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CYP1A1, GSTM1 and GSTT1 polymorphisms and lung cancer: a pooled analysis of gene–gene interactions

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Gene–environment interactions have been extensively studied in lung cancer. It is likely that several genetic polymorphisms cooperate in increasing the individual risk. Therefore, the study of gene–gene interactions might be important to identify high-susceptibility subgroups. GSEC is an initiative aimed at collecting available data sets on metabolic polymorphisms and the risks of cancer at several sites and performing pooled analyses of the original data. Authors of published papers have provided original data sets. The present paper refers to gene–gene interactions in lung cancer and considers three polymorphisms in three metabolic genes: *CYP1A1*, *GSTM1* and *GSTT1*. The present analyses compare the gene–gene interactions of the *CYP1A1*2A*, *GSTM1* and *GSTT1* polymorphisms from studies on lung cancer conducted in Europe and the USA between 1991 and 2000. Only Caucasians have been included. The data set includes 1466 cases and 1488 controls. The only clear-cut association was found with *CYP1A1*2A*. This association remained unchanged after stratification by polymorphisms in other genes (with an odds ratio [OR] of approximately 2.5), except when interaction with *GSTM1* was considered. When the OR for *CYP1A1*2A* was stratified according to the *GSTM1* genotype, the OR was increased only among the subjects who had the null (homozygous deletion) *GSTM1* genotype (OR = 2.8, 95% CI = 0.9–8.4). The odds ratio for the interactive term (*CYP1A1*2A* by GSTM1) in logistic regression was 2.7 (95% CI = 0.5–15.3). An association between lung cancer and the homozygous *CYP1A1*2A* genotype is confirmed. An apparent and biologically plausible interaction is suggested between this genotype and *GSTM1*.

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Introduction

Gene–environment interactions have become an important research issue in cancer epidemiology, under the assumption that low-penetrance susceptibility to low-dose carcinogenic agents can be a risk factor for many cancers. Gene–environment interactions have been extensively studied in lung cancer. It is likely that several genes or polymorphisms — including haplotypes — cooperate in increasing the individual risk. Therefore, the study of gene–gene interactions might be important in the identification of high-susceptibility subgroups. The paper refers to gene–gene interactions in lung cancer and considers polymorphisms in three metabolic genes: *CYP1A1, GSTM1* and *GSTT1*.

CYP1A1 is a phase I, predominantly extrahepatic, microsomal enzyme involved in the bioactivation of carcinogenic polycyclic aromatic hydrocarbons including benzo(*a*)pyrene (Vineis *et al.* 1999). Early work by Kellermann *et al.* (1973) and others (Vineis *et al.* 1999) suggested that the risk of lung cancer may be modulated by the inducibility of the CYP1A1 enzyme. Other studies, however, failed to reproduce the association with cancer risk (Vineis *et al.* 1999). The *CYP1A1*2A* allele has a T to C mutation in the 3′ region. An AG transition in exon 7 creates a second allelic variant, *CYP1A1*2B*, which leads to an amino acid substitution of Val for Ile in the haem-binding region and results in an increase in microsomal enzyme activity. The variant *CYP1A1*3* has a mutation in intron 7 and is African-American specific. Several studies on the association between lung cancer and these *CYP1A1* polymorphisms have been published (Houlston 2000, Vineis *et al.* 2003), with conflicting results.

Cytosolic glutathione *S*-transferases are a large family of isozymes involved in detoxification of many electrophilic substrates, by their conjugation with reduced glutathione. The class μ contains a specific isozyme, present in about 50% of Caucasians. The absence of the isozyme is due to an inherited deletion of both paternal and maternal alleles of the *GSTM1* gene, transmitted autosomic dominantly (Seidegard and Pero 1985). GSTM1 has been shown to play a role in the metabolism of organic epoxides and peroxides and in particular to conjugate known carcinogens as epoxides of polycyclic aromatic hydrocarbons (PAHs) (Warholm *et al.* 1981), suggesting that people who lack the gene are at greater risk of developing cancers associated with exposure to PAHs. GSTT1 seems to act through a different pathway, since smokers lacking GSTT1 cannot conjugate monohalomethanes found in tobacco smoke (Seidegard *et al.* 1998).

Previous papers have reported on the association between the *CYP1A1*2A* (Vineis *et al.* 2003), *GSTM1* (Benhamou *et al.* 2002) and *CYP1A1* exon 7 (**2B*) (Le Marchand *et al.* 2003) polymorphisms in relation to lung cancer in the GSEC study, a cooperative pooled analysis of studies on metabolic gene polymorphisms and cancer. Here, the present paper analyses interactions between two of these polymorphisms and, in addition, *GSTT1*. GSEC is currently the largest dataset available on gene–environment interactions and it has sufficient statistical power to investigate at least some of the gene–gene interactions.

Materials and methods

GSEC (Taioli 1999, Garte *et al.* 2001b) is an initiative aimed at collecting available data sets on metabolic polymorphisms and the risks of cancer at several sites and performing pooled analyses of the original data. Authors of published papers and abstracts were contacted and invited to provide data sets. The majority have participated in this collaborative effort; details are given elsewhere (Taioli 1999). None of the data included any personal identifiers. Non-informative consecutive identification numbers were assigned to each subject at the time of receipt of the data. It is therefore not possible to trace any particular subject in the database back to his/her actual identity through the identification number. All data on genotype were converted to a standard nomenclature (Garte *et al.* 2001). Data were received from the database in an Excel file, and all analyses were performed using SAS statistical software (version 8.0).

The present analyses compare the gene–gene interactions of the *CYP1A1*2A*, *GSTM1* and *GSTT1* polymorphisms from studies on lung cancer conducted in Europe and the USA between 1991 and 2000 (tables 1 and 2). Only Caucasians have been included, because (1) ethnicity is a potential confounder and (2) Asians and Africans were too few to allow separate analyses. The study design is summarized in table 1. The data set originally included 2451 cases and 3358 controls. Among these, however, smaller subsets were available for the investigation of gene–gene interactions, e.g. 1466 cases and 1488 controls had both *GSTM1* and *CYP1A1* (tables 1 and 2). In addition, studies with no cases or controls were dropped from the final analyses, leaving 1361 cases and 1247 controls for the CYP1A1–GSTM1 comparison. Cases were defined as incident (newly diagnosed) cases of lung cancer with any histology. Recurrences have been excluded.

Odds ratios (OR) and their 95% confidence intervals (CI) were computed. Multivariate logistic regression was used to assess the independent contribution of each factor on lung cancer risk and to control for confounding. Covariates include gender, age, ethnicity, smoking behaviour (ever/never smoker), and (when indicated) the study identity (as a dummy variable). Further adjustments were based on duration of smoking whenever available, which, however, did not change the estimates materially. We tested the deviation from the Hardy–Weinberg equilibrium by chi-square test (Garte *et al.* 2001).

Gene–gene interaction was tested by including an interactive term in logistic regression models. The OR for the interactive term is expected to be 1.0 for complete independence of the genes, while OR >1.0 means a positive interaction (departure from a multiplicative model). Heterogeneity among the studies has been evaluated by the Breslow–Day test (Breslow and Day 1980).

Statistical power

We computed the minimum statistically significant ORs ($\alpha = 0.05$) detectable with a statistical power of 80%. For the gene–gene interaction between *GSTM1* and *CYP1A1*2A*, the minimum detectable

Table 1. Studies available for the pooled analysis for having both GSTM1 and CYP1A1. References are in brackets. Total subjects: 1466 cases and 1488 controls.

Authors and country	Ethnicity	Case/ control	Source of controls	References
Anttila, Finland	Caucasian	62/0		Anttila *et al* (1995, 2001)
Clapper, USA	Caucasian	108/26	healthy	Dresler *et al* (2000)
Dolzan, Slovenia	Caucasian	196/98	healthy	Dolzan *et al* (2000)
Hirvoven, Finland	Caucasian	39/145	healthy/ hospitalized	Hirvoven *et al* (1992) Saarikoski *et al* (1998)
Haugen, Norway	Caucasian	130/93	healthy	Ryberg *et al* (1999) Tefre *et al* (1991)
Rannug, Sweden	Caucasian	397/423	healthy	Alexandrie *et al* (1994) Warholm *et al* (1995)
Strange, UK	Caucasian	0/97	hospitalized	Deakin *et al* (1996) Unpub (CYP1A1)
Le Marchand, USA	Caucasian	139/175	healthy	Le Marchand *et al* (1998)
Taioli, Italy and USA	Caucasian	0/144	healthy	Taioli *et al* (1998) Ford *et al* (2000)
Benhamou, France	Caucasian	150/171	hospitalized	Bouchardy *et al* (1997) Jourenkova *et al* (1997)
Pastorelli, Italy	Caucasian	43/0		Pastorelli *et al* (1998)
Schoket, Hungary	Caucasian	112/24	hospitalized	Schoket *et al* (1998, 2001)
Jacquet, Belgium	Caucasian	42/57	healthy	Jacquet *et al* (1996)
Romkes, USA	Caucasian	48/35	healthy	unpublished (CYP1A1)

Table 2. Pooled analysis of lung cancer case-control studies (GSEC): joint distribution of cases/controls (ca/co) by polymorphisms for *CYP1A1*2A*, *GSTM1* and *GSTT1*. Caucasians only.

			Common (ca/co)	Heterozygotes (ca/co)	Rare homozygotes (ca/co)
CYP1A1*2A					
	GSTM1	present	560/573	102/112	8/6
		null	653/640	127/145	16/12
CYP1A1*2A					
	GSTT1	present	615/698	96/153	14/10
		null	125/171	24/34	1/3
GSTM1			Present (ca/co)	Null (ca/co)	
	GSTT1	present	746/1038	856/1139	
		null	169/266	196/276	

OR = 3.0 (for a proportion of homozygotes for *CYP1A1*2A* of 2%), while for the interaction between *GSTT1* and *GSTM1*, the minimum significantly detectable OR = 1.5–2.0.

Results

Table 1 shows the list of the studies included in the pooled analysis, with their main characteristics (Tefre *et al.* 1991, Hirvonen *et al.* 1992, Alexandrie *et al.* 1994, Anttila *et al.* 1995, 2001, Warholm *et al.* 1995, Deakin *et al.* 1996, Bouchardy *et al.* 1997, Jacquet *et al.* 1996, Jourenkova *et al.* 1997, Ryberg *et al.* 1997, Le Marchand *et al.* 1998, Pastorelli *et al.* 1998, Saarikoski *et al.* 1998, Schoket *et al.* 1998, Taioli *et al.* 1998, Dresler *et al.* 2000, Ford *et al.* 2000, Schoket *et al.* 2001, and one unpublished study). From among the original cases and controls (tables 1 and 2), only 1361 cases and 1247 controls, respectively, were included in the analyses. The distribution of alleles in controls was in Hardy–Weinberg equilibrium (Garte *et al.* 2001).

Table 3 shows the ORs and the corresponding confidence limits for smoking habits and the gene–gene interactions, according to logistic regression models including gender and age. A clear association between the *CYP1A1*2A* homozygous genotype and lung cancer is confirmed, as published in a previous pooled analysis (Houlston 2000), with an OR of approximately 2.5, which is stable in different statistical models.

In table 3, model I is a logistic regression model that includes age (continuous), gender, smoking (ever/never) and two polymorphisms at a time (main effects). Model II is the same plus an interactive term for the gene–gene interaction.

For none of the interactive terms was statistical significance attained, and confidence intervals were usually large. The associations between *CYP1A1*2A* homozygous genotype and lung cancer remains unchanged in all the comparisons shown in table 3, except when the interactive term with *GSTM1* is introduced. In the latter model, the OR for the interactive term is 2.7 (95% CI = 0.5–15.3) and the OR for *CYP1A1*2A* (homozygote) becomes 1.0. This observation suggests

Table 3. Pooled analysis of lung cancer case-control studies (GSEC): interactions among polymorphisms for *CYP1A1*2A*, *GSTM1* and *GSTT1*. Caucasians only. Logistic regression models. All models include age (continuous) and gender. The reference category for polymorphisms is the homozygous common genotype. Interaction is between homozygous rare/null variants.

Variable	Estimate	Odds ratio	95% CI interaction	*p*-value
CYP1A1*2A alone				
Ever/never smoker	2.0	8.0	6.1–10.5	
*CYP1A1*2A* heterozygote	0.07	1.1	0.8–1.3	
*CYP1A1*2A* homozygote	0.96	2.6	1.2–5.7	
CYP1A1*2A and GSTM1				
Model I				
Ever/never smoker	1.9	7.1	5.2–9.6	
*CYP1A1*2A* heterozygote	0.02	1.0	0.8–1.3	
*CYP1A1*2A* homozygote	0.63	1.9	0.8–4.4	
GSTM1 null	−0.04	1.0	0.8–1.2	
Model II				
Ever/never smoker	2.0	7.1	5.2–9.7	
CYP1A1*2A heterozygote	−0.02	1.0	0.8–1.3	
*CYP1A1*2A* homozygote	−0.002	1.0	0.25–3.9	
GSTM1 null	−0.05	0.9	0.8–1.15	
Interaction	0.98	2.7	0.5–15.3	0.27
CYP1A1*2A and GSTT1				
Model I				
Ever/never smoker	1.9	7.0	4.6–10.8	
*CYP1A1*2A* heterozygote	0.18	0.8	0.6–1.2	
*CYP1A1*2A* homozygote	1.15	3.2	1.0–9.9	
GSTT1 null	0.11	1.1	0.8–1.6	
Model II				
Ever/never smoker	2.0	7.0	4.6–10.7	
*CYP1A1*2A* heterozygote	−0.18	0.8	0.6–1.2	
*CYP1A1*2A* homozygote	1.55	4.7	1.3–17.8	
GSTT1 null	0.14	1.15	0.8–1.6	
Interaction	−2.29	0.10	0.04–2.7	0.17
GSTM1 and GSTT1				
Model I				
Ever/never smoker	2.5	12.3	9.7–15.6	
GSTM1 null	0.13	1.13	0.97–1.33	
GSTT1 null	0.04	1.0	0.8–1.3	
Model II				
Smoking habits	2.5	12.3	9.7–15.6	
GSTM1 null	0.13	1.14	0.96–1.36	
GSTT1 null	0.05	1.0	0.8–1.4	
Interaction	−0.02	1.0	0.6–1.5	

that the effect of *CYP1A1*2A* may be seen only in conjunction with the *GSTM1* homozygous deletion. In fact, when the OR for *CYP1A1*2A* was stratified according to the *GSTM1* genotype, the OR was increased only among the subjects who had the null *GSTM1* genotype (OR = 2.8, 95% CI = 0.9–8.4).

Discussion

Three gene–gene interactions were explored in a large data set on lung cancer. The association of the *CYP1A1*2A* homozygous rare variant with lung cancer was detectable only among the subjects with the *GSTM1* homozygous deletion

genotype (OR for interaction = 2.7). Although this could be due to chance, the observation is in agreement with a priori expectations, since CYP1A1 is a phase I enzyme, i.e. it is involved in carcinogen activation, while GSTM1 is a phase II — predominantly deactivation — enzyme, and therefore they are expected to be complementary in their modulation of cancer risk. A modulation of the effect of *CYP1A1* by *GSTM1* has been already suggested in previous studies on lung cancer (Dresler *et al.* 2000, Stucker *et al.* 2000). Also studies on DNA adducts in the lungs of smokers have found that adducts levels were higher in subjects with the *GSTM1*0–CYP1A1*2* or *GSTM1*0–CYP1A* exon 7 combined genotypes (Butkiewicz *et al.* 1999, Alexandrov *et al.* 2002).

It is unlikely that *GSTT1* and *GSTM1* interact strongly, since there was sufficient power to detect an interactive OR of at least 1.5, while an OR = 1.0 (95% CI = 0.6–1.5) was found. This observation is biologically plausible since the two enzymes share overlapping substrate specificity.

It is clear from this study, based on a large pooled analysis, that the investigation of gene–gene interactions of low-penetrance genes requires very large numbers of subjects, and single studies usually do not have the power to fulfil that requirement.

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