Lack of Interaction between Asbestos Exposure and Glutathione *S*-Transferase *M1* and *T1* Genotypes in Lung Carcinogenesis

Isabelle Stücker, Paolo Boffetta, Sisko Antilla, Simone Benhamou, Ari Hirvonen, Stephanie London, and Emanuela Taioli

INSERM U170, 94807 Villejuif, France [I. S.]; International Agency for Research on Cancer, 69008 Lyon, France [P. B.]; Finnish Institute of Occupational Health, FIN-00250 Helsinki, Finland [S. A., A. H.]; INSERM U351, 94805 Villejuif, France [S. B.]; National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709 [S. L.]; and Ospedale Policlinico IRCCS, University of Milan, 20122 Milan, Italy [E. T.]

Abstract

An interaction between occupational carcinogens and genetic susceptibility factors in determining individual lung cancer risk is biologically plausible, but the interpretation of available studies are limited by the small number of exposed subjects. We selected from the international database on Genetic Susceptibility and Environmental Carcinogens the studies of lung cancer that included information on metabolic polymorphisms and occupational exposures. Adequate data were available for asbestos exposure and *GSTM1* (five studies) and *GSTT1* (three studies) polymorphisms. For *GSTM1*, the pooled analysis included 651 cases and 983 controls. The odds ratio (OR) of lung cancer was 2.0 [95% confidence interval (CI) 1.4–2.7] for asbestos exposure and 1.1 (95% CI 0.9–1.4) for GSTM1-null genotype. The OR of interaction between asbestos and *GSTM1* polymorphism was 1.1 (95% CI 0.6–2.1) based on 54 cases and 53 controls who were asbestos exposed and *GSTM1* null. The case-only approach, which was based on 869 lung cancer cases and had an 80% power to detect an OR of interaction of 1.56, also provided lack of evidence of interaction. The analysis of possible interaction between *GSTT1* polymorphism and asbestos exposure in relation to lung cancer was based on 619 cases. The prevalence OR of *GSTT1*-null genotype and asbestos exposure was 1.1 (95% CI 0.6–2.0). Our results do not support the hypothesis that the risk of lung cancer after asbestos exposure differs according to *GSTM1* genotype. The low statistical power of the pooled analysis for *GSTT1* genotypes hampered any firm conclusion. No adequate data were available to assess other interactions between occupational exposures and metabolic polymorphisms.

Introduction

A number of occupational exposures have been shown to contribute to the development of lung cancer. These exposures include asbestos fibers, mixtures of PAHs[2] such as coal tar, heavy metals such as hexavalent chromium and nickel, and crystalline silica (1). Since even under very high-exposure circumstances only a small proportion of exposed workers develop lung cancer, it is plausible that genetic susceptibility factors play a role in determining individual risk of developing ill health related to the exposures.

Eleven metabolic gene polymorphisms have been studied with respect to individual susceptibility to lung cancer (2). In particular, polymorphisms have been described for the genes encoding for the enzymes GST, which are involved in the conjugation of electrophilic metabolites of xenobiotics. These cytosolic isoenzymes are divided into five major classes (α, μ, π, θ, and ζ); genetic polymorphisms have been detected in the genes encoding GSTM1 (μ class), GSTM3, GSTT1 (θ class), and GSTP1 (π class), and GSTZ1 (ζ class) (3). GSTs are involved in the metabolism of environmental carcinogens, such as PAHs, and in the conjugation of ROS. The role of the different class of GSTs in the trap of ROS, however, is not well understood (4).

The *GSTM1* locus is deleted (null genotype) in ~50% of Caucasians and in a lower proportion of people from other ethnic groups. The *GSTM1*-null genotype has been associated with a small increased risk of lung cancer in several studies. Recent meta-analyses of the studies performed in Caucasian populations resulted in a summary estimate of 15–20% increased risk of lung cancer associated with the *GSTM1*-null genotype (5–7). The *GSTT1*-null genotype, on the other hand, occurs in 10–20% of Caucasians and in ~50% of Asians, whereas little data are available for African-Americans.[3] Only a few reports with inconsistent results are available on the association between lung cancer risk and *GSTT1*-null genotype (6, 8, 9).

Similarly, only a few studies have addressed the role of metabolic gene polymorphisms in modulating the risk of pathologies associated with occupational exposure to carcinogens, and their interpretation is hampered by small numbers. One study suggested an effect of past occupational exposure to asbestos in lung cancer risk among CYP2D6-extensive metabolisers but not among poor metabolisers (10). Another study found a nonsignificantly higher risk of lung cancer associated with the *GSTM1*-null genotype among subjects with possible or probable past occupational exposure to asbestos than among nonexposed subjects (11). In Finland, an increased risk of

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[1] To whom requests for reprints should be addressed, at INSERM U170, 16 Av Paul Vaillant Couturier, 94807 Villejuif, Cedex, France. Phone: 33-01-45-59-50-33; Fax: 33-01-45-59-51-51; E-mail: stucker@vjf.inserm.fr.

[2] The abbreviations used are: PAH, polycyclic aromatic hydrocarbons; GST, glutathione *S*-transferase; OR, odds ratio; ROS, reactive oxygen species; GSEC, Genetic Susceptibility to Environmental Carcinogens; POR, prevalence odds ratio; CI, confidence interval.

[3] Garte, this issue.

Table 1 Studies included in the pooled analysis of *GSTM1* and *GSTT1* genotype

Study (label)	Cases	Controls	Definition of the control population	Men %	Age means ± SD	Smokers %	PckY means ± SD	Asbestos (% E+)[a]
Case control studies								
London *et al.*, 1995—Caucasian (US Cauc)[b]	145	380	Healthy controls from the general population	55	62.9 ± 9.3	71	30.6 ± 34.9	17.5
London *et al.*, 1995—African-American (US-AA)[c]	121	192	Stratified on age (±10 years), sex, and ethnicity	55	62.8 ± 8.3	79	27.7 ± 30.3	23.0
Stücker *et al*, 1999 (France 1)[d]	239	242	Hospital-based controls Matched on age (±2.5 years), sex, and hospital Excluding patient with lung disease or previous cancer	100	59.4 ± 9.8	90	31.9 ± 23.1	7.1
Jourenkova *et al*, 1997 (France 2)[e]	146	169	Hospital-based controls Matched on age (±3 years), sex, and hospital Excluding patients with prior or current malignant disease	95	56.4 ± 10.6	100	43.7 ± 26.5	12.4
Case-only series								
Anttila, Hirvonen *et al.*, 1995 (Finland)[f]	218			78	61.6 ± 9.7	93	35.5 ± 23.9	35.3

[a] Prevalence of exposure on the whole population.
[b] Subjects (132) of the initial study are missing: 13 subjects were missing in the GSEC database, 123 were excluded since they have been exposed to both asbestos and PAH (cf p 6), and 1 for GSTM1 missing.
[c] Subjects (112) of the initial study are missing: 20 subjects were missing in the GSEC database; 92 were excluded since they have been exposed to both asbestos and PAH (cf p. 6).
[d] Subjects (131) of the initial study are missing: 111 with GSTM1 missing and 20 with pack-years missing.
[e] Subjects (7) of the initial study are missing, all because of pack-years.
[f] Subjects (9) of the initial study are missing.

mesothelioma has been observed among asbestos-exposed workers lacking the *GSTM1* gene (12, 13). Studies on the nonmalignant, asbestos-associated pulmonary disorders, pleural plaques, did not, on the other hand, give consistent results for the potential role of either *GSTM1* or *GSTT1* genotypes in development of the plaques (12, 14, 15).

Several cross-sectional studies have looked for an effect of occupational PAH exposure on different biomarkers, mainly adducts and 1-OH pyrene, taking into account genetic polymorphisms (16–22). Moreover, a single case control study has suggested that OR of lung cancer associated to past occupational PAH exposure might be higher among CYP2D6-extensive metabolisers than among poor metabolisers (10). To our knowledge, no studies have been reported addressing the interaction between occupational lung carcinogens other than asbestos or PAHs and metabolic gene polymorphisms in lung cancer.

The aim of this work was to assess the interaction between occupational lung carcinogens and metabolic gene polymorphisms in a pooled analysis of studies on lung cancer. However, since asbestos was the only occupational carcinogen assessed jointly in the five case control studies, the pooled analysis was restricted to this agent. Mechanisms of carcinogenicity of asbestos have been reviewed recently (23). There is increasing evidence that generation of reactive free radicals is a key factor underlying cytotoxic and cell-activation responses. These radicals may be generated through redox reactions catalyzed by metals on the surface of the fibers (24). Radicals may also be generated after the phagocytosis of fibers by inflammatory cells (25).

The role of *GSTM1* in the conjugation of ROS leads to the hypothesis of an interaction between *GSTM1* and asbestos. The work presented here examined whether asbestos and *GSTM1* genotype are independent risk factors of lung cancer or act synergistically in asbestos carcinogenicity.

Materials and Methods

The International Collaborative Study on GSEC has been established to systematically investigate the associations between polymorphisms to metabolic enzymes and cancer in humans (26). It consists of pooling data from comparable studies conducted in various countries of the world, in order to achieve a greater statistical power to analyze the main effects of polymorphisms and their interactions with environmental exposures. Relevant studies are identified from the published literature, and principal investigators are invited to provide the raw data. Data are checked before incorporation in the pooled database. The database essentially contains data from published case control studies (with heterogeneous definitions of controls), as well as published series of cases of cancer. It also contains unpublished data. Among the studies included in the GSEC database up to June 1999, we identified four published lung cancer case control studies, which included information on occupational exposures (8, 9, 11, 27), and one case series, which included lung cancer patients from two published studies (28, 29). Asbestos was the only agent whose exposure was assessed in all studies. Exposure to other agents, such as PAHs and heavy metals, had been also sporadically assessed. Therefore, no pooled analysis was performed on agents other than asbestos. The original studies included data on polymorphisms of *GSTM1*, *GSTT1*, *CYP1A1*, *CYP2E1*, and *NAT2* genes, but only the first two genes had been assessed in three or more studies and were retained in this analysis. Furthermore, the prevalence of exposure to asbestos was very low in one case control study, which was restricted to nonsmoking subjects, resulting in a high proportion of female cases and controls; therefore, we excluded this study from the pooled analysis (9). One of the case control studies included a group of Caucasians and a group of African-Americans (11), and we treated them as two separate studies. The final pooled analysis of *GSTM1* polymorphism included three published case control studies and one case series and that of *GSTT1* polymorphism included

Table 2 Assessment of asbestos exposure in each study

Study	Occupational history	Experts in charge of assessment	Exposure metrics (n of categories)
(US Cauc) and (US-AA)	All jobs held for at least 2 years and all jobs entailing possible asbestos exposure	Occupational physicians	Probability (3)
(France 1)	Jobs held for at least 3 months	Panel of industrial hygienists	Score composed of intensity (4), frequency (3), and probability (3)
(France 2)	Jobs held for at least 1 year; specific questionnaires for asbestos-exposed jobs	Authors of the study	Probability (2)
(Finland)	All jobs entailing possible asbestos exposure; nonoccupational exposure	One industrial hygienist	Probability (4)

two case control studies and one case series (Table 1). Assessment exposure to asbestos in each study is presented in Table 2.

A group from Los Angeles comprised incident cases of lung cancer between 1991 and 1994 (11). Patients were either Caucasians ($n = 189$) or African-Americans ($n = 167$). Population controls comprised 473 Caucasians and 258 African-Americans. Exposure to asbestos was classified into categories of none, possible, or probable exposure from self-reported history of employment in jobs with potential exposure by an occupational physician. Among the subjects exposed to asbestos ($n = 379$), 43% were also classified as exposed to PAH in jobs, such as foundry workers, coke-oven workers, roofing, engine repair, and rubber. In order to increase the specificity of assessment of exposure to asbestos, we excluded subjects exposed to both agents ($n = 215$) and retained the 164 subjects exposed to asbestos only. This resulted in a prevalence of exposure similar to that of the other studies. As mentioned above, these data were treated in the pooled analysis as two separate studies.

A hospital-based case control study was carried out between 1988 and 1992 in Caucasians in France (8). Incident cases (150) were included in the study. Controls were patients without a malignant disease. Only regular smokers were included in the study. Detailed information on lifetime occupational history was collected. Occupational exposure to asbestos was assessed from specific questionnaires according to jobs known to entail carcinogen exposure.

An additional hospital-based case control study was carried out among men in France during 1989–1992 (27). Cases were incident primary lung cancer patients ($n = 310$), with a histologically confirmed diagnosis. Patients with lung diseases or cancer were excluded from the controls ($n = 302$). Cases and controls were Caucasians, born in France, and of native French parents. Detailed information on lifetime occupational history was collected. Asbestos exposure was derived from an evaluation of all jobs held by the subjects by a panel of industrial hygienists trained in asbestos exposure.

A case series from Finland included 227 lung cancer patients (28, 29). Occupational history was obtained from personal interviews and a standardized questionnaire filled out by the occupational hygienist interviewer. The probability of past occupational exposure to asbestos was evaluated by the same hygienist on the basis of the occupational history.

All studies analyzed blood samples by PCR methodology to assess *GSTM1* and *GSTT1* genotypes. Details on the assays used are provided in the respective publications.

The first step of this analysis consisted of calculating for each study the OR of lung cancer for exposure to asbestos, *GSTM1* and *GSTT1* genotypes, and their combinations. ORs were calculated from unconditional logistic regression modeling, after adjustment for age, gender, and pack-years of tobacco smoking divided in four classes (<4 pack-years 5–27, 28–45, and >45). Next, the heterogeneity of the ORs was estimated according to Greenland (30). At disposal of at least three independent results, and in case of evidence of lack of heterogeneity ($P \geq 0.10$), a pooled OR was calculated based on a fixed effects model. The interaction between asbestos exposure and genotype was assessed as departure from the hypothesis of an independent effect of each agent and may be written as follows: OR interaction $= OR_{ga}/(OR_g \times OR_a)$, where OR_{ga} is the OR of lung cancer related to the joint effect of asbestos and genotype, OR_g is the OR of lung cancer associated to genotype only, and OR_a is the OR of lung cancer related to asbestos exposure only. In addition, we analyzed the series of cases from case control studies together with the study based on cases only (31). After stratification of cases on the basis of the asbestos exposure and genotype, and providing that these factors are unrelated in the population, the POR is related to the ORs for asbestos exposure and genotype according to the following formula: $POR = OR_{ge}/(OR_g \times OR_e)$ and is therefore equal to the OR of interaction derived in a case control approach. The POR was calculated by unconditional logistic regression after adjustment for age, gender, and tobacco smoking. In order to pool the PORs of the case-only analysis, we followed the same rules described above for the pooling of the ORs derived from the case control studies.

All statistical analyses were performed on a RS6000 IBM (UNIX system), using the SAS Version 6.12 (Cary, NC).

RESULTS

Interaction GSTM1-Asbestos. The four studies included altogether 651 cases and 983 controls. In all studies, a nonsignificant excess of asbestos-exposed subjects was observed among cases as compared with controls (Table 3). Study-specific ORs of lung cancer for asbestos exposure ranged from 1.1 to 3.7 and were homogeneous ($P = 0.17$). The pooled analysis yielded an overall OR of 2.0 (95% CI 1.4–2.7).

A slight excess of *GSTM1*-null genotypes was observed in all the case control studies among cases as compared with controls. However, the study-specific ORs of lung cancer were all not significantly different from one. There was little evidence of heterogeneity among them ($P = 0.65$). The pooled OR was 1.1 (95% CI 0.9–1.4) and remained unchanged after restricting the studies to those among Caucasians. Furthermore, we did not find any evidence of interaction between asbestos and smoking, neither in the separate case control studies nor in the pooled analysis [OR = 1.0 (0.9–1.1)].

All studies showed an independent effect of each risk factor on lung cancer, as displayed by nonsignificant interaction ORs. Results were highly homogenous ($P = 0.89$). On the whole population included in the pooled analysis, 53 controls and 54 cases exhibited *GSTM1*-null genotype and had been

Table 3 OR of lung cancer for asbestos exposure, *GSTM1* genotype, and their interaction

Study	Asbestos						*GSTM1*						Interaction			
	Cases		Controls		OR[a]	95% CI[b]	Cases		Controls		OR[d]	95% CI	E++[e]		OR[a]	95% CI
	E+	E−	E+	E−			Null	Present[c]	Null	Present			Cases	Controls		
(US Cauc)	34	111	58	322	2.0	1.1–3.6	70	75	199	181	1.1	0.7–1.8	28	17	1.1	0.4–3.2
(US-AA)	30	91	42	150	2.0	1.0–3.8	31	90	60	132	0.8	0.4–1.4	12	11	1.7	0.5–6.2
(France 1)	18	221	16	226	1.1	0.5–2.2	126	113	111	131	1.4	0.9–2.0	8	7	0.8	0.2–3.6
(France 2)	28	118	11	158	3.7	1.7–7.9	80	66	88	81	1.1	0.7–1.8	6	18	1.4	0.3–6.4
Pooled Analysis	110	541	127	856	2.0	1.4–2.7	307	344	458	525	1.1	0.9–1.4	54	53	1.1	0.6–2.1
Test for heterogeneity						0.17						0.65				0.89

[a] OR adjusted for age, gender, and pack-years of tobacco smoking (and study in the pooled analysis).
[b] 95% CI.
[c] Wild type.
[d] OR adjusted for age, gender, asbestos, and pack-years of tobacco smoking (and study in the pooled analysis).
[e] Number of cases and controls exposed to asbestos and with *GSTM1*-null genotype.

Table 4 POR of *GSTM1* genotype and asbestos exposure (case-only analysis)

Study	Cases[a]	Exposed to asbestos	*GSTM1* null	OR[b]	95% CI[c]
(US Cauc)	145	34	70	1.0	0.4–2.3
(US-AA)	121	30	31	2.3	0.8–6.8
(France 1)	239	18	126	0.6	0.2–1.5
(France 2)	146	28	80	1.6	0.7–3.8
(Finland)	218	77	108	1.2	0.7–2.2
Pooled analysis	869	187	415	1.2	0.9–1.8
Test for heterogeneity (*P*)					0.48

[a] Number of subjects included in the logistic regression (no missing data).
[b] OR adjusted for age, gender, and pack-years of tobacco smoking (and study for pooled analysis).
[c] 95% CI.

Table 5 Pooled POR of asbestos exposure and *GSTM1* genotype, by smoking and gender (analysis based on cases series only)

	Cases	POR[a] (95% CI)[b]
Tobacco smoking (Pack-years)		
0–4	57	0.4 (0.1–2.4)
5–27	204	1.9 (0.9–4.1)
28–45	291	0.9 (0.5–1.7)
≥46	317	1.4 (0.8–2.5)
Gender		
Male	673	1.1 (0.7–1.6)

[a] POR adjusted for gender, age, and study.
[b] 95% CI.

Table 6 OR of lung cancer related to *GSTT1* genotype and POR of *GSTT1* genotype and asbestos exposure

Study	OR − main effect[a]		POR[b]	
	OR	95% CI	OR	95% CI[c]
(France 1)	0.7	0.4–1.2	1.6	0.7–3.7
(France 2)	1.3	0.7–2.3	1.1	0.5–2.7
(Finland)			1.0	0.4–2.3
Pooled Analysis	NA		1.1	0.6–2.0
Test for heterogeneity (*P*)			0.72	

[a] OR of lung cancer related to *GSTT1*-null genotype, based on case control studies, adjusted for gender, age, and pack-years of tobacco smoking.
[b] POR of *GSTT1*-null genotype for asbestos exposure, adjusted for gender, age, and pack-years of tobacco smoking (and study in the pooled analysis).
[c] 95% CI.

exposed to asbestos; the pooled OR of interaction was 1.1 (95% CI 0.6–2.1).

In the case-only approach, a total of 869 lung cancer patients was included. The prevalence of both asbestos exposure and *GSTM1*-null genotype was significantly different between studies ($P < 0.001$ for both). We did not observe any relation between asbestos exposure and *GSTM1*-null genotype among controls ($P = 0.4$). The study-specific PORs (*i.e.*, the ORs for asbestos exposure and genetic polymorphism and equal to the OR of interaction derived in a case control approach) are reported in Table 4. The *P* value for heterogeneity was 0.48, and we obtained a pooled POR of 1.2 (0.9–1.8). Given the number of cases, the prevalence of *GSTM1*-null genotypes, and the prevalence of exposure to asbestos, this study had an 80% statistical power to detect a POR of 1.56.

The PORs were similar across strata of increasing smoking consumption (Table 5). Stratification by gender was hampered by the small number of women (eight cases and two controls) with both risk factors, resulting in a very imprecise estimates. Furthermore, seven of eight cases were obtained from one study (11).

Interaction *GSTT1*-Asbestos. We found no evidence of an association between *GSTT1* genotype and lung cancer based on two case control studies (Table 6).

After pooling the two case control studies and the Finland case series, we had 603 cases. The prevalence of *GSTT1*-null genotype was nonsignificantly different between these studies ($P = 0.4$), neither were the PORs of *GSTT1*-null genotype and asbestos exposure significantly heterogenous ($P = 0.72$); the pooled analysis resulted in a POR of 1.1 (95% CI 0.6–2.0).

Discussion

Our analyses did not demonstrate any interaction between asbestos exposure and the *GSTM1* and *T1* genotypes beyond a multiplicative model, which is consistent with the notion that the carcinogenic effect of asbestos does not depend on *GST* genotypes. The interaction estimates were homogeneous across studies, which strengthens our conclusion.

Our meta-analysis was based on four case control studies and one case series, involving different populations. Particularly, the frequency of exposure to asbestos was higher in the case series than in the case control studies. On the contrary, one of the case control studies had a low frequency of asbestos exposure (27). This was mainly attributable to the fact that the population included only Caucasian subjects, born in France

from French-native parents, resulting in the exclusion of immigrants, which comprise a large proportion of blue collar workers exposed to asbestos in the construction and manufacturing industries. In spite of these differences in the prevalence of exposure to asbestos the meta-analysis based on the four case control studies resulted in a significant main effect of asbestos on lung cancer.

The prevalence of *GSTM1*-null genotype was in the expected range of 45–55% in Caucasians. In the only study including African-Americans, the prevalence was 26%, which is also in accordance with the literature.[3] The frequency of the deletion was slightly higher in the cases as compared with the controls, but the difference was nonsignificant. Therefore, our results on the main effect of *GSTM1* polymorphism agree with recent reviews suggesting only a minor role of this factor in lung carcinogenesis (7).

We repeated the analysis of the interaction between polymorphism and asbestos exposure after restricting the data to the lung cancer cases. This approach, which allowed us to include one additional study based on case series, is valid as long as the environmental exposure is randomly distributed, as regards metabolic gene polymorphism (31). This was the case in our data. This approach, however, also failed to show any interaction between asbestos and *GST* polymorphism.

Furthermore, the PORs were homogenous according to smoking habits. Therefore, this cofactor does not confound the lack of interaction between asbestos and *GSTM1*.

The statistical power of this analysis was of 72% to detect a POR of 1.5 of *GSTM1*-null genotype for asbestos exposure. However, the power was >50% to detect a POR of 1.3. Regarding *GSTT1* polymorphism, the statistical power was of 47% to detect an OR of 1.5.

Although the GSEC does not contain all studies on genetic susceptibility, and, therefore, it is likely that other (either published or unpublished) data on *GSTM1* and/or *T1* polymorphism and asbestos exposure may be available, it is likely that lack of participation in GSEC is nondifferential with respect to case control status, *GST* polymorphism, and asbestos exposure. For the interaction between *GSTM1* genotype and asbestos exposure specifically, the sole study published to date is included in GSEC (11). Lack of participation would have therefore resulted only in reducing the statistical power. Further possible bias in our analysis could have occurred as exposure assessment, genotype measurements, and case control status may be subjected to misclassification. As regards outcome, all cases were histologically confirmed, and it is therefore very unlikely that errors have occurred in the definition of lung cancer. On the other hand, it is very likely that misclassification in assessment of asbestos exposure has occurred, possibly differential with respect to lung cancer. This may lead to an overestimation of the OR but likely nondifferential with respect to *GST* genotypes. Hence, assessment of both asbestos exposure and *GST* genotypes has been made in a totally independent way from each other, as shown by our results among controls, which did not show a relationship between these two risk factors. Finally, errors in *GST* genotyping might also have occurred, but again, very unlikely differentially from case control status; genotyping in all studies included in the pooled analysis was assessed blindly. The scenario described above leads to bias toward the null in the estimate of the interaction effect. It is of course not possible to quantify sensitivity and specificity of asbestos exposure measurement or of genotyping, but even small amounts of misclassification may substantially decrease the interaction effect (2).

On the other hand, it is unlikely that uncontrolled confounding occurred since none of the factors possibly associated with asbestos exposure (tobacco smoking and exposure to other occupational carcinogens) is known to be also associated with *GST* genotypes. The lack of confounding effect of smoking was confirmed by the results of the stratified analysis shown in Table 4. Finally, the lack of inter-study heterogeneity in the results on *GST*-asbestos interaction speaks against a major role of bias in our data.

To our knowledge, several studies have examined the relationship between *GSTM1* polymorphism and asbestos pulmonary disorders (12–15, 32, 33). As regards noncancerous pathologies, one study has found a significant excess of *GSTM1*-null genotypes among patients [OR = 1.8 (1.1–2.8)] (15). This excess was also found in another study [OR = 1.5 (0.8–3.3)] (12) but not in an additional study by Jakobsson (32). As far as mesothelioma is concerned, a population-based case control study showed a significant excess of *GSTM1*-null subjects among patients suffering from mesothelioma as compared with controls [OR = 1.8 (1.0–3.5)], with interaction [OR of 1.6 (0.5–5.8)] (13). In a case control study set up in a cohort of workers with high asbestos exposure, the results showed a nonsignificant excess of *GSTM1*-null genotypes among mesothelioma patients, but the interaction was not evaluated (12).

In conclusion, the results of our pooled analysis of five studies do not support the hypothesis that either *GSTM1* or *GSTT1* genotypes modify the risk of lung cancer after asbestos exposure. However, the statistical power being limited, in particular for *GSTT1* polymorphism, the results do not allow us to rule out the possibility that an interaction does exist. Nevertheless, we can assume in the case of *GSTM1* polymorphism, it is likely that this interaction would be of small magnitude, with OR <1.5. The interpretation of this result suggests that *GSTM1* polymorphism is a lung cancer risk factor independently from asbestos-related lung carcinogenesis.

The mechanisms involved in fiber carcinogenesis are also still poorly understood (23). One *in vitro* study suggested that mesothelioma cells lacking *GSTM1* gene have increased toxicity in response to asbestos (34). However, the relevance of these results to lung carcinogenesis is unclear.

Although our initial task was to assess the interaction between polymorphism to several metabolic genes and several occupational exposures, the data available in the GSEC database allowed us to address only one agent and two polymorphisms. This was despite the fact that the GSEC database is the largest available collection of data relevant to address the interaction between occupational exposures and metabolic polymorphisms. Additionally, large studies with a careful definition of exposure to occupational carcinogens are therefore needed to properly address the potential interaction between polymorphisms and occupational exposure.

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