

Glutathione S-Transferase M1 Status and Lung Cancer Risk: A Meta-Analysis

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Abstract

Interindividual differences in lung cancer susceptibility may be mediated in part through polymorphic variability in the bioactivation of procarcinogens. GSTM1 status has been extensively studied in this context as a lung cancer risk factor, although published studies have produced conflicting results. To clarify the impact of GSTM1 status on lung cancer risk a meta-analysis of 23 case-control studies from the literature has been carried out using a random effects model. The principal outcome measure was the odds ratio for the risk of lung cancer. There was heterogeneity between the studies attributable to differences in the methods of assigning GSTM1 status. Pooling the studies that were based on phenotyping methods, the overall odds ratio of lung cancer risk associated with GSTM1 deficiency was 2.12 (95% confidence interval, 1.43–3.13). The risk of lung cancer risk associated with GSTM1 deficiency derived from the studies based on genotyping methods was, however, lower. The overall odds ratio was 1.13 (95% confidence interval, 1.04–1.25). These findings suggest that the estimates of lung cancer risk associated with GSTM1 deficiency in the early studies, based on phenotyping, were overinflated. Moreover, it is conceivable, given publication bias, that GSTM1 status has no effect on the risk of lung cancer *per se*. A major concern in case-control studies of polymorphisms and cancer risk is bias. A review of the 23 case-control studies indicates that greater attention should, therefore, be paid to the design of future studies.

Introduction

Lung cancer accounts for 19% of all cancers and 29% of all cancer deaths. It is the commonest cause of cancer death in men, and is second only to breast cancer in women (1, 2). It is frequently cited as an example of a malignancy solely attributable to environmental exposure to carcinogens. Undoubtedly tobacco smoking is the most important etiological factor in the development of this cancer, and the risk is at least 10 times

higher in long-term smokers compared with nonsmokers (3). However, there is a growing realization that the development of most cancers results from a complex interaction of both environmental and genetic factors. Epidemiological studies have shown that relatives of lung cancer cases are at a 2-fold elevated risk of developing the disease (4). It is possible that part of the susceptibility to lung cancer may be determined by the inter-individual difference in the bioactivation of procarcinogens and detoxification of carcinogens.

*GSTM1*² has been of considerable interest as a lung cancer susceptibility gene. The biochemical basis for a possible association is that GSTM1 is one of a family of glutathione S-transferases capable of detoxifying reactive electrophiles that can act as mutagens. Hence, GSTM1 may be involved in the inactivation of this class of procarcinogens. The *GSTM1* gene is polymorphic, and at least four alleles exist (5). The *GSTM1*0* allele represents a deletion, and individuals homozygous for this null allele are less efficient at conjugating and detoxifying specific substrate intermediates of carcinogens (5).

Seidegard *et al.* (6) first reported an association between GSTM1 deficiency and lung cancer. Since the publication of this report in 1985, over 20 studies have appeared in the literature confirming or refuting an association between GSTM1 deficiency and lung cancer risk (7–26). One of the major problems of the published studies is that most of them have been based on only small numbers. To clarify the effect of GSTM1 status on the risk of lung cancer a meta-analysis of all of the studies published between 1985 and 1998 on the possible association between GSTM1 status and lung cancer risk has been undertaken.

Materials and Methods

Identification of Studies. A search of the literature was made using two electronic databases, MEDLINE and BIDS EMBASE for the years 1985–1998 to identify articles in which the GSTM1 status was determined in lung cancer patients and controls. Additional articles were ascertained through references cited in these publications. Articles included for analyses were primary references and of case-control design. In all of the studies GSTM1 status was determined by either enzymatic assay with *trans*-stilbene oxide as substrate, by immunological techniques, or by analysis of the gene through Southern blotting or PCR.

Statistical Analysis. The odds ratio of lung cancer associated with GSTM1 deficiency was estimated for each study. These odds ratios and their corresponding 95% CIs were plotted against the number of participants in each of the studies to detect any obvious sample size bias. To take into account the possibility of heterogeneity between studies, a random effects

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²The abbreviations used are: GSTM1, glutathione S-transferase M1; CI, confidence interval.

Table 1 Summary of studies of lung cancer and *GSTM1* status

Investigator	Place of study	Analytical method ^a	Cases ^b	% deficient	Controls ^b	% deficient	Exposures/other covariates	Power (RR ^c > 2.0; α = 0.05)	Power (RR > 1.5; α = 0.05)
Seidegard <i>et al.</i> , 1986 (6)	New York, NY; Lund, Sweden	TSO	66 incident cases ascertained from a US lung cancer study, patients from NY and Swedish hospitals; 88% male; age 63 (8); smokers >20 cigarettes/day; ? Caucasian	65.1	78 healthy participants in US National Lung Cancer Prevention Program; 96% male; age 63 (7); smokers >20 cigarettes/day; ? Caucasian	41.0	Smoking (heavy, light); cancer histology	47%	20%
Seidegard <i>et al.</i> , 1990 (7)	New York, NY	TSO	125 incident cases from two NY Hospitals; 56% male; ages 33–80; smokers >20 pack-years; ? Caucasian	62.4	114 healthy participants in NY Cancer Surveillance program; 47% male; ages 55–66; smokers >20 pack-years; ? Caucasian	42.1	Smoking; cancer histology	72%	30%
Zhong <i>et al.</i> , 1991 (8)	UK	S	228 prevalent cases; source: NS; age: NS; sex ratio: NS; all history of smoking; Caucasian	42.9	225 controls chosen randomly from two hospitals and a group of volunteers; age: NS; sex ratio: NS; Caucasian	41.8	Cancer histology	95%	54%
Heckbert <i>et al.</i> , 1992 (9)	Seattle, WA	TSO	66 incident cases ascertained from a cancer registry; ages 20–70; Caucasian	63.6	120 age- and sex-matched healthy population controls selected by random-digit dialing and a Social Security list; Caucasian	58.3	Smoking (<20, >20 pack-years); occupation (exposure to lung carcinogens); alcohol	49%	19%
Hayashi <i>et al.</i> , 1992 (10)	Saitama, Japan	PCR	212 prevalent cases from single center; Asian	55.7	358 age- and sex-matched population controls from same region as cases; Asian	46.6	<i>CYP1A1</i> polymorphism	97%	61%
Hiroven <i>et al.</i> , 1993 (11)	Helsinki, Finland	PCR	138 incident operable lung cancer cases; age: NS; sex ratio: NS; Caucasian	52.9	142 healthy controls (115 blood donors and 27 volunteers); age: NS; sex ratio: NS;	43.7	Smoking data (nonsmokers, <40, >40 pack-years) recorded on cases and disease controls; stratified analysis	79% vs. healthy controls	35% healthy controls
Nazar-Stewart <i>et al.</i> , 1993 (12)	Seattle	TSO ELISA S	35 incident surgical patients and autopsy specimens; all cases smokers (>30 years, >100 cigarettes in lifetime); sex ratio: NS; age: >30; 94% white	74.3	36 hospital controls with benign tumors; Caucasian	44.4		38% vs. hospital controls	14% vs. hospital controls
Brockmuller <i>et al.</i> , 1993 (13)	Berlin, Germany	TSO ELISA PCR	117 incident cases; ages 40–84; 76% male; 5% nonsmokers; Caucasian	64.0	43 surgical patients and autopsy specimens from patients with nontobacco related illnesses; ages: 30–80; >100 cigarettes in lifetime; sex ratio: NS; 93% white	46.5	Smoking (<54, >54 pack-years); cancer histology	24% phenotypes	10% phenotypes
			25/35 cases genotyped	53.0	155 patient controls (ages 32–84) from same hospital (45% lung disease); 53% male; 13% nonsmokers; Caucasian	48.3	Smoking data for cases and first group of disease controls (nonsmokers, 1–20, >20 pack-years); cancer histology	16% genotypes	7% genotypes
			76% male; 5% nonsmokers; Caucasian	55.7	200 patients from same hospital without lung disease; 65% male; smoking data: NS; Caucasian	49.5		74% vs. lung disease controls	32% vs. lung disease controls
Alexandrie <i>et al.</i> , 1994 (14)	Sweden	PCR	296 incident cases; source: NS; ages: 37–85; 71% males; Caucasian	55.7	All controls	50.0	Smoking data (pack-years) for COPD controls and some cases; cancer histology	80% vs. nonlung disease patient controls	36% vs. nonlung disease patient controls
			79 COPD patients ages 39–85; 35% male; Caucasian	49.4	329 healthy controls: laboratory staff (24%), welders (44%), and chimney sweeps (32%); ages 19–65; 91% male; Caucasian	52.9		87% vs. all controls	42% vs. all controls
					79 COPD patients ages 39–85; 35% male; Caucasian	49.4		98% vs. healthy controls	67% vs. healthy controls
								73% vs. hospital controls	31% vs. hospital controls

Table 1 Continued

Investigator	Place of study	Analytical method ^a	Cases ^b	% deficient	Controls ^b	% deficient	Exposures/other covariates	Power (RR ^c > 2.0; α = 0.05)	Power (RR > 1.5; α = 0.05)
London <i>et al.</i> , 1995 (15)	Los Angeles, CA	PCR	342 incident cases from 35 hospitals in LA; age: 64 (10); 58% male; 4% nonsmokers		All controls 716 population controls, ethnically matched; ages 63 (8); 66% male; 34% nonsmokers	52.2	Smoking (never, past, current); asbestos exposure (none, possible, probable); β-carotene, vitamin C and E intake	99% vs. all controls	72% vs. all controls
Kihara <i>et al.</i> , 1995 (16)	Yokohama, Japan	PCR	Caucasian (n = 184) African-Americans (n = 158)	51.1 27.8	469 age- and sex-matched population controls; Asian	52.5 27.1		97% 88%	60% 42%
Moreira <i>et al.</i> , 1996 (17)	Lisbon, Portugal	PCR	447 incident and prevalent cases ascertained from single center. Asian	55.9	84 Portuguese blood donors; age, sex ratio: NS; Caucasian	48.6	Stratified by smoking, histology	100%	85%
Deakin <i>et al.</i> , 1996 (18)	Staffordshire, UK	PCR	94 patients from two Lisbon hospitals; age, sex ratio: NS; Caucasian	43.9	577 hospital patients without lung disease; 48% male; age 70; 49% never smokers; Caucasian	52.3	Cancer histology	55%	22%
Harrison <i>et al.</i> , 1997 (19)	Edinburgh, UK	PCR	106 cases; all smokers; 73% male; age 68; Caucasian	47.2	128 hospital patients with COPD; all smokers; age 62; 67% male; Caucasian	54.8	GSTT1 polymorphism	86%	86%
Garcia-Closas <i>et al.</i> , 1997 (20)	Boston, MA	PCR	168 lung cancer resection specimens; age, sex ratio: NS; ? Caucasian	60.1	All controls	54.7		87%	54%
Kelsey <i>et al.</i> , 1997 (21)	Texas	PCR	416 incident cases; 54% male; age 67 (33–89); 97% Caucasian	54.3	384 blood donors; age, sex ratio: NS	52.5	All cases smokers; no data on controls; emphysema	94%	82%
To-Figueras <i>et al.</i> , 1997 (22)	Barcelona, Spain	PCR	168 volunteers; ages 61–63; 4% never smokers; Mexican-Americans (n = 60) African-Americans (n = 108)	58.1	446 friends and spouses of hospital patients; 47% male; age 64 (27–84); 98% Caucasian	53.4	Smoking: asbestos and solvent exposure; nutrition; family history; histology; CYP1A1 polymorphism	100%	100%
El-Zein <i>et al.</i> , 1997 (23)	Texas	PCR	160 consecutive patients; 91% male; age 59 (11); 53 pack-years of smoking; Caucasian	55.0 22.2	278 age- and ethnically matched healthy volunteers; source, NS; 42% never smokers; Mexican-Americans (n = 146) African-Americans (n = 132)	49.4	Smoking (current, past, never, pack-years); GSTT1 polymorphism	55% 63%	21% 23%
			54 incident cases; all smokers; 59% male; age 60.2 (11.4); ethnicity: NS	42.5	192 healthy volunteers; blood donors, employees, and hospital staff; age 43 (10); sex ratio: NS; Caucasian	49.7	Smoking (pack-years); cancer histology	87% vs. healthy controls	42% vs. healthy controls
			54 incident cases; all smokers; 59% male; age 60.2 (11.4); ethnicity: NS	42.5	120 healthy smokers (37 pack-years) attending detoxification center; sex ratio: NS; age 45 (9); Caucasian	49.7		77% vs. healthy smokers	34% vs. healthy smokers
			54 incident cases; all smokers; 59% male; age 60.2 (11.4); ethnicity: NS	42.5	All controls	49.7		93% vs. controls combined	50% vs. controls combined
			54 incident cases; all smokers; 59% male; age 60.2 (11.4); ethnicity: NS	42.5	50 age- and sex-matched healthy volunteers; all smokers; source: NS; ethnicity: NS	46.0	Smoking (pack-years); CYP2D6, CYP2E1, and GSTT1 polymorphisms	34%	13%

Table 1 Continued

Investigator	Place of study	Analytical method ^a	Cases ^b	% deficient	Controls ^b	% deficient	Exposures/other covariates	Power (RR ^c > 2.0; $\alpha = 0.05$)	Power (RR ^c > 1.5; $\alpha = 0.05$)
Ryherb <i>et al.</i> , 1997 (24)	Norway	PCR	135 incident surgical patients: all smokers; age 62.3 (10.3); sex ratio: NS; Caucasian	54.8	342 healthy male factory workers of Norwegian descent; age 54 (15); 35% never-smokers; Caucasian	47.7	Smoking (pack-years); <i>GSTP1</i> polymorphism	90%	47%
Jourenkova <i>et al.</i> , 1997 (25)	Paris, France	PCR	150 patients; age 58.4 (9.9); 93% male; Caucasian	54.0	172 patients with nonlung conditions; age 55.0 (11.0); 95% male; Caucasian	52.3	Smoking status (consumption/day, no. of years); asbestos and arsenic exposure; <i>GSTT1</i> polymorphism	83%	39%
Saarikoski <i>et al.</i> , 1998 (26)	Finland	PCR	70 incident surgical patients; age: NS; sex ratio: NS; Caucasian	38.6	294 blood donors; sex ratio: NS; ages: NS; Caucasian	46.6	Cases: smoking (<40, >40 pack-years); asbestos exposure; <i>GSTT1</i> polymorphism	66%	27%

^a *GSTM1* methodology: TSO, *trans*-stilbene oxide conjugation assay; S, Southern blot.

^b Ages of cases and controls: mean (SD) or range given wherever possible. ?, probable.

^c RR, relative risk; US, United States; UK, United Kingdom; NS, not stated; COPD, chronic obstructive pulmonary disease.

model was used for the derivation of odds ratios (27). This model assumes that the studies in question are a random sample of a hypothetical population of studies taking into account within- and between-study variability. Statistical manipulations were undertaken using the program Meta-analyst.³ The power of each study was computed as the probability of detecting an association between *GSTM1* deficiency and lung cancer at the 0.05 level of significance, assuming a genotypic risk of 1.5 and 2.0. These estimates of power were performed on the basis of the method published by Fleiss *et al.* (28), using the statistical program POWER (Epicenter Software, Version 1.30).

Results

Twenty reports detailing 23 case-control studies of the possible association between *GSTM1* status and lung cancer risk that were suitable for analysis were identified from the literature (Refs. 6–26; Table 1). Reasons for excluding reports from the analysis were: (a) the same data were available in more than one study; (b) no control group of individuals had been ascertained; or (c) only family members had been studied (29–34).

Of the 23 case-control studies, the ethnicity of cases and controls was detailed in 19 of the studies (Table 1). In 14 of the 23 studies the controls were age-matched individuals from the general population. Smoking histories had been ascertained from cases and controls in a number of studies (Table 1). In these studies, the relationship between *GSTM1* status and lung cancer risk were analyzed in a stratified manner or by logistic regression, taking into account other covariates (such as polymorphic variation in other metabolic enzymes; detailed in Table 1), however, this was not universal. In a number of the studies, there were no data on the ages of cases or controls, their source, or their ethnicity. In three of the studies, the prevalence of *GSTM1* deficiency had been determined in two control groups, one a cohort of the general population and the other a sample of patients with a plethora of noncancerous disorders (Table 1).

Of the reports selected for meta-analysis, 4 determined *GSTM1* status by phenotyping, and in the remaining 18, *GSTM1* status was based on genotypes (Table 1). In two studies *GSTM1* status had been determined by both methods but only the genotyping or phenotyping data were used in the meta-analysis to avoid counting results from these two studies twice. In the study reported by Nazar-Stewart *et al.* (12), *GSTM1* phenotypes of cases and controls were used because genotypes had been determined only on a subset of cases and controls that had been phenotyped. Because both genotypes and phenotypes were available on all of the cases and controls reported by Brockmuller *et al.* (13), only the genotypes were used in the analysis.

Table 1 shows the power of individual studies to demonstrate an association between *GSTM1* deficiency and lung cancer risk if the true risk was 1.5 or 2. A statistical power greater than 80% was attained by 11 of the 23 studies if the genotypic risk was equal to or greater than 2.0 ($\alpha = 0.05$, two tails). However, if the genotypic risk was 1.5, only 2 of 23 of the studies had power greater than 80% to demonstrate an association.

Fig. 1 shows a plot of odds ratios (95% confidence limits) for the risk of developing lung cancer associated with *GSTM1* deficiency in the 23 case-control studies. The median odds ratio value was greater than unity in 17 of the studies but was only statistically significant ($P < 0.05$) in four. A plot of *GSTM1*

³ I. Lau and T. C. Chalmers; <<http://www.familypractice.msu.edu>>.

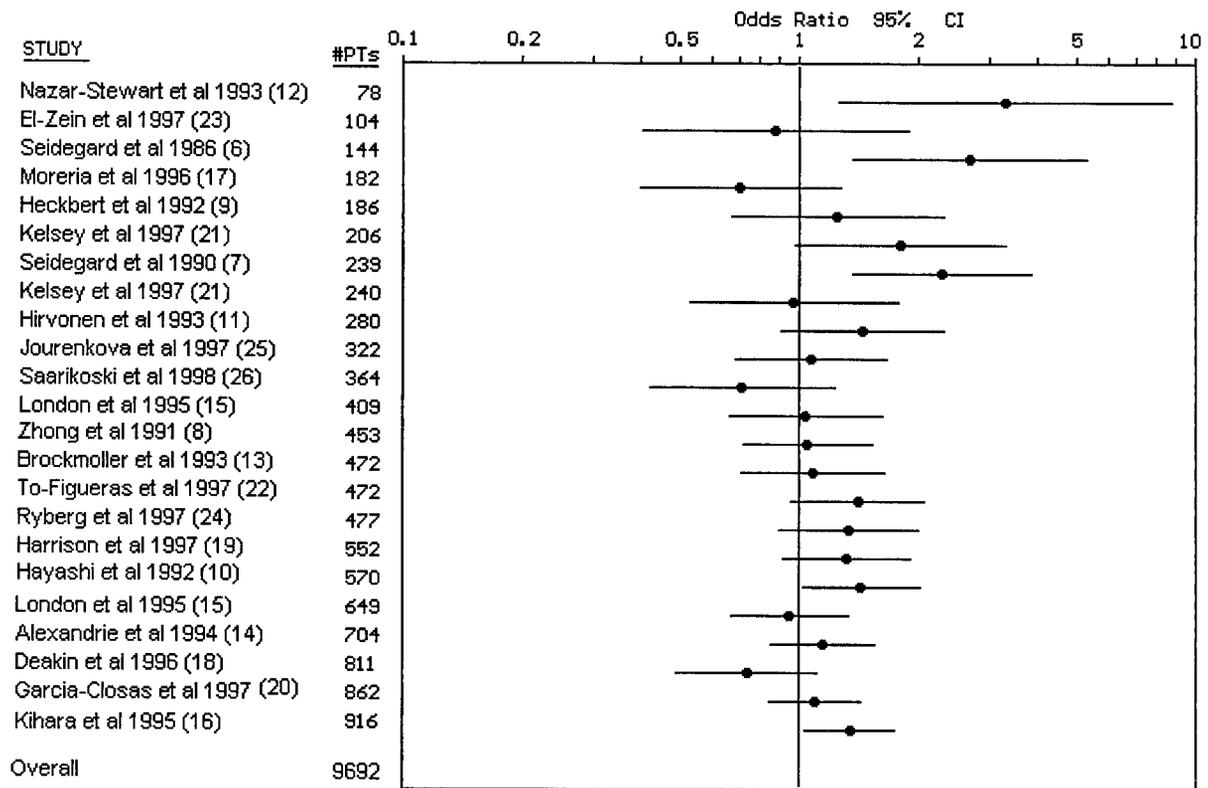


Fig. 1. All of the studies. Odds ratios and 95% CIs for the risk of developing lung cancer associated with GSTM1 deficiency. The studies are stratified by size. Summary: odds ratio 1.20 (95% CI, 1.06–1.35).

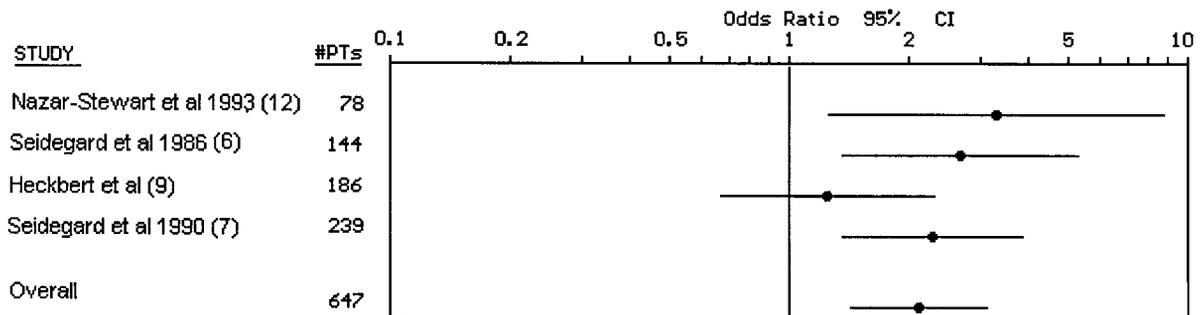


Fig. 2. Studies based on GSTM1 phenotypes. Odds ratios and 95% CIs for the risk of developing lung cancer associated with GSTM1. Summary: odds ratio, 2.12 (95% CI, 1.43–3.13).

deficiency and lung cancer risk showed a trend toward a less significant association between GSTM1 status in the larger of the studies (Fig. 1). An impression of heterogeneity between the studies was confirmed by formal statistical analysis ($\chi^2 = 37.9$; 22 *df*; $P < 0.02$). This heterogeneity could be attributed to the differences between studies in the methods of determining GSTM1 status. Stratifying the studies by methodology showed no evidence for heterogeneity between the three studies using phenotyping methods ($\chi^2 = 4.01$; 3 *df*; $P > 0.2$) or those based on genotypes ($\chi^2 = 21.08$; 18 *df*; $P > 0.2$). When the studies were pooled that were based on phenotyping methods, the overall odds ratio of lung cancer risk associated with GSTM1 deficiency was 2.54 (95% CI, 1.74–3.72; Fig. 2). The risk of

lung cancer risk associated with GSTM1 deficiency derived from the studies based on genotyping methods was, however, lower (Fig. 3). The overall odds ratio associated with GSTM1 deficiency determined from genotyping was 1.13 (95% CI, 1.03–1.25).

These analyses are based on pooling data from studies based on a number of ethnic groups. Restricting the analyses to the studies of Caucasian subjects, the major ethnic group, the odds ratio of lung cancer associated with GSTM1 deficiency defined by genotype is 1.08 (95% CI, 0.97–1.22). In the Asian populations, the odds ratio of lung cancer associated with GSTM1 deficiency was 1.38 (95% CI, 1.12–1.69). There was no evidence of significant heterogeneity in either of these

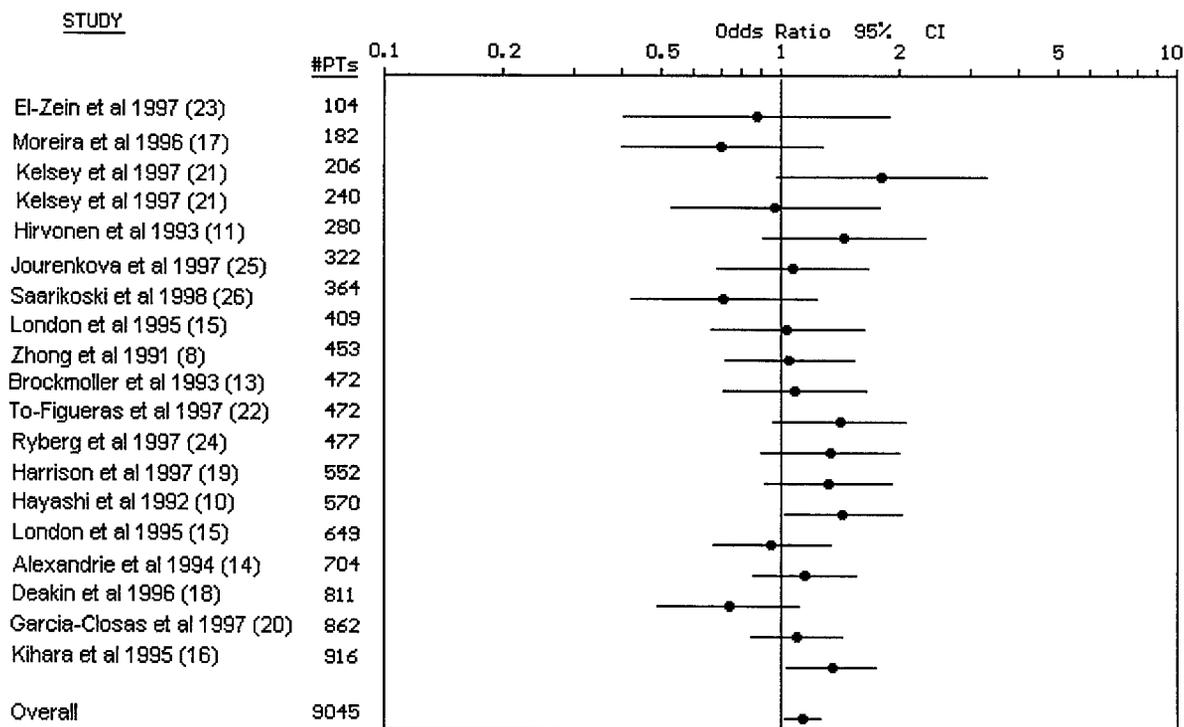


Fig. 3. Studies based on *GSTM1* genotypes. Odds ratios, 95% CIs for the risk of developing lung cancer associated with *GSTM1* deficiency. Summary: odds ratio, 1.14 (95% CI, 1.03-1.25).

subgroups. All of the studies examining the relationship between *GSTM1* phenotypes and lung cancer risk were based on the analysis of Caucasian cohorts.

It is conceivable that *GSTM1* deficiency may be associated with a specific form of lung cancer. Of 23 studies that have examined a relationship between *GSTM1* status and lung cancer risk, 13 contain information on histology in a form suitable for a pooled analysis (6-8, 10, 11, 13, 14, 16, 17, 22, 23-25). Of these 13, 10 determined *GSTM1* status by genotyping in a form that permits a pooled analysis to be undertaken (8, 10, 11, 14, 16, 17, 22, 23-25). By pooling these studies, *GSTM1* deficiency was associated with an odds ratio of 1.40 for small cell carcinoma (95% CI, 1.01-1.95), 1.26 for adenocarcinoma (95% CI, 0.97-1.64), and 1.31 for squamous carcinoma (95% CI, 1.02-1.68). Tests for heterogeneity in each of these histological subgroups analyzed showed no evidence for heterogeneity except in the squamous carcinoma group ($P < 0.05$).

Discussion

Most of the cancer susceptibility genes identified to date are rare and highly penetrant. They may cause a substantial proportion of cancers at young ages but are unlikely to make a contribution to a high percentage of all cancers. However, less penetrant genes could well do so, and there is increasing evidence for participation of this class of genes in a number of cancers (4). Given that exposure to carcinogens is a major risk factor for lung cancer, the hypothesis that the modulation of carcinogen metabolism is under genetic control is a plausible mechanism for explaining interindividual susceptibility.

Since Seidegard *et al.* (6) first drew attention to a possible relationship between *GSTM1* deficiency and lung cancer risk, 20 reports have been published examining this hypothesis (7-

26). All but two of these studies failed to demonstrate such a strong association between *GSTM1* status and lung cancer (7, 12). It is not uncommon for the first published studies to report over-inflated estimates of risk or effects that subsequent studies cannot replicate. Furthermore, it is possible for negative findings to go unreported, which leads to biased conclusions.

The frequency of *GSTM1* deficiency is approximately 50% in most Caucasian populations. If deficiency is associated with a 1.5-fold increase in lung cancer risk, most of the published studies have very limited power to demonstrate such a moderate effect. McWilliams *et al.* in 1995 (35) pooled 11 of the then available case-control studies and concluded that *GSTM1* deficiency conferred a 1.4-fold increase in the risk of lung cancer (95% CI, 1.2-1.6). This overview included the studies based on phenotyping as an analytical method to establish *GSTM1* status. Although studies have shown that *GSTM1* phenotypes and genotypes are highly correlated, the concordance between results is not absolute (coefficient of association, $\phi = 0.85-0.97$; Refs. 12, 13). Misclassification of *GSTM1* status on the basis of phenotypes is, therefore, a distinct possibility in some studies. This, coupled with the small sample sizes of many of the early reports makes the results of such studies capricious. Although it is conceivable that a rare variant of *GSTM1* may not be detected using PCR-based methods, genotypes are very unlikely to be prone to as many misclassifications as phenotyping methods.

Since the overview by McWilliams *et al.* in 1995 (35), a large number of studies have reported on the possible association between *GSTM1* status and lung cancer risk. All of these have assigned *GSTM1* status on the basis of genotyping and most were based on larger sample sizes than the reports published before 1995. The continuing debate about the possible

role of GSTM1 deficiency as a lung cancer risk factor and the fact that 20 studies based on genotyping have been published prompted the present meta-analysis to derive an estimate of the risk associated with GSTM1 status.

In this meta-analysis, only published studies were used. Publication bias is, therefore, an issue. Ideally, quality scoring of studies should be used to determine which are to be included in any meta-analyses (36). This was not undertaken because the existing scales have not been validated, and it is also unclear how they could be readily applied to the published case-control studies on GSTM1 status and lung cancer (37). It is, however, clear that some of the studies are far from perfect in design. The issue of false-positive findings in association studies is a great concern. Any stratification within a population sample can lead to spurious evidence for an association between the marker and the disease. To avoid this problem, the identification is required of subpopulations defined in terms of factors influencing disease and marker-allele frequencies. These include ethnicity and geographical origin. In a number of the studies, the ethnicity of cases and controls were probably mixed. The frequency of GSTM1 deficiency varies considerably between ethnic groups; therefore, a failure to match cases and controls represents a source of bias. Furthermore, several *GSTM* genes are localized in a cluster on chromosome 1p; therefore, it is possible that an association mediated by linkage disequilibrium may be confined to certain populations. Hence population stratification would mask such an effect.

Wolf *et al.* (38) have suggested that case-control protocols are unnecessary in genotyping studies because age, smoking, and concomitant disease do not influence genotype. The age of cases and controls is relevant, however, because the frequency of genotypes may display age-dependency. For example, it has been shown that the population frequency of ApoE polymorphisms, which influence circulating lipoprotein levels, show age-dependency (39). Furthermore, age is relevant to determining the probable exposure to carcinogens. A difference in the ages between cases and controls is, therefore, a potential source of bias. Even though adjustment for these covariates can be made using logistic regression, many studies are small, and adjustment may not be adequately achieved.

If genetic susceptibility to lung cancer is in part mediated through polymorphic variation, it is probable that the risk associated with any one locus will be small because a multiplicative model of interaction is likely to operate. Hence, combinations of certain genotypes may be more discriminating as risk factors than a single locus genotype. There is some support for this hypothesis in that both GSTM1 and GSTP1 enzymes affect the biotransformation of certain mutagens (40).

Considerable effort and resources have been put into testing possible associations between metabolic polymorphisms and cancer risk, but there are serious errors inherent in the design of some published studies. It is clear that in addition to basing studies on sample sizes commensurate with the detection of low-penetrance genes, more attention should be paid to adequate matching of cases and controls to avoid the potential problems of population stratification and other sources of bias.

The findings of this meta-analysis suggest that the estimates of lung cancer risk associated with GSTM1 deficiency in the early studies, based on phenotyping, were exaggerated. Furthermore, results from pooling the studies in which GSTM1 status was derived from genotyping alone makes it conceivable that GSTM1 status has no effect on the risk of lung cancer. This finding is perhaps not surprising because the *a priori* evidence to support the role of GSTM1 status as a lung cancer risk factor is not strong. Although the enzyme catalyzes the detoxification

of polyaromatic hydrocarbons *in vitro*, expression of GSTM1 in lung tissue is very low (41, 42). Given that the primary site for tissue expression of GSTM1 is the liver, any increased lung cancer risk directly associated with a lack of GSTM1 activity would, therefore, have to be mediated by blood-borne metabolites from the hepatic system (43).

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