review

Meta-analysis and pooled analysis of GSTM1 and CYP1A1 polymorphisms and oral and pharyngeal cancers: a HuGE-GSEC review

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The association of *GSTM1* and *CYP1A1* polymorphisms and oral and pharyngeal cancers was assessed through a meta-analysis of published case-control studies and a pooled analysis of both published and unpublished case-control studies from the Genetic Susceptibility to Environmental Carcinogens database (http://www.upci.upmc.edu/research/ccps/ccontrol/index.html). Thirty publications used in the meta-analysis included a total of 7783 subjects (3177 cases and 4606 controls); 21 datasets, 9397 subjects (3130 cases and 6267 controls) were included in the pooled analysis. The *GSTM1* deletion was 2-fold more likely to occur in African American and African cases than controls (odds ratio: 1.7, 95% confidence interval: 0.9–3.3), although this was not observed among whites (odds ratio: 1.0, 95% confidence interval: 0.9–1.1). The meta-analysis and pooled analysis showed a significant association between oral and pharyngeal cancer and the *CYP1A1* MspI homozygous variant (meta-$OR_{m2/m2}$: 1.9, 95% confidence interval: 1.4–2.7; Pooled OR_{m2m2}: 2.0, 95% confidence interval: 1.3–3.1; $OR_{m1m2 \text{ or [infi]}m2m2}$: 1.3, 95% confidence interval: 1.1–1.6). The association was present for the *CYP1A1* (*exon 7*) polymorphism ($OR_{Val/Val}$: 2.2, 95% confidence interval: 1.1–4.5) in ever smokers. A joint effect was observed for *GSTM1* homozygous deletion and the *CYP1A1 m1m2* variant on cancer risk. Our findings suggest that tobacco use and genetic factors play a significant role in oral and pharyngeal cancer. ***Genet Med* 2008:10(6):369–384.**

Key Words: *GSTM1, CYP1A1, oral and pharyngeal cancers, epidemiology, meta-analysis and pooled analysis*

Glutathione *S*-transferases

The Glutathione *S*-transferases (GSTs) comprise a family of phase II detoxifying enzymes that catalyze a large number of reactions taking place between the cytosolic glutathione and compounds containing an electrophilic center.[1] These enzymes are involved in the elimination of xenobiotics and endogenous products of oxidative stress formed as a result of aerobic metabolism, exposure to ionizing radiation or any other process that causes cellular damage. Substrates for GSTs include acetaldehyde and several polyaromatic hydrocarbons (PAHs) found in tobacco smoke. The main steps for GST catalysis includes the formation of a complex with the cytosolic glutathione and the ionization of the sulfydryl group of this enzyme bound to glutathione to yield a highly reactive thiolate anion through hydrogen bonding with the adjacent hydroxyl

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group. The enhancement of nucleophilicity activates the gluthathione and it can react with various electrophilic substrates containing carbon, nitrogen, or sulfur atoms. The result of this conjugation leads to elimination of the carcinogens from the body.

Based on sequence similarities, human cytosolic GSTs have been grouped into at least four major gene families (alpha, mu, pi, and theta). The alpha class is located in chromosome 6p12, the mu class in chromosome 1p13, pi in chromosome 11, and theta in chromosome 22. Various isoenzymes have been identified for the alpha (A1–12), mu (M1–M5), pi (P1–P2), and theta class gene families (T1–T2). The *GSTM1*, M2, M3, T1, and P1 are expressed in a variety of tissues including the squamous epithelium of the oral cavity[2] and are involved in the detoxification of various polycyclic aromatic hydrocarbons, including benzo[a]pyrene-7,8-diol-9,10-epoxide,[3] one of the most important carcinogens found in tobacco smoke, by catalyzing the conversion of the reactive electrophiles to inactive, water soluble conjugates that can be easily excreted.[4] The *GSTM1* isoenzyme together with the alcohol dehydrogenase is also involved in the oxidation of ethanol to acetaldehyde.[5]

Three alleles have been identified at the *GSTM1* locus: GSTM1*0, GSTM1*A, and GSTM1*B. The GSTM1*A and *GSTM1*B* differ by a C→G substitution at base position 534.[6] This C→G substitution results in a substitution of Lys→Asn at amino acid 172. These result in monodimers (GSTM1A-1A, GSTM1B-1B) or heterodimers (GSTM1A-1B), but in vitro studies suggest that their activities are similar.[7] The GSTM1*0, also called the null allele, is a huge deletion at *GSTM1* and homozygotes express no GSTM1 protein activity.[8] These subjects may potentially accumulate more DNA adducts and mutagen induced damage that may cause differences in susceptibility to tumorigenesis.[9]

Cytochrome P450s

The cytochrome P450 family (CYP) of heme monooxygenases comprise phase I enzymes that oxidate a wide variety of endogenous and exogenous compounds using atmospheric oxygen.[10] Currently, more than 270 CYP gene families are known. Humans have 57 potentially functional P450 genes and 33 pseudogenes arranged into 18 families and 42 subfamilies.[11]

The *CYP1A1* gene belongs to the CYP1 subfamily and encodes for the enzyme aryl hydrocarbon hydrolase, which is involved in the activation of PAHs and aromatic amines[12] and is expressed in oral tissue.[13] Various studies show that *CYP1A1* catalyzes the initial metabolism of benzo[a]pyrene.[4,14] The *CYP1A1* gene is located in chromosome 15, band 15q22–24[15] and several important single nucleotide polymorphisms have been identified. The nomenclature of these polymorphisms is now standardized[16,17] but different nomenclatures were used for several years.[12] The first allele presents a single base substitution of thymine by cytosine in a noncoding region of the gene at position 3801 that creates a MspI (*m1*) restriction site (CYP1A1*2A). A single base substitution of adenine to guanine at position 2455 in the heme binding region of exon 7 induces an amino acid change in isoleucine to valine at codon 462 and is known as the *Ile/Val* or exon 7 polymorphism ($Ile^{462}Val$) or CYP1A1*2C.[18] In whites, this polymorphism is in complete linkage disequilibrium with the *CYP1A1* MspI (*CYP1A1*2B*).[19] Another polymorphism in exon 7, a base substitution of cytosine by adenine at position 2453, leading to the $Thr^{461}Asn$ polymorphism (*CYP1A1*4*) has been described.[20] Some *CYP1A1* polymorhisms have been shown to increase microsomal catalytic activity for converting procarcinogens, including PAH and aromatic amines, but the results are inconsistent.[12,21–23] It has been suggested that DNA damage may depend on the link of *CYP1A1* to other polymorphisms that can affect *CYP1A1* transcription levels, such as polymorphisms for promoter genes, Ah receptor genes, or other metabolic genes such as *GSTM1*.[23,24]

Oral and pharyngeal cancers and risk factors

According to the International Classification of Diseases-10th revision (ICD-10) oral and pharyngeal tumors are defined as those cancers comprising the locations C00–C14. These cancers represent an important problem worldwide, with 484,628 new cases and 262,784 deaths estimated per year.[25] The highest incidence and prevalence rates are observed in Melanesia, Central Asia, and Western Europe, even though rates vary depending on the gender and cancer location.[25] In men, cancers of the oral cavity are eighth in terms of incidence worldwide and they are responsible for 3% of the cancers diagnosed in this gender. Pharyngeal tumors are also common in European and Central Asian countries but the incidence rates are lower.

Mortality rates are substantially lower than incidence rates, with 2.2 deaths per 100,000 people worldwide.[25] The highest values are recorded in several countries of Central and Eastern Europe and the lowest in Central America and Northern Europe. In Hungary, the mortality rate is as high as 21.2 per 100,000.

Risk factors for oral and pharyngeal cancers

Since 1988, tobacco and alcohol consumption have been recognized as independent risk factors for oral cancer. Epidemiologic studies performed in all continents have found an increased risk in smokers and a dose-response relationship with daily cigarettes and duration of habit.

An excessive consumption of alcoholic beverages has been associated with oral and pharyngeal cancer, with relative risks sometimes higher than those found for smokers.[26–28] The risk associated with alcohol increases with consumption[26,29–32], duration, starting age and type of alcohol beverage.[26,29,33,34] When joint consumption of alcohol and tobacco was investigated, the great majority of the literature suggests that the joint effect is multiplicative or, at least, greater than additive.[26,35]

Human papillomavirus (HPV) is another possible key factor in the etiology of oral and pharyngeal cancers[36–38]; two recent studies reported a high risk of oral and pharyngeal cancer associated with HPV16 and HPV18 (odds ratio [OR]: 61 and OR: 63).[31,39]

Metabolic genes and risk of oral and pharyngeal cancers

CYP1A1 and GSTM1 are important enzymes in the metabolism of tobacco carcinogens, which involves a balance between the activation steps mediated by the cytochrome P450 system and the detoxification steps involving GSTM1 that catalyze the conversion of the reactive electrophiles to inactive, water soluble conjugates that can be easily removed.[4]

Previous systematic reviews, meta-analysis and pooled analysis, have reported a relationship between the *GSTM1* null genotype and the risk of head and neck cancer[2,40–43] but the only report that stratified the analysis for cancer site[41] found important differences in risk for oral and laryngeal tumors. No association was found for the *CYP1A1* (*Ile/val*) polymorphism in this last assessment. Because different patterns of GST and CYP1A1 enzyme expression have been shown in oral and pharyngeal epithelium in comparison with laryngeal epithelium,[12,44] we conducted a pooled and meta-analysis to evaluate the relationship between these polymorphisms and oral and pharyngeal tumors, and we explored the combined effects of polymorphisms in these two genes along with their interaction with smoking.

METHODS

Selection criteria

The association of *GSTM1* and *CYP1A1* with oral and pharyngeal cancers was determined by meta-analysis of publications identified in a systematic review as well as by a pooled analysis using both published and unpublished data from the Genetic Susceptibility to Environmental Carcinogens (GSEC) database. A bibliographic search was carried out in the MEDLINE and EMBASE databases to identify studies on oral and pharyngeal cancers published up to October 17, 2007. The search strategy used was: (oral or buccal or mouth or "head and neck" or pharyngeal or pharynx or oropharyngeal) and (cancer or neoplasms or tumor* or tumour* or carcinoma* or carcinogenesis) and ("glutathione transferase" or "glutathione *S* transferase" or "glutathione *S*-transferase" or *GSTM1* or "cytochrome P450 enzyme system" or "cytochrome P450 *CYP1A1*" or *CYP1A1*). A manual review of the bibliographic references cited in the selected articles was undertaken to retrieve articles that might have been missed in the search. Articles were independently reviewed by two researchers and the inclusion/exclusion was made by consensus on the basis of pre-established selection criteria. The inclusion criteria were: (1) articles published in English, Spanish, Italian, or French, and (2) studies that assessed the association between the polymorphisms of the genes under study and oral and pharyngeal cancers. The exclusion criteria were: (1) studies that included only cases; (2) studies that assessed the risk of secondary tumors, recurrence, or response to treatment; (3) studies where patients were overlapped; and (4) studies that included nasopharyngeal cases. When several studies included the same population we included only the most updated one.

The meta-analysis included only those articles that provided results that allowed for the calculation of crude risks for oral and/or pharyngeal tumors. Crude ORs were used to obtain comparable estimates across studies. For each study included the author, year of publication, country where the study was carried out, number, race, and gender of patients and controls, control source (hospital based or population based), tumor site, and matching of cases and controls were rigorously tabulated. The bibliographic search led to the identification of 56 original articles. Of these, five did not include data on the genes involved in this analysis,[45–49] three did not provide the data that was needed to calculate the ORs for oral and pharyngeal sites,[50–52] therefore were not further evaluated. Of the remaining 48 articles, 18 were excluded from the meta-analysis because they did not provide head and neck subsite specific data and subjects with laryngeal tumors were not distinguished from the oral/pharyngeal group.[53–70] Thirty publications were used in the meta-analysis including a total of 7783 subjects (3177 cases and 4606 controls). They were all case-control studies. There were two studies with overlapping subjects but reported data separately for *GSTM1*[71] and *CYP1A1*.[72] Two other studies each reported separately data for *CYP1A1* Msp1[73] and exon 7.[74] However, both publications reported overlapping data for *GSTM1*. Therefore, there were 26 studies with results on *GSTM1* deletion, 11 on *CYP1A1 Ile/Val* polymorphism, 6 on *CYP1A1* MspI polymorphism. Only three studies assessed the combined *GSTM1*/*CYP1A1* MspI polymorphisms and one the *GSTM1*/*CYP1A1* exon 7 polymorphisms.

Data collection

The pooled analysis was performed using information from the GSEC database (http://www.upci.upmc.edu/research/ccps/ccontrol/g_intro.html).[75,76] Briefly, the GSEC study is a collection of data from both published and unpublished case-control studies of metabolic gene polymorphisms and cancer. All of the investigators of the published studies for which the GSEC database did not contain their data were contacted and invited to provide their data for this specific pooled analysis. The investigators for the other studies that were excluded because of insufficient head and neck subsite specific data were also contacted. Of the 30 studies in the meta-analysis, data for 14 studies were obtained for *GSTM1* and/or *CYP1A1*.[5,44,71,72,77–86] However, two of these studies reported *CYP1A1* and *GSTM1* data separately for the same subjects and were counted as a single study.[71,72] Among these 13 published studies, three provided unpublished data for *CYP1A1* polymorphisms for the same subjects. The GSEC database also had one study with unpublished data for *GSTM1* deletion (Foulkes et al., unpublished data) and another study with unpublished data for both *GSTM1* and *CYP1A1* (Ruano-Ravina et al., unpublished data). There were also seven additional published studies that were previously excluded from the meta-analysis, which were now included in the pooled analysis because the raw data allowed us to define specific head and neck subsites.[57,59,65,66,69,70,87] Although there were 22 studies available, 2 of them reported overlapping data for *GSTM1*. Therefore, the pooled analysis included 21 datasets, with 9397 subjects (3130 cases and 6267 controls).

Statistical analysis

All statistical analyses were carried out using STATA SE (version 10) software (StataCorp LP, College Station, TX). For the meta-analysis, the frequency of cases and controls was extracted from each publication and study-specific crude ORs were calculated along with their 95% confidence intervals (CIs). The Q statistics were used to test for heterogeneity among the studies for *GSTM1* deletion and *CYP1A1* polymorphisms. When heterogeneity was observed a random-effects model was used to calculate the summary ORs for the combined studies, when heterogeneity was not observed a fixed-effects model was used. Publication bias was determined by performing the Eggers test. To explore the between study heterogeneity, sensitivity analyses were performed, to identify the influence of the individual studies on the combined OR. When a study was identified, the analysis was repeated excluding such study to assess if homogeneity between the remaining studies was reached.

In the pooled analysis for each gene, crude ORs for their overall association with oral/pharyngeal cancer were calculated. ORs adjusted for potential confounders were calculated using multivariable logistic regression models. Crude and adjusted ORs were also calculated for each gene, stratifying by control source (healthy versus hospital), smoking status, race and tumors site (oral cavity versus pharynx). The Mantel-Haenszel test was used to assess differences between stratum-specific ORs.

From south east/south Asia publications, three of the five available studies included data on consumption of other tobacco or had tobacco chewing habits; these patients were included in the pooled analysis, but the data on other tobacco was not analyzed for the present publication. Smoking status was defined as never and ex, current, or ever smokers. All smoking data were recoded into a standardized variable: ever/never smoking. Patients were classified as never smokers if they smoked $<$ 100 cigarettes in their lifetime, and ever smokers if defined by the individual studies either as ex, current, or ever (current and ex) smokers.

RESULTS

Of the 30 studies included in the meta-analysis, 17 were carried out in Asian countries,[73,74,77,78,80,84,86–96] seven in American countries,[71,72,79,83,85,97,98] and six in Europe.[5,44,81,82,99,100] Hospital patients were used as controls in 16 studies.[5,44,71,72,78,81–85,88,92,93,97–99] The number of cases in the studies included in the meta-analysis for *GSTM1* deletion varied from 21 to 451 patients. All studies undertaken in Europe included $<$150 cases, with two of these having $<$50 cases.[5,82] For the *CYP1A1* analysis, the case numbers ranged from 45 to 446 subjects.

Population frequencies

The frequency of the *GSTM1* null in the control group ranged from 24% to 58.9%, with considerable variation depending on the area the study was carried out. In Asia, large differences could be observed between countries. The frequencies in India varied from 24% to 37%,[78,80,84,90,96] in Japan from 39.8% to 48.7%[73,77,91–94], although the only study from Taiwan observed a frequency of 57.7%.[95] In South America these values ranged from 38.2% to 48.7%[71,79,97,98] and in Europe and United States from 51% to 54.8%.[5,44,81–83,99,100]

For the *CYP1A1* exon 7 polymorphism, large geographical heterogeneity could be observed. The frequency of the homozygote genotype for the variant allele in the controls was absent or very low in Europe (0–6%) whereas the heterozygous genotype was very rare (6–9.3%).[44,100] In Asia, the heterozygous genotype was present in 32.4–53.4% of the control subjects.[74,87,88,93] In Brazil and Puerto Rico this polymorphism was found in 19–30% of the subjects.[72,79,85] The combined frequency of the homozygous and heterozygous genotype of the variant allele for the single study in the United States was 7.4%.[83] The *CYP1A1* MspI heterozygous variant allele (*m1/m2*) was present in 30–59.5% of the Asian control population.[73,84,86,88,92] The only European study that assessed this polymorphism reported a frequency of 9.3% for the variant allele.[44] The homozygous allele was very rare in all populations (1–10.6%).

Meta-analysis

The overall meta-OR for *GSTM1* null was not reported because of the large heterogeneity between studies (Q test *P* value $<$ 0.001; data not shown). We performed a sensitivity analysis and identified one study that appeared to influence the overall meta-OR,[80] however, heterogeneity was still observed after exclusion of this study. In an effort to further explore the observed heterogeneity, we stratified the studies by race. The study-specific and meta-ORs for *GSTM1* are shown for whites, Asians, and others (i.e., studies that did not specify ethnicity or included more than one ethnic group) in Table 1. There was no increased risk of oral and pharyngeal cancer with the *GSTM1* deletion among whites (OR: 1.1, 95% CI: 0.9–1.3), and no evidence of publication bias (Eggers test *P* value = 0.19). For Asians and all other ethnic groups and studies with mixed populations, there was still large heterogeneity between studies (Q test, *P* value $<$ 0.001); therefore, the overall meta-OR was not reported although there was no evidence of publication bias (Eggers test *P* value = 0.77 for Asian studies and 0.80 for other studies). Sensitivity analysis of the Asian studies identified a data set that seemed to influence the meta-ORs. When this study was excluded, homogeneity was observed among the remaining studies (Q test, *P* value = 0.186). There was a statistically significant increase in the risk of oral and pharyngeal cancer with the *GSTM1* deletion (OR: 1.6, 95% CI: 1.3–2.0). There was no evidence of publication bias (Eggers test *P* value = 0.819). For the remaining studies (i.e., studies that did not specify ethnicity or included more than one ethnic group), heterogeneity was still observed even after exclusion of the outlier,[80] (Q test, *P* value 0.005); this was likely due to the mixed populations grouped in this category.

The 15 studies with data reported on *CYP1A1* MspI and/or exon7 (*Ile/Val*) are summarized in Table 2. There were 11 stud-

Table 1
Description of studies included in the meta-analysis for *GSTM1*

Author	Control source	Country	Tumor site	Matching	Cases	Controls	OR (95%CI) *GSTM1* deleted vs. present
Whites							
Deakin et al.[82a]	Hospital	UK	Oral cavity		40	577	1.0 (0.5–1.9)
Coutelle et al.[5a]	Alcoholic clinic	France	Oropharynx	Alcohol	21	37	1.7 (0.6–5.1)
Park et al.[83a]	Healthy and hospital	USA	Oral cavity		109	109	0.9 (0.5–1.5)
Matthias et al.[48a]	Hospital	Germany	Oral cavity and pharynx		122	178	1.2 (0.8–1.9)
Jourenkova-Mironova et al.[81a]	Hospital	France	Oral cavity and pharynx	Smoking	121	172	0.8 (0.5–1.3)
Hahn et al.[100]	Healthy	Germany	Oral cavity	Ethnicity	94	92	1.3 (0.7–2.3)
Gronau et al.[61]	Hospital	Germany	Oral cavity	Smoking and alcohol	73	129	1.2 (0.7–2.2)
META					580	1294	1.1 (0.9–1.3)[b]
P, Q test							0.796
P, Eggers test							0.194
Asians							
Katoh et al.[77a]	Healthy	Japan	Oral, NOS		45	91	1.6 (0.8–3.3)
Hung et al.[95]	Healthy	Taiwan	Oral, NOS		41	123	1.0 (0.5–2.1)
Kihara et al.[94]	Healthy	Japan	Oral cavity, Pharynx, Maxillary sinuses		75	472	1.8 (1.1–2.9)
Tanimoto et al.[92]	Hospital	Japan	Oral cavity	Age and sex	100	100	1.0 (0.6–1.8)
Katoh et al.[93]	Hospital	Japan	Oral cavity		92	147	1.7 (1.0–2.8)
Morita et al.[87a]	Healthy	Japan	Pharynx		45	164	1.0 (0.5–2.0)
Sato et al.[73,74]	Healthy	Japan	Oral cavity[c]	Age and sex	142	142	2.2 (1.4–3.6)
Nomura et al.[91]	Healthy	Japan	Oral cavity and Pharynx		114	33	2.5 (1.1–5.5)
Kietthubthew et al.[89]	Healthy	Thailand	Oral cavity	Age, sex, smoking, betel-chewing and occupation	53	53	3.0 (1.4–6.7)
Cha et al.[86]	Healthy	Korea	Oral, NOS		72	209	0.7 (0.4–1.3)
P, Q test					779	1534	0.037
P, Eggers test							0.777
Other studies[d]							
Sreelekha et al.[90]		India	Oral, NOS	Age and sex	98	60	1.9 (1.0–3.7)
Buch et al.[80a]	Healthy	India	Oral cavity	Region of origin	297	450	3.0 (2.2–4.0)
Xie et al.[79a]	Healthy	Puerto Rico	Oral, NOS		132	143	0.7 (0.4–1.2)
Sikdar et al.[78a]	Hospital	India	Oral cavity		256	259	1 .0 (0.7–1.4)
Drummond et al.[98]	Dental clinic	Brazil	Oral cavity[e]	SES, age and sex	70	82	2.0 (1.0–3.9)
Gattas et al.[97]	Hospital	Brazil	Oral cavity and Pharynx	Age and sex	81	102	2.5 (1.4–4.5)
Sharma et al.[96]	Healthy	India	Oral, NOS		40	87	2.2 (1.0–5.1)

(*Continued*)

Table 1
(Continued)

Author	Control source	Country	Tumor site	Matching	Cases	Controls	OR (95%CI) *GSTM1* deleted vs. present
Anantharaman et al.[84a]	Healthy and dental clinic	India	Oral, NOS	Age, sex, tobacco habits	451	727	1.3 (1.0–1.7)
Hatagima et al.[71f]	Hospital	Brazil	Oral, Oropharynx	Sex, age, race	231	212	0.9 (0.6–1.3)
P, Q test					1446	2122	<0.001
P, Eggers test							0.801

[a]Studies included in the pooled analysis.
[b]Fixed effects estimate.
[c]Plus other unspecified oral subsites.
[d]Meta estimate was not reported because of the statistically significant test for heterogeneity. These studies had mixed ethnic groups.
[e]Smokers.
[f]Same subjects as Marques et al. in Table 2.
NOS, not otherwise specified; SES, socioeconomical status.

ies overall with *CYP1A1* (*Ile/Val*) data and 7 studies with *CYP1A1* MspI data. Nine studies reported data on the associations between the *Ile/Val* polymorphism and risk of oral and pharyngeal cancers, 6 studies reported associations for the *Val/Val* polymorphism, and 10 reported associations for all variants combined (i.e., *Ile/Val* and *Val/Val*). For each of these groups, the studies were statistically significantly heterogeneous (Q test, *P* value < 0.001), therefore no overall meta-ORs were reported. There was no evidence of publication bias (Eggers test *P* value: *Ile/Val* = 0.945, *Val/Val* = 0.625, and *Ile/Val* + *Val/Val* = 0.199). Sensitivity analysis of these studies identified a data set that appeared to influence the meta-ORs. However, exclusion of this study did not resolve the heterogeneity between the remaining studies. The observed heterogeneity is likely due to misclassification, because most of the earlier studies used a laboratory method that may not accurately distinguish between the exon 7 variant alleles.

Among the five studies with *CYP1A1* MspI data, all except for one study reported the associations for the *m1m2*, *m2m2,* and combined variants (*m1m2* + *m2m2*). The studies that reported data for the *m1m2* and combined variants (*m1m2* + *m2m2*) were statistically significantly heterogeneous; therefore the meta-ORs were not reported. No publication bias was observed (Eggers test *P* value: *m1m2* = 0.389 and *m1m2* + *m2m2* = 0.339). There was an increased risk of oral and pharyngeal cancers for patients with the m2m2 variant (meta-OR: 1.9, 95% CI: 1.4–2.7). There was no evidence of publication bias (Eggers test *P* value: *m2m2* = 0.595). Sensitivity analyses identified a study that influenced the meta-ORs for the *m1m2* and combined variants (*m1m2* + *m2m2*).[92] After excluding this data set, homogeneity was obtained; no association for the *m1m2* or combined variants and oral and pharyngeal cancer was observed (*m1m2* + *m2m2*) (*m1m2,* Q test, *P* value = 0.625, OR: 0.9, 95% CI: 0.8–1.1, *m1m2* + *m2m2,* Q test, *P* value = 0.798, OR: 1.0, 95% CI: 0.9–1.2). There was no evidence of publication bias (Eggers test *P* value: *m1m2* = 0.628, *m1m2* + *m2m2* = 0.407).

Only one study evaluated the interaction between the *GSTM1* null and *CYP1A1* (*Ile/Val*) polymorphism, and three evaluated the interaction between the *GSTM1* null and *CYP1A1* MspI polymorphism (Table 3). The overall meta-OR for *GSTM1* null + *m1m1* was not reported because the studies were statistically significantly heterogeneous (Q test *P* value = 0.002). There seemed to be an increased risk of oral and pharyngeal cancers for the *GSTM1 wt* + *m1m2* or *m2m2* (meta-OR: 1.6, 95% CI: 1.0–2.7) and the *GSTM1* null + *m1m2* or *m2m2* (meta-OR: 3.0, 95% CI: 1.8–5.0). However, the association was not statistically significant for all other polymorphic isoforms. There was no publication bias observed for any of these analyses.

Pooled analysis

The GSEC pooled analysis included 21 studies (3130 cases and 6267 controls).

Significant heterogeneity was observed between the 20 studies that contained data for G*STM1*. Similar to the meta-analysis, one study seemed to contribute to the heterogeneity.[80] Analyses were then stratified by various covariates. There was no association between the *GSTM1* deletion and oral and pharyngeal cancers (Table 4), even when the analysis was limited to healthy controls (Adjusted odds ratio [AdjOR]: 1.1, 95% CI: 0.8–1.4). A marginal statistically significant association was observed for current smokers (AdjOR: 1.2, 95% CI: 1.0–1.4) or ever smokers (AdjOR: 1.1, 95% CI: 1.0–1.3), but not in never smokers (AdjOR: 1.0, 95% CI: 0.8–1.2). The differences observed between the stratum-specific ORs for smoking were not statistically significant ($P > 0.1$) (data not shown). The datasets for never, ex, and current were homogeneous. (Q test, *P* value > 0.05) but was not for ever smokers (Q test, *P* value = 0.018). The *GSTM1* deletion was statistically significantly associated with oral and pharyngeal cancer in African Americans and Africans (OR: 1.9, 95% CI: 1.1–3.3), but was no longer statistically significant after adjusting for confounding variables (AdjOR: 1.7, 95% CI: 0.9–3.3). There was no association

Table 2
Description of the studies included in the meta analysis for *CYP1A1*

Author	Control source	Country	Tumor site	Matching	Cases	Controls	OR (95% CI) *Ile/Ile*	OR (95% CI) *Ile/Val*	OR (95% CI) *Val/Val*	OR (95% CI) *Ile/Val + Val/Val*
CYP1A1 (exon7)[a]										
Park et al.[83b]	Healthy + hospital	USA	Oral cavity		108	108	1.0 (ref)			2.5 (1.0–6.0)
Matthias et al.[48b]	Hospital	Germany	Oral cavity and Pharynx		124	186	1.0 (ref)	1.1 (0.5–2.3)		1.0 (0.5–2.1)
Katoh et al.[93]	Hospital	Japan	Oral cavity		92	147	1.0 (ref)	1.3 (0.7–2.2)	1.3 (0.4–4.1)	1.3 (0.8–2.2)
Morita et al.[87a]	Healthy	Japan	Pharynx		45	164	1.0 (ref)	0.7 (0.4–1.2)	2.4 (0.9–6.4)	0.9 (0.5–1.5)
Sato et al.[74c]	Healthy	Japan	[d]Oral cavity	Age and sex	142	142	1.0 (ref)	1.6 (1.0–2.6)	4.2 (1.6–11.1)	1.9 (1.2–3.0)
Kao et al.[88]	Hospital	Taiwan	Oral cavity		106	146	1.0 (ref)	5.1 (2.6–9.8)	18.9 (3.6–98.5)	5.4 (2.8–10.4)
Hahn et al.[100]	Healthy	Germany	Oral cavity	ethnicity	94	92	1.0 (ref)	0.6 (0.2–2.3)		
Sreelekha et al.[90]		India	Oral, NOS	Age and sex	98	60	1.0 (ref)			5.2 (2.4–11.4)
Xie et al.[79b]	Healthy	Puerto Rico	Oral, NOS		132	143	1.0 (ref)	0.9 (0.6–1.6)	0.5 (0.2–1.8)	0.9 (0.5–1.4)
Marques et al.[72e]	Hospital	Brazil	Oral, NOS	Age, sex and skin color	231	212	1.0 (ref)	1.1 (0.7–1.8)	2.9 (0.6–14.3)	1.2 (0.7–1.9)
Leichsenring et al.[85b]	Hospital	Brazil	Oral, NOS		72	60	1.0 (ref)	1.0 (0.4–2.3)		1.0 (0.5–2.5)
P, Q test					1199	1296		0.001	0.014	<0.001
P, Eggers test								0.945	0.625	0.199
							m1/m1	*m1/m2*	*m2/m2*	*m1/m2 + m2/m2*
CYP1A1 MspI[a]										
Matthias et al.[44b]	Hospital	Germany	Oral cavity and pharynx		122	205	1.0 (ref)	1.6 (0.8–3.2)	0.9 (0.1–9.9)	1.5 (0.8–3.0)
Sato et al.[73c]	Healthy	Japan	[d]Oral cavity	Age and sex	142	142	1.0 (ref)	0.9 (0.6–1.6)	2.3 (1.1–4.7)	1.2 (0.7–1.9)
Tanimoto et al.[92]	Hospital	Japan	Oral cavity	Age and sex	100	100	1.0 (ref)	3.4 (1.8–6.4)	3.6 (1.4–9.5)	3.5 (1.9–6.2)
Kao et al.[88]	Hospital	Taiwan	Oral cavity		106	146	1.0 (ref)	0.9 (0.5–1.5)	1.3 (0.6–3.1)	0.9 (0.6–1.6)
Gattas et al.[97]	Hospital	Brazil	Oral cavity and pharynx	Age and sex	81	102	1.0 (ref)			0.9 (0.5–1.6)
Anantharaman et al.[84b]	Healthy + dental clinic	India	Oral, NOS	Age, sex, tobacco habits	446	727	1.0 (ref)	0.9 (0.7–1.2)	1.5 (0.9–2.3)	1.0 (0.8–1.3)
Cha et al.[86]	Healthy	Korea	Oral, NOS		72	163	1.0 (ref)	0.8 (0.4–1.6)	3.2 (1.3–7.8)	1.1 (0.6–2.2)
META							1.0 (ref)		1.9 (1.4–2.7)[f]	
P, Q test					1069	1585		0.003	0.342	0.007
P, Eggers test								0.389	0.595	0.339

[a]Meta estimate was not reported because of the statistically significant test for heterogeneity.
[b]Studies included in the pooled analysis.
[c]Sato et al., 1999 and Sato et al., 2000 included the same subjects.
[d]Plus other unspecified oral subsites.
[e]Same subjects as Hatagima et al. in Table 1.
[f]Fixed effects estimate.
NOS, not otherwise specified.

Table 3
Description of studies included in the meta analysis for *GSTM1-CYP1A1* interaction

Author	Control source	Country	Tumor site	Matching	Cases	Controls	(+)*Ile/Ile* OR (95% CI)	(−) *Ile/Ile* OR (95% CI)	(+) *Ile/Val* or *Val/Val* OR (95% CI)	(−) *Ile/Val* or *Val/Val* OR (95% CI)	All polymorphic isoforms OR (95% CI)
GSTM1/CYP1A1 exon7											
Sato et al.[74a]	Healthy	Japan	Oral cavity[b]	Age and sex	142	142	1.0 (ref)	2.3 (1.2–4.3)	1.9 (0.9–3.9)	4.0 (2.0–7.9)	2.6 (1.5–4.6)
							(+) *m1/m1*	(−) *m1/m1*	(+) *m1/m2* or *m2/m2*	(−) *m1/m2* or *m2/m2*	All polymorphic isoforms
GSTM1/CYP1A1 MspI											
Gattas et al.[97]	Hospital	Brazil	Oral cavity and pharynx	Age and sex	103	102	1.0 (ref)				2.4 (1.1–5.1)
Sato et al.[73a]	Healthy	Japan	Oral cavity[b]	Age and sex	142	142	1.0 (ref)	2.7 (1.3–5.6)	1.4 (0.7–2.8)	2.7 (1.4–5.3)	2.2 (1.2–3.9)
Tanimoto et al.[92]	Hospital	Japan	Oral cavity	Age and sex	100	100	1.0 (ref)	0.4 (0.2–1.0)	2.0 (0.9–4.1)	3.5 (1.6–8.0)	1.6 (0.9–3.0)
META					345	344	1.0 (ref)		1.6 (1.0–2.7)[c]	3.0 (1.8–5.0)[c]	2.0 (0.4–2.9)[c]
P, Q test								0.002	0.485	0.597	0.704

[a]Sato et al., 1999 and Sato et al., 2000 included the same subjects.
[b]Plus other unspecified oral subsites.
[c]Fixed effects estimate.

between *GSTM1* deletion and oral and pharyngeal cancer risk in white, Asian populations, or other ethnic groups.

The adjusted summary OR for the association of *CYP1A1* MspI polymorphism and oral and pharyngeal cancers (Table 5) was not significant for the *m1m2* genotype but was for the *m2m2* genotype (AdjOR: 2.0, 95% CI: 1.3–3.1). Among oral and pharyngeal cancers, there was a 2-fold likelihood of having the *m2m2* genotype compared with the controls in never smokers (AdjOR: 1.8, 95% CI: 1.1–2.9) but not in current or ever smokers. There was a statistically significant difference when the stratum-specific ORs for never and current smokers were compared (P value = 0.019). The association of the *m2m2* variant also differed when limited to healthy controls (AdjOR- healthy controls: 1.2, 95% CI: 0.7–2.2) versus hospital controls: 1.7, 95% CI: 1.1–2.7). A statistically significant association of the *m2m2* genotype was observed for white (AdjOR: 2.1, 95% CI: 1.4–3.3) but not for other ethnic groups, although these were a mixed population.

In contrast, there was no association between the *CYP1A1* (exon7) variant and oral and pharyngeal cancers regardless of the type of controls used in the analysis (Table 6). However, there was a statistically significant association of the *Val/Val* genotype for ever smokers (AdjOR: 2.2, 95% CI: 1.1–4.5). Asian cases seemed to have almost a 4-fold likelihood of having the *Val/Val* genotype when compared with the controls; however, this was only marginally statistically significant (AdjOR: 3.5, 95% CI: 1.0–12.6).

A marginal increased risk of cancer with the *GSTM1* deletion was observed when examining oral cavity (AdjOR: 1.1, 95% CI: 1.0–1.2) and pharyngeal (AdjOR: 1.3, 95% CI: 1.1–1.6) cases independently. Among subjects with oral cavity tumors, no associations were observed for *CYP1A1* (exon7) but for *CYP1A1* MspI polymorphisms there was a marginal association; the *m2m2* genotype was significantly associated with oral cavity tumors (AdjOR: 2.0, 95% CI: 1.3–3.1) (Table 7). We were unable to determine the association of this variant genotype for subjects with pharyngeal tumors.

When evaluating alcohol use, a marginal increased risk of cancer with *GSTM1* deletion was observed for both never and ever drinkers (never drinkers, AdjOR: 1.2, 95% CI: 1.0–1.5, ever drinkers, AdjOR: 1.2, 95% CI: 1.0–1.3) (Table 4). There was no association of the *CYP1A1* (exon7) polymorphisms with oral and pharyngeal cancer according to alcohol consumption (Table 5), but an increase risk associated with the *CYP1A1 m2m2* genotype in never drinkers only was observed (AdjOR: 2.6, 95% CI: 1.5–4.3) (Table 6).

Complete *GSTM1* and *CYP1A1* genotype

The combination of the *CYP1A1* MspI and *CYP1A1* (exon7) polymorphisms was not associated with the risk of oral and pharyngeal cancers (data not shown). The combination of the *GSTM1* null plus the *CYP1A1* (*m1m2*) variant genotypes increased the risk of oral and pharyngeal cancers (AdjOR: 1.3, 95% CI: 1.0–1.7), similar observations were made when the homozygous *CYP1A1* variant (*m2m2*) was considered (AdjOR: 1.9, 95% CI: 1.0–3.9—Table 8). This marginal association was also observed in never smokers, but not in current or ever smokers. Similarly, the *GSTM1* null plus the *CYP1A1*

Table 4
Overall and stratified odds ratios of the association of *GSTM1* deletion with oral and pharyngeal cancers—pooled analysis

GSTM1	Controls (*N*)	Cases (*N*)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
No. studies = 19[b]				
N = 7046	4658	2388		
Present	2436	1242	1.0 (ref)	1.0 (ref)
Null	2222	1146	1.0 (0.9–1.1)[c]	1.0 (0.9–1.1)
Healthy controls (*N* = 926)[d]				
	556	370		
Present	299	199	1.0 (ref)	1.0 (ref)
Null	257	171	1.0 (0.8–1.3)	1.1 (0.8–1.4)
Hospital controls (*N* = 2966)[d]				
	1922	1044		
Present	943	542	1.0 (ref)	1.0 (ref)
Null	979	502	0.9 (0.8–1.0)	0.9 (0.8–1.1)
Never smokers (*N* = 2751)				
	1974	777		
Present	1059	428	1.0 (ref)	1.0 (ref)
Null	915	349	0.9 (0.8–1.1)	1.0 (0.8–1.2)
Ex smokers (*N* = 864)				
	548	316		
Present	265	157	1.0 (ref)	1.0 (ref)
Null	283	159	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Current smokers (*N* = 1963)				
	1150	813		
Present	645	423	1.0 (ref)	1.0 (ref)
Null	505	390	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Ever smokers (*N* = 3651)				
	2126	1525		
Present	1122	776	1.0 (ref)	1.0 (ref)
Null	1004	749	1.1 (1.0–1.2)	1.1 (1.0–1.3)
Never drinkers (*N* = 4822)				
	1280	579		
Present	691	282	1.0 (ref)	1.0 (ref)
Null	589	297	1.2 (1.0–1.5)	1.2 (1.0–1.5)
Ever drinkers (*N* = 2963)				
	1776	1187		
Present	938	587	1.0 (ref)	1.0 (ref)
Null	838	600	1.1 (1.0–1.3)	1.2 (1.0–1.3)
Whites (*N* = 5851)				
	3857	1994		
Present	1987	1034	1.0 (ref)	1.0 (ref)
Null	1870	960	1.0 (0.9–1.1)	1.0 (0.9–1.1)
African Americans + Africans (*N* = 294)				
	195	99		
Present	149	62	1.0 (ref)	1.0 (ref)
Null	46	37	1.9 (1.1–3.3)	1.7 (0.9–3.3)
Asians (*N* = 681)				
	491	190		
Present	236	93	1.0 (ref)	1.0 (ref)
Null	255	97	1.0 (0.7–1.4)	1.2 (0.8–1.8)
Other (*N* = 220)				
	115	105		
Present	64	53	1.0 (ref)	1.0 (ref)
Null	51	52	1.2 (0.7–2.0)	1.2 (0.7–2.1)

[a]Adjusted for study number, age (<54, 54–95), sex, race, and smoking (never/ever) where appropriate.
[b]One dataset conducted in an Indian population was excluded from the analysis because of heterogeneity.
[c]Q test (P = 0.048); Eggers test (P = 0.825); Q test (P for all strata >0.05) except for Ever smokers, P = 0.018).
[d]Healthy controls: includes 5 studies with healthy controls; Hospital controls: includes 8 studies with hospital controls; 6 studies were excluded from this subanalysis because they consisted of both hospital and healthy controls combined. Other = Latinos and other ethnicities not specified.

m1m1 or *m1m2* genotypes were marginally associated with the risk of oral and pharyngeal cancers in never smokers (AdjOR: 1.4, 95% CI: 0.9–2.0) but not in ever smokers (AdjOR: 1.3, 95% CI: 0.8–2.2). When oral cavity and pharyngeal cancer case subjects were examined independently, the interaction between the *GSTM1* null and *CYP1A1* MspI polymorphism was observed for oral cancer but not for cancer of the pharynx (Table 8).

DISCUSSION

To our knowledge, this is the first meta-analysis and pooled analysis carried out to assess the role of *GSTM1* and *CYP1A1* in oral and pharyngeal cancers and to evaluate potential gene-gene and gene-environment joint effects. The results obtained in this study support the hypothesis that *GSTM1* deletion and certain *CYP1A1* polymorphisms may play a role in the carcinogenesis process leading to oral and pharyngeal cancers. Both the

Table 5
Overall and stratified odds ratios of the association of *CYP1A1* MspI polymorphism with oral and pharyngeal cancers—pooled analysis

CYP1A1 MspI	Controls (*N*)	Cases (*N*)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
No. studies for *CYP1A1 MspI* = 8				
N = 4063	2581	1482		
m1m1	1415	796	1.0 (ref)	1.0 (ref)
m1m2	980	525	1.0 (0.8–1.1)[b]	1.2 (1.0–1.5)
m2m2	186	161	1.5 (1.2–1.9)[b]	2.0 (1.3–3.1)
m1m2 + m2m2	1166	686	1.1 (0.9–1.2)[b]	1.3 (1.1–1.6)
Never smokers (*N* = 2119)				
	1318	801		
m1m1	652	365	1.0 (ref)	1.0 (ref)
m1m2	566	337	1.1 (0.9–1.3)	1.2 (0.9–1.5)
m2m2	100	99	1.8 (1.3–2.4)	1.8 (1.1–2.9)
m1m2 + m2m2	666	436	1.2 (1.0–1.4)	1.2 (1.0–1.6)
Current (*N* = 822)				
	545	277		
m1m1	283	127	1.0 (ref)	1.0 (ref)
m1m2	219	114	1.2 (0.9–1.6)	1.3 (0.8–2.3)
m2m2	43	36	1.9 (1.1–3.0)	2.6 (0.9–7.5)
m1m2 + m2m2	262	150	1.3 (1.0–1.7)	1.5 (0.9–2.5)
Ever smokers (*N* = 1320)				
	772	548		
m1m1	468	355	1.0 (ref)	1.0 (ref)
m1m2	258	154	0.8 (0.6–1.0)	1.2 (0.8–1.8)
m2m2	46	39	1.1 (0.7–1.8)	2.4 (0.9–5.8)
m1m2 + m2m2	304	193	0.8 (0.7–1.1)	1.3 (0.9–1.9)
Never drinker (*N* = 1045)				
	635	410		
m1m1	356	210	1.0 (ref)	1.0 (ref)
m1m2	248	162	1.1 (0.9–1.4)	1.3 (1.0–1.7)
m2m2	31	38	2.1 (1.3–3.4)	2.6 (1.5–4.3)
m1m2 + m2m2	279	200	1.2 (1.0–1.6)	1.5 (1.1–1.9)
Ever drinker (*N* = 919)				
	546	373		
m1m1	346	281	1.0 (ref)	1.0 (ref)
m1m2	178	83	0.6 (0.4–0.8)	1.1 (0.8–1.5)
m2m2	22	9	0.5 (0.2–1.1)	1.0 (0.4–2.5)
m1m2 + m2m2	200	92	0.6 (0.4–0.8)	1.1 (0.8–1.5)
Healthy controls (*N* = 1109)[c]				
	161	948		
m1m1	137	438	1.0 (ref)	1.0 (ref)
m1m2	23	391	0.9 (0.7–1.1)	1.1 (0.8–1.6)[d]
m2m2	1	119	1.3 (0.8–1.9)	1.2 (0.7–2.2)[d]
m1m2 + m2m2	24	510	0.9 (0.7–1.2)	1.1 (0.8–1.6)[d]
Hospital controls (*N* = 1546)[c]				
	968	578		
m1m1	665	366	1.0 (ref)	1.0 (ref)
m1m2	256	168	1.2 (1.0–1.5)	1.3 (1.0–1.7)[d]
m2m2	47	44	1.7 (1.1–2.6)	1.7 (1.1–2.7)[d]
m1m2 + m2m2	303	212	1.3 (1.0–1.6)	1.4 (1.1–1.8)[d]
Whites (*N* = 2880)				
	1769	1111		
m1m1	1059	645	1.0 (ref)	1.0 (ref)
m1m2	612	375	1.0 (0.9–1.2)	1.2 (1.0–1.5)
m2m2	98	91	1.5 (1.1–2.1)	2.1 (1.4–3.3)
m1m2 + m2m2	710	466	1.1 (0.9–1.3)	1.3 (1.1–1.6)
Other (*N* = 1183)				
	812	371		
m1m1	356	151	1.0 (ref)	1.0 (ref)
m1m2	368	150	1.0 (0.7–1.3)	1.0 (0.7–1.4)
m2m2	88	70	1.9 (1.3–2.7)	1.6 (0.9–2.6)
m1m2 + m2m2	456	220	1.1 (0.9–1.5)	1.1 (0.8–1.6)

[a]Adjusted for study number, age (<54, 54–95), race, alcohol use (never/ever) and smoking (never/ever) where appropriate.
[b]Q test (*P*): m1m2 = 0.973, m2m2 = 0.403, m1m1 + m12m2 = 0.980; Eggers test (*P*): m1m2 = 0.666, m2m2 = 0.327, m1m1 + m2m2 = 0.515.
[c]Healthy controls: includes 2 studies with healthy controls; Hospital controls: includes 4 studies with hospital controls; 2 studies were excluded from this subanalysis because it consisted of both hospital and healthy controls combined; Other = African Americans, Africans, Asians, Latinos, and other ethnicities not specified.
[d]Alcohol use (never/ever) was excluded from the adjustment due to collinearity.

meta-analysis and pooled analysis showed a significant association between oral and pharyngeal cancer and the homozygous variant genotype of the *CYP1A1* MspI polymorphism. In addition, the data suggest that the combined effect of *GSTM1* and *CYP1A1* may be associated with oral and pharyngeal cancers. In the meta-analysis, the *GSTM1* null genotype was not found to be associated with oral and pharyngeal tumors in whites. Sensitivity analysis of the Asian studies identified a data set that determined the heterogeneity. This result suggests that differences in oral and pharyngeal cancer risk factors may be present according to the geographic origin of the subjects. Ethnic differences in the associ-

Table 6
Overall and stratified odds ratios of the association of *CYP1A1* (*exon7*) polymorphism with oral and pharyngeal cancers—pooled analysis

CYP1A1 (*exon 7*)	Controls (*N*)	Cases (*N*)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
No. studies for *CYP1A1* (*exon 7*) = 10				
N = 3814	2295	1519		
Ile/Ile	1778	1183	1.0 (ref)	1.0 (ref)
Ile/Val	479	298	0.9 (0.8–1.1)[b]	1.0 (0.8–1.1)
Val/Val	38	38	1.5 (1.0–2.4)[b]	1.5 (0.9–2.4)
Ile/Val + Val/Val	517	336	1.0 (0.8–1.1)[b]	1.0 (0.8–1.2)
Never smokers (*N* = 1194)				
	741	453		
Ile/Ile	568	352	1.0 (ref)	1.0 (ref)
Ile/Val	159	94	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Val/Val	14	7	0.8 (0.3–2.0)	0.9 (0.3–2.2)
Ile/Val + Val/Val	173	101	0.9 (0.7–1.2)	1.0 (0.7–1.3)
Current (*N* = 1048)				
	533	515		
Ile/Ile	403	392	1.0 (ref)	1.0 (ref)
Ile/Val	123	104	0.9 (0.7–1.2)	0.9 (0.6–1.2)
Val/Val	7	19	2.8 (1.2–6.7)	2.3 (0.9–5.8)
Ile/Val + Val/Val	130	123	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Ever smokers (*N* = 1751)				
	832	919		
Ile/Ile	641	712	1.0 (ref)	1.0 (ref)
Ile/Val	180	179	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Val/Val	11	28	2.3 (1.1–4.6)	2.2 (1.1–4.5)
Ile/Val + Val/Val	191	207	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Never drinkers (*N* = 144)				
	81	63		
Ile/Ile	66	56	1.0 (ref)	1.0 (ref)
Ile/Val	14	6	0.5 (0.2–1.4)	0.3 (0.1–1.3)
Val/Val	1	1	1.2 (0.1–19.3)	4.9 (0.3–92.3)
Ile/Val + Val/Val	15	7	0.6 (0.2–1.4)	0.5 (0.1–1.7)
Ever drinkers (*N* = 1115)				
	534	581		
Ile/Ile	405	476	1.0 (ref)	1.0 (ref)
Ile/Val	121	92	0.7 (0.5–0.9)	0.8 (0.5–1.0)
Val/Val	8	13	1.4 (0.6–3.4)	2.0 (0.8–5.0)
Ile/Val + Val/Val	129	105	0.7 (0.5–0.9)	0.8 (0.6–1.1)
Healthy controls (*N* = 1.876)[c]				
	1286	590		
Ile/Ile	952	442	1.0 (ref)	1.0 (ref)
Ile/Val	305	128	0.9 (0.7–1.1)	0.8 (0.6–1.0)
Val/Val	29	20	1.5 (0.8–2.7)	1.0 (0.5–1.9)
Ile/Val + Val/Val	334	148	1.0 (0.8–1.2)	0.8 (0.6–1.0)
Hospital controls (*N* = 1787)[c]				
	949	838		
Ile/Ile	782	686	1.0 (ref)	1.0 (ref)
Ile/Val	158	143	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Val/Val	9	9	1.1 (0.4–2.9)	1.1 (0.4–2.6)
Ile/Val + Val/Val	167	152	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Whites (*N* = 2085)				
	1095	990		
Ile/Ile	872	793	1.0 (ref)	1.0 (ref)
Ile/Val	207	180	1.0 (0.8–1.2)	0.9 (0.8–1.2)
Val/Val	16	17	1.2 (0.6–2.3)	1.1 (0.5–2.3)
Ile/Val + Val/Val	223	197	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Asians (*N* = 261)				
	189	72		
Ile/Ile	122	45	1.0 (ref)	1.0 (ref)
Ile/Val	61	18	0.8 (0.4–1.5)	0.7 (0.4–1.3)
Val/Val	6	8	3.5 (1.2–10.8)	3.5 (1.0–12.6)
Ile/Val + Val/Val	67	26	1.0 (0.6–1.8)	0.9 (0.5–1.7)
Other (*N* = 1468)				
	1011	457		
Ile/Ile	784	344	1.0 (ref)	1.0 (ref)
Ile/Val	211	100	1.1 (0.8–1.4)	1.0 (0.7–1.3)
Val/Val	16	13	1.9 (0.9–3.9)	1.4 (0.6–3.2)
Ile/Val + Val/Val	227	113	1.1 (0.9–1.5)	1.0 (0.8–1.4)

[a]Adjusted for study number, age (<54, 54–95), sex, race where appropriate.
[b]Q test (*P*): Ile/Val = 0.435, Val/Val = 0.425, Ile/Val + Val/Val = 0.282; Eggers test (*P*): Ile/Val = 0.968, Val/Val = 0.766, Ile/Val + Val/Val = 0.967.
[c]Healthy controls: includes 4 studies with healthy controls; hospital controls: includes 5 studies with hospital controls; one study was excluded from this subanalysis because it consisted of both hospital and healthy controls combined. Other = African Americans, Africans, Latinos, and other ethnicities not specified.

ation between metabolic polymorphisms and tobacco related cancers may be related to gene-gene interactions, different linkages to the polymorphisms determining oral and pharyngeal cancer risk, and different lifestyles. For example other forms of tobacco in addition to tobacco smoke, such as chewed tobacco with

Table 7
The association of *GSTM1*, *CYP1A1* polymorphisms with oral and pharyngeal cancers according to tumor site—pooled analysis

	Controls	Cases	Crude OR (95% CI)	Adjusted OR (95% CI)
GSTM1[a] Oral cavity ($N = 7306$)				
	5329	1977		
Present	3002	1070	1.0 (ref)	1.0 (ref)
Null	2327	907	1.1 (1.0–1.2)	1.1 (1.0–1.2)
Pharynx ($N = 5807$)				
	5329	478		
Present	3002	232	1.0 (ref)	1.0 (ref)
Null	2327	246	1.4 (1.1–1.7)	1.3 (1.1–1.6)
CYP1A1 MspI[b] *Oral cavity* ($N = 3936$)				
	2581	1355		
m1m1	1415	687	1.0 (ref)	1.0 (ref)
m1m2	980	507	1.1 (0.9–1.2)	1.2 (1.0–1.5)
m2m2	186	161	1.8 (1.4–2.2)	2.0 (1.3–3.1)
m1m2 + m2m2	1166	668	1.2 (1.0–1.4)	1.3 (1.1–1.6)
Pharynx ($N = 2708$)				
	2581	127		
m1m1	1415	109	1.0 (ref)	1.0 (ref)
m1m2	980	18	0.2 (0.1–0.4)	1.1 (0.6–2.1)
m2m2	186	0	—	—
m1m2 + m2m2	1166	18	0.2 (0.1–0.3)	1.0 (0.5–1.9)
CYP1A1 (exon7)[c] Oral cavity ($N = 3102$)				
	2083	1019		
Ile/Ile	1608	795	1.0 (ref)	1.0 (ref)
Ile/Val	439	201	0.9 (0.8–1.1)	0.9 (0.7–1.1)
Val/Val	36	23	1.3 (0.8–2.2)	1.1 (0.6–1.9)
Ile/Val + Val/Val	475	224	1.0 (0.8–1.1)	0.9 (0.8–1.1)
Pharynx ($N = 2351$)				
	2083	268		
Ile/Ile	1608	208	1.0 (ref)	1.0 (ref)
Ile/Val	439	51	0.9 (0.7–1.2)	1.0 (0.7–1.4)
Val/Val	36	9	1.9 (0.9–4.1)	1.8 (0.8–4.0)
Ile/Val + Val/Val	475	60	1.0 (0.7–1.3)	1.1 (0.8–1.5)

[a]Adjusted for study number, age (<54, 54–95), sex, and smoking (never/ever) where appropriate.
[b]Adjusted for study number, age (<54, 54–95), race, smoking (never/ever), and alcohol use (never/ever) where appropriate.
[c]Adjusted for study number, age (<54, 54–95), sex, race where appropriate.

areca nut or wrapped in betel quid or pan[101] are used in certain geographic areas. We were unable to evaluate the other ethnic groups because of heterogeneity among the studies included in this very mixed stratum.

Table 8
Overall and stratified odds ratios of the association of *GSTM1/CYP1A1 MspI* polymorphism with oral and pharyngeal cancers—pooled analysis

GSTM1/CYP1A1 MspI	Controls (*N*)	Cases (*N*)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
No. studies: 8				
$N = 4004$	2536	1468		
+/m1m1	809	419	1.0 (ref)	1.0 (ref)
+/m1m2	608	292	0.9 (0.8–1.1)	1.4 (1.0–1.8)
+/m2m2	116	96	1.6 (1.2–2.2)	2.4 (1.4–4.2)
+/m1m2 + m2m2	724	388	1.0 (0.9–1.2)	1.5 (1.1–2.0)
−/m1m1	571	368	1.2 (1.0–1.5)	1.3 (1.0–1.7)
−/m1m2	362	228	1.2 (1.0–1.5)	1.3 (1.0–1.7)
−/m2m2	70	65	1.8 (1.3–2.6)	1.9 (1.0–3.9)
−/m1m2 + m2m2	432	293	1.3 (1.1–1.6)	1.3 (1.0–1.8)
Never smokers ($N = 2098$)				
	1304	794		
+/m1m1	407	196	1.0 (ref)	1.0 (ref)
+/m1m2	332	195	1.2 (1.0–1.6)	1.5 (1.0–2.1)
+/m2m2	63	58	1.9 (1.3–2.8)	2.3 (1.2–4.3)
+/m1m2 + m2m2	395	253	1.3 (1.1–1.7)	1.6 (1.1–2.2)
−/m1m1	239	166	1.4 (1.1–1.9)	1.6 (1.1–2.3)
−/m1m2	226	138	1.3 (1.0–1.7)	1.3 (0.9–1.9)
−/m2m2	37	41	2.3 (1.4–3.7)	2.1 (0.9–4.6)
−/m1m2 + m2m2	263	179	1.4 (1.1–1.8)	1.4 (0.9–2.0)
Ever smokers ($N = 1285$)				
	743	542		
+/m1m1	245	182	1.0 (ref)	1.0 (ref)
+/m1m2	163	79	0.7 (0.5–0.9)	1.2 (0.7–2.0)
+/m2m2	27	25	1.3 (0.7–2.2)	2.9 (1.0–8.8)
+/m1m2 + m2m2	190	104	0.7 (0.5–1.0)	1.3 (0.8–2.3)
−/m1m1	196	168	1.2 (0.9–1.5)	1.0 (0.7–1.5)
−/m1m2	93	74	1.1 (0.8–1.5)	1.3 (0.7–2.2)
−/m2m2	19	14	1.0 (0.5–2.0)	1.7 (0.3–8.4)
−/m1m2 + m2m2	112	88	1.1 (0.8–1.5)	1.3 (0.8–2.2)
Oral cavity ($N = 3880$)				
	2536	1344		
+/m1m1	809	369	1.0 (ref)	1.0 (ref)
+/m1m2	608	285	1.0 (0.9–1.2)	1.4 (1.0–1.8)
+/m2m2	116	96	1.8 (1.4–2.4)	2.5 (1.4–4.2)
+/m1m2 + m2m2	724	381	1.2 (1.0–1.4)	1.5 (1.1–2.0)
−/m1m1	571	312	1.2 (1.0–1.4)	1.3 (1.0–1.6)

(*Continued*)

Table 8
(Continued)

GSTM1/CYP1A1 MspI	Controls (*N*)	Cases (*N*)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
−/m1m2	362	217	1.3 (1.1–1.6)	1.3 (0.9–1.8)
−/m2m2	70	65	2.0 (1.4–2.9)	2.0 (1.0–4.0)
−/m1m2 + m2m2	432	282	1.4 (1.2–1.7)	1.3 (1.0–1.8)
Pharynx ($N = 2660$)				
	2536	124		
+/m1m1	809	50	1.0 (ref)	1.0 (ref)
+/m1m2	608	7	0.2 (0.1–0.4)	1.7 (0.6–5.1)
+/m2m2	116	0	—	—
+/m1m2 + m2m2	724	7	0.2 (0.1–0.4)	1.7 (0.6–4.7)
−/m1m1	571	56	1.6 (1.1–2.4)	1.5 (0.9–2.6)
−/m1m2	362	11	0.5 (0.3–1.0)	1.0 (0.4–2.4)
−/m2m2	70	0	—	—
−/m1m2 + m2m2	432	11	0.4 (0.2–0.8)	0.9 (0.4–2.1)

[a]Adjusted for study number, race, smoking status (never/ever), and alcohol use (never/ever) where appropriate.

Previous meta-analysis and pooled analysis have reported an association between the *GSTM1* null genotype and head and neck tumors,[40–42] but did not analyze ethnic specific or subsite specific differences. We were able to evaluate ethnic specific and subsite specific differences in the pooled analysis. We confirmed that there was no association of the *GSTM1* null genotype with oral and pharyngeal cancers in whites. In contrast to the meta-analysis, there was also no association observed for Asians (OR: 1.2, 95% CI: 0.8–1.8). This difference in result may be attributed to differences in the number of subjects in the meta-analysis and pooled analysis (2313 Asian subjects in the meta-analysis versus 681 in the pooled analysis). Although not statistically significant, African American and African populations seemed to be almost two times more likely to have the *GSTM1* null genotype. (Adj OR: 1.7, 95% CI: 0.9–3.3). This lack of statistical significance might also be attributed to the small number of African American and African subjects included in this pooled analysis.

Although the head and neck tumors have been historically grouped together because of the similar risk factors involved in their etiology, several authors suggest that the role of genetic susceptibility might be different in the head and neck subsites.[44,83,92,94] The oral cavity, pharynx, and larynx are unique structures with different functions and possibly different sensitivities to carcinogens, especially alcohol and tobacco. Studies suggest that HPV may be the etiologic agent involved in most pharyngeal tumors (particularly those in the oropharynx).[102,103] The presence of HPV along with the polymorphisms of the genes in question would certainly be relevant to our analysis. However, these data were not available in the studies included in this meta-analysis and pooled analysis. In the pooled analysis, a difference in risk for oral and pharyngeal tumors was seen for the *CYP1A1* MspI variant, with oral cavity tumors statistically significantly associated with the *m1m2* and *m2m2* variant genotypes. We also observed that the combination of *GSTM1* deletion and *CYP1A1* MspI variant was significantly associated with oral cavity cancer but not with pharyngeal cancer.

There is great discrepancy in the literature as to the association of *CYP1A1* genotypes with various smoking related cancers.[12,20,41,43,104] The pooled analysis results confirm the association found in the meta-analysis for the variant allele of the *CYP1A1* MspI polymorphism (*m2/m2*) and oral and pharyngeal cancers. Regarding the *CYP1A1* exon 7 polymorphism, the pooled analysis revealed that the association of the *Val/Val* genotype with oral and pharyngeal cancers was limited only to ever smokers. One caveat is the possibility that individuals could have been misclassified because most of the earlier studies used a laboratory method that may not accurately distinguish between the exon 7 variant alleles having a C2455 base change and another recently described allele having a C2453 base change.[20]

The pooled analysis showed a role of tobacco consumption on the association between *GSTM1* deletion and oral and pharyngeal cancer, that could be explained by the involvement of this enzyme in the metabolism of PAHs. However, there is no consistent evidence supporting this association. Some studies have found a higher level of DNA adducts and chromosome damage in lymphocytes of coke oven workers, bus drivers and tobacco smokers who lack the *GSTM1* gene,[24,105–108] whereas others failed to find a significant relationship.[109,110] The same can be said for *CYP1A1* polymorphisms.[24,109,111,112] When we stratified the pooled analysis by smoking status we also observed that combined effects of *GSTM1* null and *CYP1A1* MspI were only present among nonsmokers. This might seem controversial because it has been demonstrated that smokers with high activating *CYP1A1*/low deactivating *GSTM1* genotypes tend to have higher benzo[a] pyrene diolepoxide-DNA adducts.[24,113,114] It has been suggested that the role of *CYP1A1* and *GSTM1* on lung cancer risk might be more important at low levels of exposure, but these findings need further investigation.[43] Other risk factors such as alcohol must be into account. Alcohol might act as a solvent for other carcinogens, or perhaps generate and exacerbate coincident inflammation and modify the effect of susceptibility for tobacco.[8,115] It might also be recommendable to assess the combined effects among other polymorphisms of the GST and CYP genes (*GSTM3*, *GSTT1*, *GSTP1*, *CYP1A2*), and of other genes involved in the detoxification of tobacco and alcohol such as *N*-acetyltransferases (*NAT1*, *NAT2*), microsomal epoxide hydrolase, UDP-glucuronosyltransferases, and alcohol dehydrogenase.[20,41,100,116–120]

The presence of heterogeneity and/or publication bias may compromise the interpretation of the meta-analyses and result in an erroneous and potentially misleading conclusion. We performed sensitivity and stratified analyses to identify the sources of heterogeneity. Potential sources of heterogeneity include ethnic group, sample size, tumor location, case-con-

trol recruitment and tobacco and alcohol consumption, most of which were easily evaluated in the pooled analysis. A general limitation to the results obtained with both the meta-analysis and the pooled analysis is the potential selection bias that may have been introduced by a poorly defined study base. Some of the publications do not provide sufficient details on the characteristics of the cases and controls, the way controls have been recruited or even the period where this occurred.[66,77,79,85,88,92,94] In some hospital-based studies information on the causes for hospital admission were not provided. Nevertheless, we were able to evaluate the influence of control group source in this analysis.

There were 18 published studies that were excluded from the meta-analysis because they included laryngeal cases and did not provide site-specific data.[53–69] This unavoidable exclusion was a major loss of the literature. Efforts were made to obtain these datasets for inclusion in the pooled analysis; we were successful in obtaining 6 of the 18 datasets.[57,59,65,66,69,87] However, the potential for publication bias in the pooled analysis cannot be dismissed because the datasets did not entirely represent all of the published studies. Nonetheless, we did not observe any evidence of publication bias for the overall associations of *GSTM1* or *CYP1A1* with oral and pharyngeal cancers.

An important shortcoming to the investigation of the gene-environment effects is the possibility of misclassification of exposure. The categorization of individuals as never/ex/current/ever smokers could be inaccurate and not sufficiently standardized across studies.[77,79,81,88,92,94] Misclassification of exposure could lead to biased results so this must be taken into account when interpreting the findings. It would be preferable to further characterize tobacco consumption as lifetime exposure (pack-years), but in the present meta-analysis and pooled analysis this was not possible because of the heterogeneous categorization of the smoking habits. In the majority of studies there was no information of alcohol intake, thus making it impossible to stratify for this factor.

Laboratory methods

The methods for determining the gene polymorphisms discussed in this review are described in each article. The majority of the studies used genomic DNA extracted from lymphocytes with PCR as the method for genotyping.

CONCLUSIONS

Overall, the association of *GSTM1* deletion and oral and pharyngeal cancers may be dependent upon ethnicity. A possible association observed for Asians and African American/African groups and not for whites cannot be ruled out. The *CYP1A1* exon 7 polymorphism was associated with oral and pharyngeal cancer only for ever smokers, when studied independently in the pooled analysis, although the *CYP1A1* MspI variant homozygote allele (*m2/m2*) was significantly associated with this cancer in both the meta-analysis and pooled analysis. When analyzing the complete genotype of *GSTM1* deletion and *CYP1A1* MspI polymorphism, the risk of oral and pharyngeal cancers seems to be higher for never smokers than for ever smokers. It should be highlighted that the results of the pooled analysis varied according to the type of controls considered, indicating that a selection bias might be present in some studies and therefore the results should be considered with caution. There is no indication at this point for population testing of these genes as risk factors for oral and pharyngeal cancer.

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