for (a) exon 3 and (b) exon 4 polymorphisms. The ORs are reported from the original publications for published papers and derived from the analysis of the GSEC data set for unpublished papers.

(a) Exon 3 polymorphisms

	Tyr/Tyr (reference)		Tyr/His			His/His		
Study[a]	OR	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI	Cases/controls
Benhamou *et al.* 1998	1.0	82/64	0.47	0.29–0.76	46/77	0.55	0.29–1.04	22/31
London *et al.* 2000	1.0	85/237	1.24	0.89–1.78	82/184	1.13	0.60–2.15	15/37
London *et al.* 2000	1.0	106/153	0.90	0.58–1.39	48/77	0.17	0.02–1.35	1/12
Persson *et al.* 1999	1.0	21/41	1.09	0.56–2.14	33/59	1.77	0.80–3.94	20/22
Rannug, unpublished	1.0	98/223	1.26	0.89–1.79	90/162	0.66	0.33–1.33	11/38
Shields, unpublished	1.0	5/7	1.23	0.28–5.44	7/8	3.03	0.70–13.13	13/6
Shields, unpublished	1.0	3/4	3.33	0.40–27.07	5/2	1.42	0.20–6.67	16/15
Smith and Harrison 1997	1.0	25/91	0.74	0.39–1.41	20/99	1.40	0.48–4.16	5/13
To-Figueras *et al.* 2001	1.0	95/72	0.63	0.41–0.98	71/85	0.47	0.19–1.16	8/13
Yoshikawa *et al.* 2000	1.0	24/35	1.00	0.51–1.96	35/51	0.83	0.35–1.99	12/21
Zhou *et al.* 2001	1.0	465/581	1.17	0.96–1.42	332/355	1.07	0.85–1.36	177/206

(b) Exon 4 polymorphisms

	His/His (reference)		His/Arg			Arg/Arg		
Study[a]	OR	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI	Cases/controls
Benhamou *et al.* 1998	1.0	94/121	1/39	0.87–2.23	53/49	1.8	0.35–9.38	3/2
London *et al.* 2000	1.0	125/302	0.89	0.61–1.30	50/136	0.85	0.36–2.00	7/20
London *et al.* 2000	1.0	70/119	1.13	0.74–1.73	70/105	1.42	0.68–2.96	15/18
Persson *et al.* 1999	1.0	54/97	2.11	1.03–4.34	20/17	0.26	0.01–5.03	0/3
Rannug, unpublished	1.0	126/240	0.73	0.51–1.05	61/159	1.09	0.53–2.26	12/21
Shields, unpublished	1.0	16/13	1.05	0.31–3.48	9/7	0.27	0.01–7.27	0/1
Shields, unpublished	1.0	12/9	0.60	0.17–2.09	8/10	1.50	0.25–8.58	4/2
Smith and Harrison 1997	1.0	33/147	1.35	0.69–2.62	16/53	1.89	0.26–13.26	1/3
To-Figueras *et al.* 2001	1.0	115/111	0.97	0.61–1.53	53/53	0.48	0.13–1.81	3/6
Yoshikawa *et al.* 2000	1.0	45/75	1.43	0.74–2.75	24/28	0.83	0.01–4.08	2/4
Zhou *et al.* 2001	1.0	643/772	1.10	0.91–1.33	300/327	0.87	0.54–1.38	31/43

[a]See table 1 for details on the studies.

Table 4. Results of meta-analysis of mEH (published studies).

	All populations (seven studies)				Caucasians (four studies)			
	OR	85% CI	Q[d]	Publication bias[e]	OR	85% CI	Q[d]	Publication bias[e]
Exon 3 polymorphisms[a]								
Tyr/His	0.93	0.72–1.21	0.03	0.15	0.88	0.59–1.33	<0.01	0.37
His/His	0.98	0.72–1.35	0.17	0.55	0.98	0.71–1.34	0.24	0.50
Exon 4 polymorphisms[b]								
His/Arg	1.15	0.99–1.32	0.43	0.48	1.10	0.94–1.29	0.48	0.99
Arg/Arg	1.00	0.71–1.41	0.80	0.23	0.93	0.63–1.38	0.74	0.33
Predicted activity[c]								
Intermediate	1.21	0.93–1.58	0.32	0.91	0.31	0.90–1.91	0.22	—
High	1.54	0.77–3.07	0.01	0.35	1.37	0.33–5.66	<0.01	—

[a] Tyr/Tyr genotype used as reference.
[b] His/His genetype used as reference.
[c] Low activity used as reference. Only four groups (Benhamou *et al.* 1998, Persson *et al.* 1999, both ethic groups in London *et al.* 2000) for all populations and two groups (Benhamou *et al.* 1998, Caucasian population London *et al.* 2000) for Caucasians could be analysed because of different classifications of predicted activity in each study.
[d] *p* value of Q statistics test for heterogeneity (DerSimonian and Laid 1986).
[e] *p* value of test for publication bias (Egger *et al.* 1997).

Table 5. Results of pooled analysis of mEH (data submitted to GSEC database).

	All populations (eight studies)		Caucasians (five studies)		Healthy controls (four studies)		Hospital controls (three studies)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Exon 3 polymorphisms[a]								
Tyr/His	0.92	9.76–1.11	0.92	0.74–1.14	1.12	0.89–1.42	0.57	0.36–0.90
His/His	0.70	0.51–0.96	0.73	0.51–1.05	0.73	0.48–1.14	0.70	0.41–1.21
Exon 4 polymorphisms[b]								
His/Arg	1.00	0.82–1.21	0.96	0.77–1.20	0.92	0.73–1.18	1.22	0.80–1.86
Arg/Arg	1.04	0.67–1.61	0.92	0.53–1.60	1.09	0.66–1.79	1.51	0.44–5.23
Predicted activity[c]								
Intermediate	1.19	0.97–1.46	0.96	0.67–1.36	1.06	0.82–1.38	1.32	0.85–2.05
High	1.18	0.92–1.52	0.95	0.50–1.87	0.97	0.72–1.32	1.95	1.09–3.50

All ORs are adjusted for age (in tertiles), sex, smoking and study centre.
[a] Tyr/Tyr genotype used as reference.
[b] His/His genotype used as reference.
[c] Low activity used as reference.

Table 6. Results of pooled analysis stratified by histological type of lung cancer (data submitted to GSEC database).

	Adenocarcinoma (268 cases)		Squamous cell carcinoma (336 cases)		Small cell carcinoma (146 cases)	
	OR	95% CI	OR	95% CI	OR	95% CI
Exon 3 polymorphisms[a]						
Tyr/His	0.86	0.63–1.15	0.97	0.73–1.27	1.19	0.81–1.76
His/His	0.45	0.26–0.79	0.77	0.49–1.19	1.13	0.67–1.90
Exon 4 polymorphisms[b]						
His/Arg	1.05	0.78–1.42	0.97	0.74–1.28	1.24	0.85–1.80
Arg/Arg	0.87	0.44–1.72	1.17	0.62–2.21	1.46	0.62–3.41
Predicted activity[c]						
Intermediate	1.34	0.97–1.85	1.00	0.75–1.34	1.35	0.92–1.99
High	1.39	0.95–2.05	1.12	0.79–1.59	0.93	0.54–1.58

All ORs are adjusted for age (in tertiles), sex, smoking and study centre.
[a] Tyr/Tyr genotype used as reference.
[b] His/His genotype used as reference.
[c] Low activity used as reference.

odds with the lack of a clear effect of predicted enzymatic activity (and in fact an opposite effect of predicted activity among non-smokers).

The difference between the results of the meta-analysis and the pooled analysis can be explained (i) by the different populations included in the two approaches; (ii) by the different methods used to adjust for study centre; or (iii) by a confounding effect exerted by the variables adjusted for in the pooled analysis (age, sex, smoking). We have tested these three hypotheses by repeating the analysis after restriction to the studies included in both approaches (Benhamou *et al.* 1998, Persson *et al.* 1999, London *et al.* 2000). The meta-analysis of exon 3 His/His genotype resulted in a OR of 0.88 (95% CI = 0.55–1.37). The OR of the pooled analysis adjusted only for study centre was 0.84 (95% CI = 0.63–1.12), and that of the fully adjusted pooled analysis was 0.70 (95% CI = 0.51–0.96). We therefore concluded that the pooled analysis approach is more appropriate than meta-analysis to control for bias and confounding.

Our analysis suggests some heterogeneity in the results of individual studies. One possible reason for the heterogeneity is linkage disequilibrium, with additional allelic variants that modulate overall enzyme activity. It is also possible that interaction with polymorphisms at other genes may be important. For example, Lin *et al.* (2000) found that a combination of susceptible CYP1A1 and mEH genotypes was highly associated with lung cancer (OR = 6.76, 95% CI = 2.29–19.10) compared with mEH polymorphism alone (OR = 1.96, 95% CI = 1.04–3.70) in squamous cell lung cancer. Furthermore, genotype information alone might be insufficient to explain the variation in mEH enzyme activity seen in population studies (Hassett *et al.* 1997). For example, dietary factors such as fish oil may induce mEH and thus increase enzyme activity (Yang *et al.* 1993), and such phenotypic determinants may vary across populations. Differences in age, proportion of smokers and sources of control group may also contribute to the heterogeneity. In the pooled analysis, the heterogeneity was generally stronger than in the meta-analysis, and it was increased when the studies were restricted to

Table 7. Results of analysis of interaction between smoking and mEH polymorphisms (data submitted to GSEC database).

	Smoking								
	Never			Light			Heavy		
	OR	95% CI	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI	Cases/controls
Exon 3 polymorphisms[a]									
Tyr/Tyr	1.0 (ref)	—	9/44	10.95	6.50–18.45	43/65	22.94	13.47–39.05	124/88
Tyr/His	1.05	0.57–1.94	28/197	8.03	4.70–13.74	115/235	20.74	12.09–35.59	212/167
His/His	0.79	0.28–2.17	21/248	8.59	4.33–17.04	171/262	13.45	7.08–25.57	201/158
Exon 4 polymorphisms[b]									
His/His	1.0 (ref)	—	44/300	7.96	4.89–12.95	189/345	18.12	11.0–29.71	343/268
His/Arg	0.72	0.36–1.45	13/161	8.25	4.95–13.73	121/197	19.30	11.42–32.61	169/124
Arg/Arg	—	—	0/25	15.54	6.90–35.00	19/18	14.03	6.55–30.08	24/21
Predicted activity[c]									
Low	1.0 (ref)	—	30/169	6.63	3.70–11.85	113/221	16.05	8.97–28.72	261/198
Intermediate	0.76	0.40–1.45	20/200	8.52	4.80–15.13	135/213	18.22	10.14–32.76	181/145
High	0.59	0.24–1.48	7/115	8.63	4.70–15.85	80/124	16.40	8.75–30.76	92/69

All ORs are adjusted for age (in tertiles), sex, smoking and study centre.
[a] Tyr/Tyr genotype used as reference.
[b] His/His genotype used as reference.
[c] Low activity used as reference.

Caucasians. Therefore the random effects model was more appropriate than a fixed effect model for calculating the ORs in this study.

In our pooled analysis, the decreased risk from exon 3 polymorphism was more apparent for adenocarcinoma, and in particular among smokers with adenocarcinoma (results not shown in detail). Although we could not exclude chance because of the small number of adenocarcinoma cases with the exon 3 His/His genotype, this finding suggests mEH polymorphism have stronger effect on carcinogenic pathways in adenocarcinoma than in other types of lung cancer. There were no significant risks for healthy controls, while hospital controls showed significantly increased risk in the high activity group. These results suggest caution in the interpretation of our findings, since hospital-based case-control studies are more prone to bias than population-based studies (Wacholder *et al.* 1992). Explanations for this difference could be that the disease for which controls have been hospitalized is related to mEH polymorphism, or alternatively that mEH activity is modified by the disease for which the controls have been hospitalized.

When performing a meta-analysis, publication bias can be an issue. This bias can be reduced in a pooled analysis by adding unpublished studies. The test we used to assess the presence of publication bias, however, is not powerful when the meta-analysis is based on relatively few studies. However, there was no evidence of lack of studies with either positive or negative results in both the meta- and pooled analysis.

We also did not find any suggestion of a consistent modification of the carcinogenic effect of smoking according to mEH polymorphism. These null findings persisted after adjusting for age, sex and study centre, and also after stratifying by ethnicity. However, the possible decreased risk associated with high mEH activity among never smokers and with the exon 3 polymorphism among heavy smokers suggests that further assessment of the interaction between mEH and smoking should be performed.

In conclusion, this study suggested a decreased risk for lung cancer with the exon 3 His/His genotype. The apparent protective effect of exon 3 polymorphism was stronger for adenocarcinoma of the lung and among heavy smokers. This result, however, was only present in the pooled analysis of individual data. Our study suggests caution in the interpretation of meta-analysis based on a combination of published results.

Acknowledgements

Dr Won Jin Lee worked on this study under the tenure of a Special Training Award from the International Agency for Research on Cancer.

References

Benhamou, S., Reinikainen, M., Bouchardy, C., Dayer, P. and Hirvonen, A. 1998, Association between lung cancer and microsomal epoxide hydrolase genotypes. *Cancer Research*, **58**, 5291–5293.

DerSimonian, R. and Laird, N. 1986, Meta-analysis in clinical trials. *Controlled Clinical Trials*, **7**, 177–188.

Egger, M., Davey Smith, G., Schneider, M. and Minder, C. 1997, Bias in meta-analysis detected by a simple graphical test. *British Medical Journal*, **315**, 629–634.

Hassett, C., Aicher, L., Sidhu, J. S. and Omiecinski, C. J. 1994, Human microsomal epoxide hydrolase: genetic polymorphism and functional expression in vitro of amino acid variants. *Human Molecular Genetics*, **3**, 421–428.

Hassett, C., Lin, J., Carty, C. L., Laurenzana, E. M. and Omiecinski, C. J. 1997, Human hepatic microsomal epoxide hydrolase: comparative analysis of polymorphic expression. *Archives of Biochemistry and Biophysics*, **337**, 275–283.

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. *British Journal of Cancer*, **82**, 852–857.

London, S. J., Smart, J. and Daly, A. K. 2000, Lung cancer risk in relation to genetic polymorphisms of microsomal epoxide hydrolase among African-Americans and Caucasians in Los Angeles County. *Lung Cancer*, **28**, 147–155.

Lu, A. Y. and Miwa, G. T. 1980, Molecular properties and biological functions of microsomal epoxide hydrolase. *Annual Review of Pharmacology and Toxicology*, **20**, 513–531.

Oesch, F. 1973, Mammalian epoxide hydrolase: inducible enzymes catalysing the inactivation of carcinogenic and cytotoxic metabolites derived from aromatic and olefinic compounds. *Xenobiotica*, **3**, 305–340.

Pastorelli, R., Guanci, M., Cerri, A., Negri, E., La Vecchia, C., Fumagalli, F., Mezzetti, M., Cappelli, R., Panigalli, T., Fanelli, R. and Airoldi, L. 1998, Impact of inherited polymorphisms in glutathione S-transferase M1, microsomal epoxide hydrolase, cytochrome P450 enzymes on DNA, and blood protein adducts on benzo[*a*]pyrene-diolepoxide. *Cancer Epidemiology, Biomarkers and Prevention*, **7**, 703–709.

Persson, I., Johansson, I., Lou, Y. C., Yue, Q. Y., Duan, L. S., Bertilsson, L. and Ingelman Sunderg, M. 1999, Genetic polymorphism of xenobiotic metabolizing enzymes among Chinese lung cancer patients. *International Journal of Cancer*, **81**, 325–329.

Smith, C. A. and Harrison, D. J. 1997, Association between polymorphism in gene for microsomal epoxide hydrolase and susceptibility to emphysema. *Lancet*, **350**, 630–633.

Taioli, E. 1999, International collaborative study on genetic susceptibility to environmental carcinogens. *Cancer Epidemiology, Biomarkers and Prevention*, **8**, 727–728.

To-Figueras, J., Gene, M., Gomez-Catalan, J., Pique, E., Borrego, N. and Corbella, J. 2001, Lung cancer susceptibility in relation to combined polymorphisms of microsomal epoxide hydrolase and glutathione S-transferase P1. *Cancer Letters*, **173**, 155–162.

Wacholder, S., Silverman, D. T., McLaughlin, J. K. and Mandel, J. S. 1992, Selection of controls in case-control studies. II. Types of controls. *American Journal of Epidemiology*, **135**, 1029–1041.

Yang, E. K., Radominska, A., Winder, B. S. and Dannenberg, A. J. 1993, Dietary lipids coinduce xenobiotic metabolizing enzymes in rat liver. *Biochimica Biophysica Acta*, **1168**, 52–58.

Yoshikawa, M., Hiyama, K., Ishioka, S., Maeda, H., Maeda, A. and Yamakido, M. 2000, Microsomal epoxide hydrolase genotypes and chronic obstructive pulmonary disease in Japanese. *International Journal of Molecular Medicine*, **5**, 49–53.

Zhou, W., Thurston, S. W., Liu, G., Xu, L. L., Miller, D. P., Wain, J. C., Lynch, T. J., Su, L. and Christiani, D. C. 2001, The interaction between microsomal epoxide hydrolase polymorphisms and cumulative cigarette smoking in different histological subtypes of lung cancer. *Cancer Epidemiology, Biomarkers and Prevention*, **10**, 461–466.