BASIC SCIENCE REVIEW

Robert L. Ferris, MD, PhD, *Section Editor*

EPIDEMIOLOGY OF CARCINOGEN METABOLISM GENES AND RISK OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Tang Ho, MD, MSc,[1,2] Qingyi Wei, MD, PhD,[3] Erich M. Sturgis, MD, MPH[1,3]

[1] Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas. E-mail: esturgis@mdanderson.org
[2] Bobby R. Alford Department of Otolaryngology—Head and Neck Surgery, Baylor College of Medicine, Houston, Texas
[3] Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Accepted 6 October 2006
Published online 1 February 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20570

Abstract: The risk association between tobacco and alcohol use with squamous cell carcinoma of the head and neck (SCCHN) is well recognized. However, clearly not all individuals who smoke or drink develop SCCHN. Individual genetic susceptibility differences in carcinogen-metabolizing enzyme function, mutagen sensitivity, apoptosis, and chromosomal aberrations either alone or in combination have been theorized to modify the risk of SCCHN. Nearly all carcinogens and procarcinogens require activation by metabolizing enzymes. Similarly, detoxifying enzymes exist and deactivate carcinogens as well as their intermediate by-products. Together these enzymes are termed xenobiotic-metabolizing enzymes; genetic polymorphisms of these enzymes can modify an individual's response to carcinogens and hence the carcinogenic potential of such exposures. In this review, we explore the available evidence in recent literature regarding the risk association between SCCHN and various xenobiotic-metabolizing enzymes, including cytochrome P450s, glutathione *S*-transferases, *N*-acetyltransferases, NAD(P)H:quinone oxidoreductase 1, alcohol dehydrogenase, and aldehyde dehydrogenase. ©2007 Wiley Periodicals, Inc. *Head Neck* **29:** 682–699, 2007

Keywords: humans; squamous cell carcinoma; head and neck; genetic polymorphisms; risk factors

Correspondence to: E. M. Sturgis

Squamous cell carcinoma of the head and neck (SCCHN) accounts for approximately 3% of all newly diagnosed cancer cases in the United States, with an absolute incidence of 41,000 estimated in 2006.[1] Globally, SCCHN (including the oral cavity, oro/hypo/nasopharynx, and larynx) represents one of the most common malignancies encountered, with more than 644,000 new cases reported in 2002 worldwide with a high case fatality (ratio of mortality to incidence) of 0.53 and a male predominance (sex ratio of 3:1).[2] Although the cause of SCCHN is multifactorial, its risk association with a history of tobacco and alcohol use is well recognized, and in populations in which both habits are common there is an increased incidence of the disease. However, clearly not all smokers develop cancer. In fact, it has been estimated that only between 10% and 15% of smokers will develop lung cancer in their lifetimes, and even fewer will develop SCCHN.[3] Furthermore, the converse also holds true in that not all patients with SCCHN are current or former

Table 1. Main carcinogen metabolizing enzymes in SCCHN.

Enzyme	Abbreviation	Function
Cytochrome P450	CYP	Phase I enzymes
CYP1A1		
CYP1B1		
CYP2D6		
CYP2E1		
Glutathione-S-transferase	GST	Phase II enzymes
GSTM1		
GSTP1		
GSTT1		
N-Acetyl transferase	NAT	Phase II enzyme
NADPH:quinone reductase	NQO	Phase II enzyme
Alcohol dehydrogenase	ADH	Phase I enzyme
Aldehyde dehydrogenase	ALDH	Phase II enzyme

Abbreviation: SCCHN, squamous cell carcinoma of the head and neck.

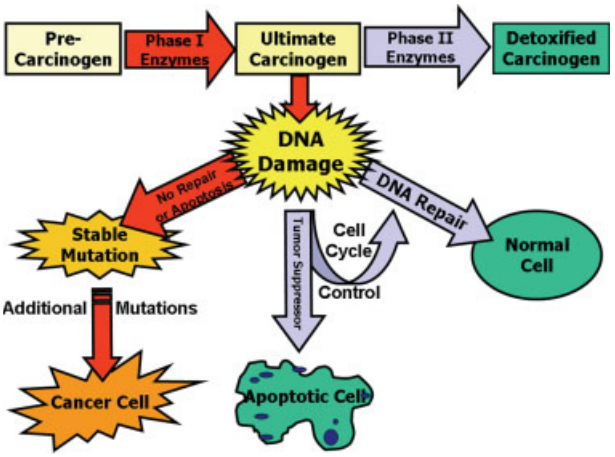


FIGURE 1. Phase I and phase II enzymes in carcinogenesis (Reproduced from Ref. 10, with permission from Lippincott Williams and Wilkins). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

smokers. Therefore, individual variations in genetic susceptibility would appear to contribute to the development of SCCHN.

A genetic component to SCCHN has been implicated in several large case-control studies in which a 2-fold to 14-fold increase in SCCHN risk was detected in patients with a first-degree family history of cancer, and a dose–response relationship was evident and persisted after multivariate adjustment, including for smoking.[4–7] The term *molecular epidemiology* has been used to describe the "incorporation of molecular, cellular, and physiologic biomarkers as dependent and independent variables in epidemiologic explorations of relationships between markers with either health outcomes or other markers within populations."[8] Biomarkers can be broadly categorized into 3 types: exposure, effect, and susceptibility biomarkers. Regardless of the type, the ultimate goal of using a biomarker is to provide a more accurate risk assessment. In cancer susceptibility biomarker research, individual differences in carcinogen-metabolizing enzyme function, mutagen sensitivity, apoptosis, and chromosomal aberrations, either alone or in combination, have been demonstrated to modify cancer risk, including that for SCCHN.[9–11]

Processed tobacco contains more than 3000 chemical compounds, including at least 30 known carcinogens, and cigarette smoke contains approximately 50 known carcinogens and procarcinogens. Although not a focus of this review, the process of cigarette combustion also produces a high concentration of reactive oxygenated species.[12] The most prominent procarcinogens in tobacco smoke that require metabolic activation prior to exerting their effect are polycyclic aromatic hydrocarbons (eg, benzo(a)pyrene), tobacco-specific nitrosamines (eg, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone), and aromatic amines (eg, 4-aminobiphenyl).[13] However, prior to interacting with cellular macromolecules such as DNA, chemical carcinogens require activation by phase I oxidative enzymes such as cytochrome P450. Phase II xenobiotic-metabolizing enzymes such as glutathione-*S*-transferases (GSTs), on the other hand, are involved in carcinogen detoxification.

Nearly all carcinogens and procarcinogens require activation by metabolizing enzymes. Similarly, detoxifying enzymes exist to deactivate carcinogens as well as their intermediate byproducts. Together these enzymes are termed xenobiotic-metabolizing enzymes and are found in the liver as well as in upper aerodigestive tract mucosa. Genetic polymorphisms of these enzymes can modify an individual's response to carcinogens and hence the carcinogenic potential of such exposures. The main carcinogen-metabolizing enzymes are listed in Table 1, and their roles in carcinogenesis are illustrated in Figure 1. New evidence has emerged since the publication of reviews and meta-analyses on this subject.[14–16] The focus of this article is to examine and update the role of carcinogen-metabolizing gene polymorphisms on the risk of SCCHN.

Cytochrome P450. Cytochrome P450 (CYP) enzymes are the predominant phase I xenobiotic-metabolizing enzymes. The metabolism of nearly

all chemicals that humans are exposed to involves either a single member or multiple members of the CYP superfamily. The current nomenclature system divides the cluster of *CYP* genes into families and subfamilies based on comparisons of the divergent evolution of amino acid sequences and their protein products. It has been estimated that 20 subfamilies and nearly 60 separate P450 genes may be found in humans.[17,18] The *CYP* genes in families *CYP1*, *CYP2*, and *CYP3* account for the enzymes mostly responsible for the oxidative metabolism of procarcinogens and drugs. These enzymes have been found in various extrahepatic sites, including upper aerodigestive tract tissue.[19]

CYP1A1. The murine *CYP1A1* gene was the first *CYP* gene to be cloned and sequenced.[20] The gene encodes the enzyme benzo(a)pyrene hydroxylase (or arylhydrocarbon hydroxylase), which is involved in the activation of polycyclic aromatic hydrocarbons and aromatic amines to highly electrophilic metabolites such as benzo(a)pyrene diol epoxide and other carcinogenic phenol products.[21] It is present in many epithelial tissues, including oral tissue in the upper aerodigestive tract.[22]

A thymine to cytosine (T → C) nucleotide polymorphism at the 264th base downstream from an additional polyadenylation signal in the 3′-flanking region of the *CYP1A1* gene affecting the size of *Msp*I fragments is present in 5% to 30% of the population and has been associated with an increased risk of lung carcinoma.[23,24] In 2 separate Japanese case-control studies, the *Msp*I polymorphism was found to be associated with an increased risk of oral cavity carcinoma (Table 2), with the rare homozygous mutant genotype significantly more prevalent in the case group (OR [odds ratio] = 3.6, 95% CI [confidence interval] = 1.4–9.5 [Ref. 25]; OR = 2.3, 95% CI = 1.1–4.7 [Ref. 26]). The risk association was also found to be inversely proportional to the amount of tobacco use. Furthermore, in both studies the frequency of the combined genotypes of *CYP1A1* m/m and *GSTM1* null was significantly higher in the patients with cancer than in the control population (60.0% vs 37.5% [Ref. 25]; 14.1% vs 2.1% [Ref. 26]). However, the sample sizes of these studies were limited (n = 100 [Ref. 25] and 142 [Ref. 26] cases and controls). In European populations, the *CYP1A1 Msp*I polymorphism has also been investigated in four case-control studies of SCCHN (1 with laryngeal cancer cases only), with no statistically significant difference in genotype distribution between cases and controls.[27–30] In 1 of these European studies, the *CYP1A1* genotype was combined with the *GSTM1* null genotype, and no significant risk elevation was seen.[27]

An adenine to guanine (A → G) single nucleotide polymorphism (SNP) at exon 7 of the *CYP1A1* gene, which results in a substitution from isoleucine to valine (Ile462Val), has also been linked with increased SCCHN risk and has been studied extensively. A meta-analysis of 12 case-control studies (published prior to 2003) on the association between the *CYP1A1* Ile462Val polymorphic allele and SCCHN risk calculated a summary OR of 1.4 (95% CI = 1.0–1.8), and no difference in the ORs was identified in stratified analysis.[14] The review here will thus focus on the more recent and larger investigations. The Val allele codes for a more inducible form of the enzyme, and the rare homozygous Val:Val genotype of CYP1A1 was more frequent in SCCHN patients than in controls (9.0% and 3.7%, respectively) in a study of 145 Japanese patients and 164 controls. On logistic-regression analysis, the Val:Val genotype was associated with a 4-fold increased risk of SCCHN (OR = 4.1, 95% CI = 1.1–15.0) when compared with Ile:Ile and Ile:Val genotypes, and this was particularly true for carcinoma of the pharynx (OR = 5.7, 95% CI = 1.1–28.0) but not the larynx (p = .2).[31] Others, including Gajecka et al,[30] also did not find a statistically significant difference in the Val allele distribution between laryngeal cancer cases and controls in a study of Polish men.

Sato et al[34] also demonstrated an increased risk for the homozygous Val:Val genotype in a series of 142 Japanese patients with oral cavity squamous cell carcinoma. In this study, the risk elevation observed for the combined genotypes of Val:Val and GSTM1 null was significantly higher than that observed for either genotype alone (OR = 10.2, 95% CI = 2.7–38.5). The observed risk with the susceptible Val:Val genotype was highest in the group with the lowest cigarette dose level. In a North American study restricted to whites, Park et al[32] also found the variant Val allele to be associated with oral cavity cancer risk (OR = 2.6, 95% CI = 1.2–5.7). However, in 5 other case-control studies of the Ile:Val polymorphisms in whites there were no statistically significant differences in distribution between SCCHN cases and controls,[27–29,35,36] and one additional North American study found a nonsignificant protective effect (OR = 0.5, 95% CI = 0.2–1.5) after adjustment for other risk factors.[33] Overall, there appears to be a mild risk association between CYP1A1 exon 7 polymorphism and SCCHN (Figure 2).

Table 2. CYP genotypes, frequency distributions, and odds ratios.

Gene	Mutation	Site	Ethnicity	*N* (Cases/Ctrl)	Frequency, % (Cases/Ctrl)	Adjusted OR* (95% CI)	Reference
CYP1A1	*Msp*I, m/m	Oral	Japanese	100/100	15.0/8.0	3.6 (1.4–9.5)†	Tanimoto et al[25]
CYP1A1	*Msp*I, m/m	Oral	Japanese	142/142	21.8/10.6	2.3 (1.1–4.7)	Sato et al[26]
CYP1A1	*Msp*I, m/m	SCCHN	Dutch white	185/207	17.8/15.9	NS	Oude Ophuis et al[27]
CYP1A1	*Msp*I, wt/m + m/m	SCCHN	German white	187/139	24.1/19.3	NS	Gronau et al[28]
CYP1A1	*Msp*I, wt/m + m/m	SCCHN	German white	312/300	20.5/18.6	0.9 (0.6–1.5)	Ko et al[29]
CYP1A1	*Msp*I, mutant allele	Larynx	Polish males	289/316	5.5/3.8	1.6 (0.9–2.7)	Gajecka et al[30]
CYP1A1	Exon 7, Val:Val	SCCHN	Japanese	145/164	9.0/3.7	4.1 (1.1–15)	Morita et al[31]
CYP1A1	Exon 7, Val:Val	SCCHN	Dutch white	185/207	18.4/16.4	NS	Oude Ophuis et al[27]
CYP1A1	Exon 7, Ile:Val + Val:Val	Oral	American white	131/131	17.6/7.6	2.6 (1.2–5.7)	Park et al[32]
CYP1A1	Exon 7, Ile:Val + Val:Val	SCCHN	American white	139/121	6.5/14.0	0.5 (0.2–1.5)	McWilliams et al[33]
CYP1A1	Exon 7, Val:Val	Oral	Japanese	142/142	13.4/4.2	4.2 (1.6–11.1)	Sato et al[32]
CYP1A1	Exon 7, Ile:Val + Val:Val	SCCHN	German white	187/139	17.1/13.6	NS	Gronau et al[28]
CYP1A1	Exon 7, Ile:Val + Val:Val	SCCHN	German white	312/300	9.6/8.3	1.0 (0.5–1.9)	Ko et al[29]
CYP1A1	Exon 7, Ile:Val	SCCHN	American white	108/165	10/7	1.6 (0.6–3.8)	Olshan et al[35]
CYP1A1	Exon 7, Val:Val	SCCHN	American white	281/208	1/1	1.4 (0.3–6.9)	Evans et al[36]
CYP1A1	Exon 7, Val allele	Larynx	Polish males	289/316	4.5/5.7	0.9 (0.5–1.4)	Gajecka et al[30]
CYP1B1	V432L, *wt/m + m/m*	SCCHN	German white	312/300	74.3/63.7	1.4 (0.9–2.1)	Ko et al[29]
CYP1B1	V432L, *m/m*	SCCHN	American white	724/1226	19.9/20.9	0.9 (0.7–1.2)	Li et al[37]
CYP1B1	V432L, *wt/m + m/m*	SCCHN	American white	724/1226	67.1/70.2	0.9 (0.7–1.1)	Li et al[37]
CYP2D6	PM (*Dra*III)†	SCCHN	German white	187/139	6.9/5.1	NS	Gronau et al[28]
CYP2D6	PM (*Bst*NI)†	SCCHN	Spanish white	75/200	4/3	NS	Gonzalez et al[38]
CYP2D6	PM (G1934A)	Larynx	Polish males	289/316	24.6/19.6	1.3 (1.0–1.7)	Gajecka et al[30]
CYP2E1	*Rsa*I/*Pst*I (c2/c2)	SCCHN	Japanese	145/164	5.5/4.3	NS	Morita et al[31]
CYP2E1	*Rsa*I/*Pst*I (c1/c2 + c2/c2)	SCCHN	Spanish white	75/200	9/10	NS	Gonzalez et al[38]
CYP2E1	G1532C (CC)	SCCHN	American white	724/1226	0.4/0.23	2.0 (0.4–9.9)	Li et al[37]
CYP2E1	G1532C (CG + CC)	SCCHN	American white	724/1226	5.5/7.2	0.8 (0.5–1.1)	Li et al[37]
CYP2E1	*Rsa*I/*Pst*I (c1/c2 + c2/c2)	Oral/pharyngeal	French white	121/172	10.0/4.7	2.6 (1.0–6.6)	Bouchardy et al[39]
CYP2E1	*Rsa*I/*Pst*I (c1/c2 + c2/c2)	Larynx	French white	129/172	7.0/4.7	1.4 (0.5–4.0)	Bouchardy et al[39]
CYP2E1	*Rsa*I/*Pst*I (c1/c2+ c1/c3 + c2/c3 + c4/c4)	SCCHN	American white	113/226	7.1/7.1	0.5 (0.1–1.7)	Liu et al[40]
CYP2E1	*Rsa*I/*Pst*I (c1/c2+ c1/c3 + c2/c3 + c4/c4)	SCCHN	African American	61/173	9.8/10.4	0.9 (0.2–3.1)	Liu et al[40]
CYP2E1	c2 allele	Larynx	Polish males	289/316	1.6/2.8	0.6 (0.2––1.2)	Gajecka et al[30]

Abbreviations: CYP, cytochrome P450; SCCHN, squamous cell carcinoma of the head and neck; NS, not statistically significant; OR not calculated; PM, poor metabolizers.
**Adjusted for age, sex, tobacco, and alcohol consumption; ethnicity adjusted if applicable.*
†Denotes the restriction enzyme site used to identify digested genomic DNA product.

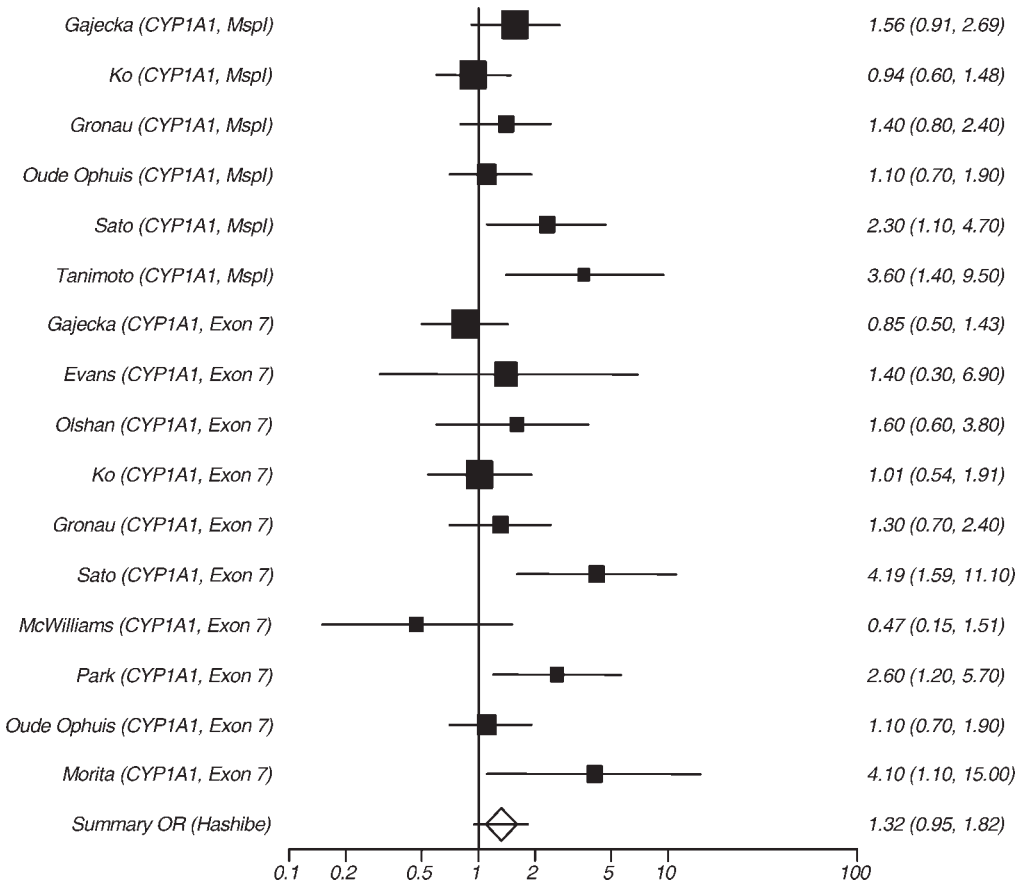


FIGURE 2. Forest plot of CYP1A1 polymorphism odds ratios.

CYP1B1. CYP1B1 is another phase I enzyme that catalyzes the 2- and 4-hydroxylation of 17β-estradiol, a key reaction in hormonal carcinogenesis. Many studies have focused on its role in breast cancer risk, albeit with mixed results.[41–43] However, CYP1B1 also activates numerous environmental procarcinogens, including polycyclic aromatic hydrocarbons, as well as heterocyclic and aromatic amines.[44] The enzyme is found in a variety of human tissues, including the kidney, prostate, breast, and upper aerodigestive tract.[22,45] Among potential functional polymorphisms, a G → A substitution in exon 3 results in an amino acid change from valine to leucine (Val432Leu) and has been reported to affect the enzyme's catalytic activity toward procarcinogens and steroid hormones, including estrogen.[44,46,47] The Val432-Leu genotype was associated with a borderline elevated risk of SCCHN in a case-control study from Germany (OR = 1.4, 95% CI = 0.9–2.1) (Table 2). The polymorphic genotype was a significant risk factor in the subgroup analysis restricted to smokers (OR = 2.7, 95% CI = 1.5–4.9), and a synergistic effect was observed when combined with the polymorphic variants of GSTM1 and GSTT1.[29] However, a larger case-control study by Li et al[37] in American whites did not find any risk association overall or in subgroup analysis.

CYP2D6. CYP2D6 (debrisoquine hydroxylase) is an important enzyme in drug metabolism and has been estimated to be responsible for the metabolism of nearly 25% of prescribed drugs. It has been found to be expressed in human liver, lung, intestine, kidney, and brain.[48] A high individual variability in CYP2D6 enzyme activity has been observed in vivo and has been attributed to the presence of at least 29 allelic variants.[49] In regard to carcinogen activation, the enzyme has been shown to metabolically activate 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone.[50] Individuals deficient in the enzyme, termed poor metabolizers, have been reported to have a lower risk of developing lung carcinoma.[51] Greater than 90% of cases of poor metabolizers can be attributed to 3 defective allelic *CYP2D6* variants: (1) guanine to adenine (G → A) transition at the junction of

intron 3/exon 4 (G1934A), (2) a base pair deletion in exon 5, and (3) a total gene deletion.

In 2 separate investigations of European whites with SCCHN, no significant difference in the distribution of CYP2D6 poor metabolizer genotypes was found between cases and controls (Table 2).[28,38] Also, in a case-control study of CYP2D6 enzyme activity in 140 patients with laryngeal cancer, no significant correlation was seen between enzyme activity level and cancer risk, although an elevated risk for laryngeal cancer was seen among patients with high levels of CYP2D6 enzyme activity and also tobacco consumption.[52] In a recent investigation, Gajecka et al[30] found a statistically significant risk association between the G1934A polymorphic allele and laryngeal cancer. Given the limited evidence available, the contribution of *CYP2D6* polymorphisms on risk of SCCHN remains to be clarified.

CYP2E1. CYP2E1 metabolically activates a number of low-molecular-weight toxins and carcinogens, including nitrosamines, ethanol, benzene, carbon tetrachloride, vinyl chloride, and acrylonitriles. Several substrates, including ethanol, can also act as inducers of the enzyme. The CYP2E1 enzyme is present within the liver at high levels and at lower concentrations in several extrahepatic sites, including the lung and upper aerodigestive tract.[39,53]

A number of polymorphisms have been identified within the *CYP2E1* gene, including 2 polymorphisms detectable by *Rsa*I or *Pst*I restriction fragment length polymorphisms in the 5′ flanking region of the gene. The common wild-type allele is referred to as c1 ($RsaI^+/PstI^-$) and the variant allele as c2 ($RsaI^-/PstI^+$).[54] In a study of French whites, a significant risk elevation was seen for the c2 allele in patients with oral/pharyngeal cancer (OR = 2.6, 95% CI = 1.0–6.6) but not for patients with laryngeal cancer (Table 2). However, the number of subjects with the c2 allele was small.[39] Interestingly, in a recent case-control study of laryngeal carcinoma the c2 allele seemed to have a protective effect, although the number of subjects with the c2 allele was also small.[30]

These *CYP2E1* polymorphisms were also investigated in a Japanese case-control study of SCCHN, and no significant difference was detected between cases and controls in the distribution of c1/c2 and c2/c2 polymorphisms of *CYP2E1*.[31] These findings have been confirmed in 2 other studies of whites with SCCHN.[37,38] In a study of these polymorphisms in oral carcinoma, no risk correlation was found for either whites or African Americans, although a significant increase in the *CYP2E1* c1/c1 genotype was observed in persons with lower tobacco consumption.[40] Given the rarity of the *CYP2E1* polymorphic genotype, as evidenced by the published studies reviewed, a large sample size would be necessary to have the sufficient power to detect any risk association. Hence, no conclusive evidence regarding the association is available.

Glutathione S-Transferase. The glutathione *S*-transferases (GSTs) consist of a multigene family of phase II detoxification enzymes that catalyze the conjugation of electrophilic function groups of toxic and mutagenic compounds with the tripeptide glutathione. The resulting conjugate is more water soluble and in general less toxic, thus protecting against potential DNA damage. The human cytosolic GST system consists of 7 gene classes of isoenzymes, designated GST-α, -μ, -π, -σ, -ω, -θ, and -ζ. Each gene class can include several genes.[55] Many of these enzymes are expressed in the liver consistent with their role in detoxification. Some of the GST enzymes have also been found to be expressed in lung tissue.[56,57] However, GST expression in human tissue has not been extensively investigated.[58] *GSTM1*, *GSTP1*, and *GSTT1* have been the most commonly investigated genes of the GST superfamily. Recent meta-analyses as well as human genome epidemiology (HuGE) reviews are available on the risk association between GSTs and SCCHN. Therefore, recent and larger studies are preferentially reviewed here, and readers are encouraged to refer to these reviews for a comprehensive survey of the literature.[14,15]

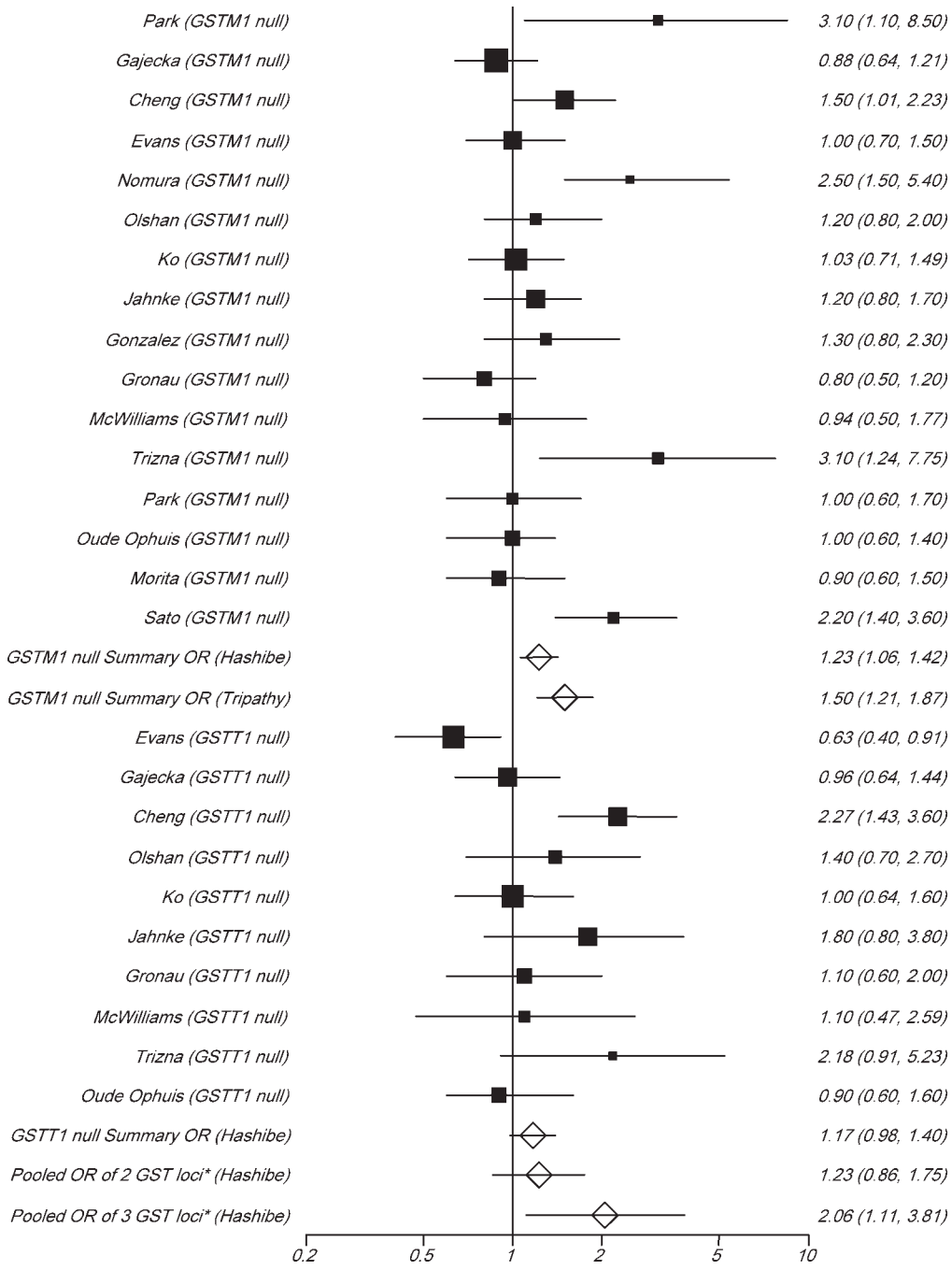
GSTM1. The *GSTM1* isoenzyme gene locus contains 3 alleles: *GSTM1A* and *GSTM1B*, which differ by a single amino acid, and a *GSTM1* null allele. A meta-analysis of more than 10,000 subjects identified the *GSTM1* null genotype in 53% of whites (range, 42% to 62%). The frequency was similar in Asians but lower in African Americans (27%; range, 16% to 36%).[59] In lung cancer, a meta-analysis has shown that the *GSTM1* null genotype was associated with a modest yet significant elevated risk (OR = 1.4, 95% CI = 1.2–1.6).[60]

In 2 Japanese studies of oral squamous carcinoma, the frequency of the *GSTM1* null genotype was significantly higher in cases than in controls (Table 3, Figure 3).[26,63] When subjects were fur-

Table 3. GST genotypes, frequency distributions, and odds ratios.

Gene	Mutation	Site	Ethnicity	*N* (Cases/Ctrl)	Frequency, % (Cases/Ctrl)	Adjusted OR (95% CI)	Reference
GSTM1	GSTM1 null	Oral	Japanese	142/142	64.8/45.1	2.2 (1.4–3.6)	Sato et al[26]
GSTM1	GSTM1 null	SCCHN	Japanese	145/164	49.0/50.6	NS	Morita et al[31]
GSTM1	GSTM1 null	SCCHN	Dutch white	185/207	50.8/51.7	NS	Oude Ophuis et al[27]
GSTM1	GSTM1 null	Oral	American white	133/133	51.1/51.1	1.0 (0.6–1.7)	Park et al[32]
GSTM1	GSTM1 null	SCCHN	American white	186/42	68/48	3.1 (1.2–7.8)*	Trizna et al[61]
GSTM1	GSTM1 null	SCCHN	American white	147/129	46.3/46.5	0.9 (0.5–1.8)	McWilliams et al et al[33]
GSTM1	GSTM1 null	SCCHN	German white	187/139	42.8/48.9	NS	Gronau et al[28]
GSTM1	GSTM1 null	SCCHN	Spanish white	75/200	58/54	NS	Gonzalez et al[38]
GSTM1	GSTM1 null	Larynx	German white	269/216	56.2/52.0	NS	Jahnke et al[62]
GSTM1	GSTM1 null	SCCHN	German white	312/300	53.2/48.3	1.0 (0.7–1.5)	Ko et al[29]
GSTM1	GSTM1 null	SCCHN	American white	109/168	50/45	1.2 (0.8–2.0)	Olshan et al[35]
GSTM1	GSTM1 null	Oral	Japanese	114/33	67.5/45.5	2.5 (1.5–5.4)	Nomura et al[63]
GSTM1	GSTM1 null	SCCHN	American white	282/208	48/49	1.0 (0.7–1.5)	Evans et al[36]
GSTM1	GSTM1 null	SCCHN	American	162/315	53.1/42.9	1.5 (1.0–2.2)	Cheng et al[64]
GSTM1	GSTM1 null	Larynx	Polish male	289/316	48.0/51.1	0.9 (0.6–1.2)	Gajecka et al[30]
GSTM1	GSTM1 null	Oral	African American	63/132	32/16	3.1 (1.1–8.5)	Park et al[65]
GSTP1	I105V, wt/m + m/m	SCCHN	Japanese	145/164	24.9/31.1	NS	Morita et al[31]
GSTP1	I105V, wt/m + m/m	SCCHN	American white	146/124	58.9/53.2	0.9 (0.4––1.7)	McWilliams et al[33]
GSTP1	I105V, wt/m + m/m	SCCHN	German white	312/300	53.5/56.7	0.8 (0.5–1.1)	Ko et al[29]
GSTP1	I105V, wt/m	SCCHN	American white	109/168	57/48	1.3 (0.8–2.2)	Olshan et al[35]
GSTP1	I105V, m/m	SCCHN	American white	109/168	6/12	0.6 (0.2–1.5)	Olshan et al[35]
GSTP1	I105V, wt/m	SCCHN	Dutch white	235/285	38.3/42.5	NS	Oude Ophuis et al[66]
GSTP1	I105V, m/m	SCCHN	Dutch white	235/285	12.3/13.6	NS	Oude Ophuis et al[66]
GSTP1	I105V, m/wt	SCCHN	American white	282/206	47/41	NS	Evans et al[36]
GSTP1	I105V, m/m	SCCHN	American white	282/206	10/12	NS	Evans et al[36]
GSTP1	I105V, m/wt	Larynx	French white	129/172	40.3/37.2	NS	Jourenkova-Mironova et al[67]
GSTP1	I105V, m/m	Larynx	French white	129/172	11.6/12.8	NS	Jourenkova-Mironova et al[67]
GSTT1	GSTT1 null	SCCHN	Dutch white	185/207	19.5/20.3	NS	Oude Ophuis et al[27]
GSTT1	GSTT1 null	SCCHN	American white	127/42	45/36	2.2 (0.9–5.2)*	Trizna et al[61]
GSTT1	GSTT1 null	SCCHN	American white	142/109	16.9/18.3	1.1 (0.5–2.6)	McWilliams et al[33]
GSTT1	GSTT1 null	SCCHN	German white	187/139	16.1/15.1	NS	Gronau et al[28]
GSTT1	GSTT1 null	Larynx	German white	269/216	20.9/12.9	1.8 (0.8–3.8)	Jahnke et al[62]
GSTT1	GSTT1 null	SCCHN	German white	312/300	20.5/20.3	1.0 (0.6–1.6)	Ko et al[29]
GSTT1	GSTT1 null	SCCHN	American white	109/168	17/13	1.4 (0.7–2.7)	Olshan et al[35]
GSTT1	GSTT1 null	SCCHN	American white	283/208	19/28	0.6 (0.4–0.9)	Evans et al[36]
GSTT1	GSTT1 null	SCCHN	American	162/315	32.7/17.5	2.3 (1.4–3.6)	Cheng et al[64]
GSTT1	GSTT1 null	Larynx	Polish male	289/316	18.6/19.3	1.0 (0.6–1.4)	Gajecka et al[30]

Abbreviations: GST, Glutathione-S-transferase; SCCHN, squamous cell carcinoma of the head and neck.
**OR calculated based on 42 matched case-control pairs.*



* at-risk GST loci = GSTM1 null, GSTT1 null, GSTP1 I105V SNP

FIGURE 3. Forest plot of GST polymorphism odds ratios.

ther divided into subgroups by levels of tobacco use, a dose–response relationship was observed between the OR of the *GSTM1* null genotype and increasing tobacco dose.[26] This is in contradistinction to a study of American whites with oral carcinomas by Park et al,[32] in which an identical *GSTM1* null genotype distribution was seen between cases and controls (51.1% for cases and controls). In another case-control study by Park et al[65] involving African Americans with oral carcinomas, a statistically significant risk increase was seen in cases with the *GSTM1* null genotype (OR = 3.1, 95% CI = 1.1–8.5); however, the sample size was fairly limited, with only 63 case sub-

jects. In a large case-control study of SCCHN, the *GSTM1* null genotype was found to be associated with a statistically significant risk elevation (OR = 1.5, 95% CI = 1.0–2.2), and an additive effect was seen with the *GSTT1* null genotype.[64] Similar findings were seen in a smaller matched case-control study (OR = 3.1, 95% CI = 1.2–7.8).[61] However, in a study of Dutch whites with SCCHN, no significant difference in *GSTM1* null genotype distribution was seen between cases and controls (50.8%, compared with 51.7%) or in subgroup analyses based on tumor site; nor was an elevated risk found when the *GSTM1* null genotype was combined with *CYP1A1 Msp*I and *GSTT1* null polymorphic genotypes.[27] Additionally, in a Japanese study of SCCHN, no significant difference was seen in the distribution of the *GSTM1* null genotype between cases and controls or in subgroup analyses of the tumor site.[31] A lack of a statistically significant risk association between the *GSTM1* null genotype and SCCHN was also reported in 6 other studies of white subjects.[28,29,33,35,36,38]

Gronau et al[28] reported that the combined null genotypes of *GSTM1* and *GSTT1* were more prevalent in SCCHN cases than in controls (13.5% vs 6.1%), and that the *GSTM1* null genotype was more prevalent in patients with laryngeal cancer upon tumor subsite analysis (73.6%, compared with 26.4%). However, the *GSTM1* null genotype frequency was not significantly different in 2 case-control studies of European whites with laryngeal carcinoma.[30,62] In the meta-analysis by Hashibe et al,[14] 26 case-control studies on risk association between the *GSTM1* null genotype and SCCHN were included with a mildly elevated summary OR of 1.2 (95% CI = 1.1–1.4). Another meta-analysis that included 25 studies of the *GSTM1* null genotype and SCCHN risk reported a similar summary OR of 1.2 (95% CI = 1.1–1.3).[68] The effect was more pronounced in a recent meta-analysis of *GSTM1* null genotype and SCCHN (OR = 1.5, 95% CI = 1.2–1.9).[69] Therefore, the available evidence appears to support a mild yet significant risk association between *GSTM1* null genotype and SCCHN.

GSTT1. The *GSTT1* null polymorphic genotype is present in approximately 15% to 38% of the white population but varies in frequency among different ethnicities.[15,70] The enzyme encoded by *GSTT1* catalyzes the conjugation of glutathione with halomethanes. The absence of the *GSTT1* gene corresponds to the nonconjugator phenotype.[70]

In a large case-control study of SCCHN, the *GSTT1* null genotype was noted to correlate with a statistically significant risk elevation (OR = 2.3, 95% CI = 1.4–3.6), and an additive effect was seen with the *GSTM1* null genotype (Table 3, Figure 3).[64] A similar finding was noted in a smaller case-control study of 42 matched American whites with SCCHN (OR = 2.2, 95% CI = 0.9–5.2).[61] An increased risk (though not significantly so) was also seen in an investigation of German whites with laryngeal carcinoma (20.9% vs 12.9%, OR = 1.8, 95% CI = 0.8–3.8).[62] Also, a larger study of Dutch whites with SCCHN found no significant difference in *GSTT1* null genotype distribution between cases and controls (19.5% vs 20.3%).[27] No statistically significant risk association was reported in 4 other separate studies of SCCHN,[28,29,33,35] although in 1 of these 4 studies, the combined null genotype of *GSTM1* and *GSTT1* was statistically more prevalent in cases than in controls (13.5% vs 6.1%).[28] In a recent large case-control study of SCCHN, a statistically significant risk increase was found to be associated with the presence of the *GSTT1* gene (OR = 1.6, 95% CI = 1.1–2.5). Further stratification by sex in the same study showed an increased risk for women for the presence of *GSTT1* (OR = 2.7, compared with 1.2 in males). However, the sample size was rather limited, and confirmation of this finding with a larger series is needed.[36] A meta-analysis of 21 studies on SCCHN and the *GSTT1* null genotype published prior to 2003 showed a borderline risk of SCCHN associated with the *GSTT1* null genotype (adjusted OR = 1.2, 95% CI = 1.0–1.4), confirming the trend seen in the studies reviewed.[14]

GSTP1. GSTP1 is overexpressed in human carcinomas of various sites, including the esophagus, lung, stomach, colon, bladder, and cervix. Immunohistochemical study has also found that GSTP1 is expressed predominantly in normal human epithelial cells of the urinary, digestive, and respiratory tracts.[71] GSTP1 participates in the detoxification of reactive oxygen species by binding to reduced glutathione and maintaining cellular redox balance. A *GSTP1* single-nucleotide polymorphism at nucleotide 313 (A313G, Ile105Val) as described by Ali-Osman et al[72] results in an enzymatic product with reduced detoxification capacity and affinity for the electrophilic substrates. The *GSTP1* 105Val homozygous genotype has been estimated to be present in approximately 10% of the population.

Table 4. NAT, NQO1 genotypes, frequency distributions, and odds ratios.

Gene	Mutation	Site	Ethnicity	*N* (Cases/Ctrl)	Frequency, % (Cases/Ctrl)	Adjusted OR (95% CI)	Reference
NAT1	NAT1*10 (wt/m)	Oral	Japanese	62/122	58.1/41.0	4.0 (1.7–9.5)	Katoh et al[81]
NAT1	NAT1*10 (m/m)	Oral	Japanese	62/122	27.4/21.3	3.7 (1.6–8.5)	Katoh et al[81]
NAT1	NAT1*10 (wt/m)	SCCHN	American white	109/168	38/33	1.1 (0.7–1.9)	Olshan et al[35]
NAT1	NAT1*10 (m/m)	SCCHN	American white	109/168	4/8	0.6 (0.2–1.9)	Olshan et al[35]
NAT1	NAT1*10 allele	Oral/pharynx	German white	143/300	15.4/15.7	NS	Fronhoffs et al[82]
NAT1	NAT1*10 allele	Larynx	German white	148/300	17.6/15.7	NS	Fronhoffs et al[82]
NAT1	NAT1*10 (wt/m, m/m)	Larynx	Portuguese	88/172	45.5/37.8	1.4 (0.8–2.4)	Varzim et al[83]
NAT2	IA + SA (NAT2*6, NAT2*7)	SCCHN	Japanese	145/164	55.2/42.7	2.0 (1.0–3.8)	Morita et al[31]
NAT2	SA (NAT2*5, NAT2*6)	SCCHN	Spanish white	75/200	37/21	2.6 (1.5–4.7)†	S. Gonzalez et al[38]
NAT2	SA (NAT2*5, *6, *7, *14)	Oral	Japanese	62/122	11.3/5.7	2.3 (0.8–7.2)	Katoh et al[81]
NAT2	IA + SA	Oral	Japanese	62/122	58.1/50.0	2.1 (0.7—6.1)	Katoh et al[81]
NAT2	SA (NAT2*5, *6, *7)	Larynx	Portuguese	88/172	53.4/44.2	1.5 (0.8–2.5)	Varzim et al[83]
NAT2	NAT2*5B allele	Larynx	Polish male	289/316	41.0/43.7	0.8 (0.6–1.0)	Gajecka et al[30]
NAT2	NAT2*6A allele	Larynx	Polish male	289/316	26.1/28.8	0.8 (0.5–1.0)	Gajecka et al[30]
NAT2	NAT2*7B allele	Larynx	Polish male	289/316	1.2/1.5	1.5 (0.5–4.0)	Gajecka et al[30]
NAT2	SA	Oral	American white	320/520	58.4/56.5	0.9 (0.5–1.7)	Chen et al[84]
NAT2	IA	Oral	American white	320/520	34.737.1	0.9 (0.5–1.5)	Chen et al[84]
NQO1	P187S, m/m	SCCHN	American white	724/1226	4.3/2.7	1.6 (0.9–2.6)	Li et al[37]
NQO1	P187S, wt/m + m/m	SCCHN	American white	724/1226	33.2/34.3	0.9 (0.8–1.2)	Li et al[37]
NQO1	P187S, wt/m	SCCHN	American white	350/366	26.9/29.0	0.9 (0.6–1.2)	Begleiter et al[85]
NQO1	R139W, wt/m	SCCHN	American white	350/364	6.3/5.8	1.1 (0.6–2.1)	Begleiter et al[85]

Abbreviations: NAT, N-acetyltransferase; NQO, NAD(P)H:quinone oxidoreductose; SCCHN, squamous cell carcinoma of the head and neck; IA, intermediate acetylators; SA, slow acetylators.
†OR calculated based on data presented.

In a Japanese case-control study of SCCHN, the distribution of *GSTP1* 105Val was not significantly different from the controls both for the SCCHN group as a whole and for the pharyngeal cancer subgroup (Table 3). The frequency of the 105Val:Val homozygous polymorphic genotype was, however, borderline significant in the laryngeal carcinoma subgroup (OR = 2.4, 95% CI = 1.0–5.9).[31] This finding was not confirmed in 6 other case-control studies of SCCHN, chiefly in Western populations.[29,34–36,71] A meta-analysis of the 105Val polymorphism and SCCHN, including 9 case-control studies, did not suggest that a risk of SCCHN is associated with this polymorphism (summary OR = 1.1, 95% CI = 0.9–1.3).[14]

N-Acetyltransferases. *N*-acetyltransferases (NAT) participate in the metabolism of xenobiotics and carcinogens through the transfer of an acetyl group. Compared with CYPs and GSTs, the involvement of NATs in detoxification is more limited to chiefly the detoxification of amines and hydrazines. For instance, NATs have been shown to catalyze both activation (O-acetylation) and deactivation (N-acetylation) of arylamine carcinogens.[73] In the human NAT family, 3 genes have been identified, including a pseudogene and 2 functional genes, *NAT1* and *NAT2*. Compared with NAT1, the human NAT2 isoenzyme is more restricted in its tissue-expression pattern, being found primarily in the intestine and liver.[74] The activity of both functional genes seems to be polymorphic and appears to modulate the risk of various human cancers, including those of the colon, bladder, and larynx.[75–78]

NAT1. *NAT1* was once referred to as the monomorphic *NAT*; however, several *NAT1* polymorphisms have since been identified. In particular, the *NAT1**10 polymorphic allele [thymidine to adenine (T → A) at nucleotide position 1088 and cytosine to adenine (C → A) at nucleotide position 1095 substitutions], an allele that contains a variant polyadenylation signal resulting in a 2-fold higher enzyme activity, has been associated with a risk of colon and bladder cancer.[79,80] One Japanese pilot study of oral squamous carcinoma found a significantly increased risk associated with the *NAT1**10 variant allele (OR = 3.7, 95% CI = 1.4–9.8 for the homozygous genotype) that is independent of smoking (Table 4).[81] An unmatched Portuguese case-control study of laryngeal squamous carcinoma also found a mildly increased risk associated with fast acetylators containing the *NAT1**10 allele (OR = 1.4, 95% CI = 0.8–2.4). A statistically significant higher frequency of the *NAT1**10/*11 genotype was observed among the

cases, compared with controls, but this finding was based on very few subjects.[83]

However, a decreased though statistically nonsignificant risk association was seen for the *NAT1**10 homozygous genotype in a study of American whites with SCCHN (OR = 0.6, 95% CI = 0.2–1.9).[35] In another investigation of German whites with SCCHN, no statistically significant *NAT1**10 allele frequency differences were seen between patients with oral/pharyngeal and laryngeal carcinoma and controls (15.4% and 17.6% vs 15.7%, respectively). The presence of other *NAT1* polymorphic alleles (*NAT1**3, *4, *11, *14, *17) in the same investigation was not associated with an increased risk of SCCHN.[82] Thus, further investigations, including larger studies, are needed to elucidate the risk relationship between *NAT1* polymorphisms and SCCHN.

NAT2. Heterocyclic amines are metabolized by NAT2, and single-nucleotide polymorphisms in the *NAT2* coding sequence result in different forms of the NAT2 protein. More than 30 *NAT2* alleles based from 13 SNPs have been reported. These polymorphisms often result in enzymes with impaired function, known as slow acetylators. The actual proportion of slow acetylation status is largely dependent on ethnicity. It is most prevalent in the North African population (80% to 90%), followed by whites of Central European origin (50% to 65%) and Asians (6% to 13%).[86]

NAT2 slow and intermediate acetylators as identified by the presence of *NAT2**6 and *NAT2**7 polymorphic alleles were present at a higher proportion in Japanese SCCHN patients than in controls, with a borderline level of significance (OR = 2.0, 95% CI = 1.0–3.8) (Table 4). This difference was more pronounced for the subgroup of patients with laryngeal cancer (OR = 2.7, 95% CI = 1.3–5.8).[31] This is consistent with the findings from a phenotypic study on Polish patients with laryngeal carcinoma, which showed a higher prevalence of the slow acetylator phenotype in cases than in controls (83.6% vs 60.3%, $p < .001$).[78] An unmatched case-control study of Portuguese laryngeal squamous cell carcinoma cases also found a mildly elevated risk associated with the slow acetylator genotypes (OR = 1.5, 95% CI = 0.8–2.5). The finding was particularly striking for the *NAT2**5/*7 genotype (OR = 8.5, 95% CI = 1.6–59.4), though this was based on very few subjects.[83] An investigation of slow acetylators, defined as homozygosity of the *NAT2**5 and/or *NAT2**6 alleles, also showed a statistically significant higher proportion of slow acetylators in Spanish whites with SCCHN than in controls (37% vs 21%, OR = 2.6, 95% CI = 1.5–4.7).[38] A pilot study involving 62 Japanese patients with oral squamous carcinoma, however, found no significant risk associated with the slow acetylator genotype, defined as possessing 2 of the 4 low-activity alleles studied (*NAT2**5, *NAT2**6, *NAT2**7, and *NAT2**14).[81] A large case-control analysis involving American whites with oral cavity squamous cell carcinoma also demonstrated no significant risk association based on acetylator genotypes.[84] A recent case-control study on laryngeal carcinoma similarly did not find a significant risk correlation with *NAT2**5B, *6A, and *7B alleles.[30] In summary, the *NAT2* slow acetylator polymorphic genotypes seem to be associated with a mildly increased risk of SCCHN in the majority of those studies reviewed. However, larger series are needed to confirm this finding.

NAD(P)H:Quinone Oxidoreductase 1. Several human NAD(P)H:quinone oxidoreductase (NQO) genes have been identified, although *NQO1* seems to be the most important in carcinogen metabolism.[87,88] The *NQO1* gene, located on chromosome 16q2.2, with 6 exons and 5 introns, is 20 kb in length.[87] NQO1, a phase II enzyme, is a cytosolic 2-electron reductase that catalyzes the reductive activation of such carcinogens as nitrosamines and heterocyclic amines. It also acts to protect cells against oxidative damage from reactive oxygen species by decreasing 1-electron reductions and associated redox cycling.[89] It is found in various human tissues, and levels are elevated in several tumors, including those of the liver, lung, colon, and breast.[90]

Among the reported polymorphisms, a cytosine to thymine (C → T) substitution at nucleotide 609 of exon 6 results in an amino acid change from proline to serine at codon 187.[91] The Pro187Ser polymorphic form of the NQO1 protein has decreased activity, and the allele is present in approximately 50% of the population, with significant ethnic variations.[92,93] Because NQO1 has been shown to inhibit carcinogenesis, individuals with the Pro187Ser NQO1 variant may be at a higher risk for cancer. Investigations have shown an increased frequency of the polymorphic allele in renal, esophageal, colon, and gastric cancers, among others.[94–96]

In 2 separate large case-control studies involving American whites with SCCHN, no significant risk association was found for the Pro187Ser vari-

Table 5. ADH1C, ALDH2 genotypes, frequency distributions, and odds ratios.

Gene	Mutation	Site	Ethnicity	*N* (Cases/Ctrl)	Frequency, % (Cases/Ctrl)	Adjusted OR (95% CI)	Reference
ADH1C†	*1/*1	SCCHN	American white	106/168	36/33	1.2 (0.6–2.5)	Olshan et al[107]
ADH1C†	*1/*2	SCCHN	American white	106/168	49/51	1.0 (0.5–2.1)	Olshan et al[107]
ADH1C‡	*1/*2	Oral/pharynx	American white	229/575	49.8/52.2	1.0 (0.7–1.4)	Sturgis et al[108]
ADH1C‡	*2/*2	Oral/pharynx	American white	229/575	19.7/16.5	1.2 (0.8–1.9)	Sturgis et al[108]
ADH1C†	*1/*1	SCCHN	American§	348/330	31.0/38.1	0.7 (0.4–1.1)	Wang et al[109]
ADH1C†	*1/*2	SCCHN	American§	348/330	47.4/48.5	0.8 (0.5–1.2)	Wang et al[109]
ADH1C†	*1/*1	Oral	American	333/541	34.5/36.4	1.1 (0.7–1.6)	Schwartz et al[110]
ADH1C†	*1/*2	Oral	American	333/541	47.8/43.3	1.3 (0.9–1.9)	Schwartz et al[110]
ADH1C‡	*1/*2	Oral	Greek white	93/99	NA	0.8 (0.4–1.6)	Zavras et al[111]
ADH1C‡	*2/*2	Oral	Greek white	93/99	NA	0.9 (0.3–2.5)	Zavras et al[111]
ADH1C†	*1/*1	Oral/pharynx	French white	119/167	41.2/36.5	1.1 (0.6–2.2)	Bouchardy et al[39]
ADH1C†	*1/*2	Oral/pharynx	French white	119/167	35.3/41.3	0.7 (0.4–1.4)	Bouchardy et al[39]
ADH1C†	*1/*1	Larynx	French white	125/167	30.4/36.5	0.7 (0.4–1.4)	Bouchardy et al[39]
ADH1C†	*1/*2	Larynx	French white	125/167	46.4/41.3	1.0 (0.5–1.8)	Bouchardy et al[39]
ADH1C‡	*1/*2	SCCHN	American	521/599	46.4/45.6	1.1 (0.9–1.4)	Peters et al[112]
ADH1C‡	*2/*2	SCCHN	American	521/599	15.7/14.4	1.2 (0.9–1.8)	Peters et al[112]
ADH1C†	*1/*1	UADT	Europeans	760/945	19.9/15.9	1.4 (1.0–1.9)	Hashibe et al[106]
ADH1C†	*1/*2	UADT	Europeans	760/945	48.2/49.1	1.1 (0.9–1.4)	Hashibe et al[106]
ALDH2	*2 allele	Oral	Japanese	92/147	46.5/46.9	1.1 (0.6–2.0)	Katoh et al[113]
ALDH2	*1/*2	Oral	Japanese	114/33	34.2/15.1	2.9 (1.1–7.8)	Nomura et al[63]
ALDH2	*1/*2	Oropharynx	Japanese	33/526	60.6/9.5	18.5 (7.7–44.4)	Yokoyama et al[114]

Abbreviations: SCCHN indicates squamous cell carcinoma of the head and neck; NA, data not available; UADT, upper aerodigestive tract.
*†ADH1C*2/*2 homozygote genotype: reference group.*
*‡ADH1C*1/*1 homozygote genotype: reference group.*
§Not adjusted for race.

ant (Table 4).[37,85] A second *NQO1* polymorphism involving a cytosine to thymine (C → T) substitution at nucleotide 465 (resulting in replacement of arginine with tryptophan at codon 139) has also recently been investigated. The Arg139Trp polymorphic variant occurs at a lower frequency than does the Pro187Ser polymorphism and has been shown to cause decreased enzyme stability and activity.[97,98] However, thus far there has been no evidence correlating the Arg139Trp polymorphism with a risk of SCCHN.[85] Because of the very limited data available, further studies of the *NQO1* polymorphisms are needed to explore their roles in SCCHN.

Alcohol Dehydrogenase. One postulated mechanism by which alcohol influences the risk of SCCHN is through the conversion of ethanol to acetaldehyde, which has been shown to inhibit DNA repair and cause genetic mutations.[99,100] One of the major enzymes involved in first-pass ethanol metabolism is alcohol dehydrogenase (ADH), which converts ethanol to acetaldehyde. ADH is composed of 5 subunits encoded by 7 genes, ADH1 to ADH7. Class I ADH includes ADH1A, ADH1B, and ADH1C, which were formerly known as ADH1, ADH2, and ADH3 respectively.[101] Enzymatic activities of class III and class IV, but not class I and II, ADH isoenzymes had been detected in human lingual and gingival mucosa.[102] Class I ADH enzymes are most prominently expressed in the liver, adrenals, kidneys, and lungs.[103]

ADH1C (ADH3). *ADH3* or *ADH1C* gene loci possess 2 alleles that code for the γ1 and γ2 subunits of the dimeric ADH1C enzyme. The 2 subunits differ by one amino acid at position 271 (γ1 = Arg, γ2 = Gln), and isoenzymes formed by combination of these alleles exhibit different in vitro kinetic properties. The *ADH1C* polymorphic site is Ile349Val located in exon 8; presence of the amino acid valine denotes the *ADH1C*1* allele. The *ADH1C*1* allele, present at a frequency between 50% to 60% depending on the ethnicity, has been noted to be associated with a 2.5-fold increased rate of conversion of ethanol to acetaldehyde when compared with the *ADH1C*2* allele.[104,105] Therefore, it has been suggested that the presence of the *ADH1C*1* allele confers a greater risk for alcohol-associated cancers.

Recently Hashibe et al[106] found that *ADH1C*1* homozygotes have an increased risk for upper aerodigestive tract cancers (OR = 1.38, 95% CI =

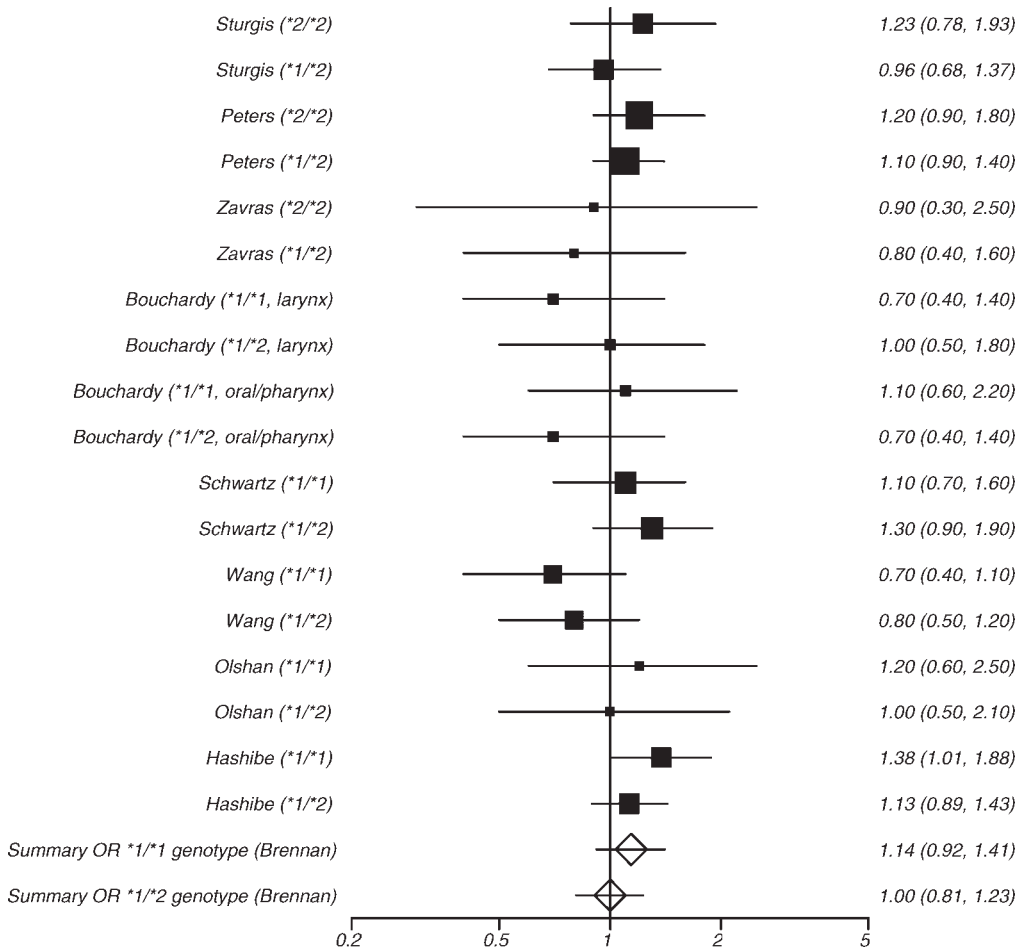


FIGURE 4. Forest plot of ADH1C polymorphism odds ratios.

1.0–1.9). The risks were particularly prominent in cancers of the oral cavity and pharynx (OR = 1.9 and 2.3, respectively). Previously, in a matched case-control study of American whites with SCCHN, a mildly elevated but nonsignificant risk association was seen for *ADH1C*1* homozygotes (OR = 1.2, 95% CI = 0.6–2.5) and heterozygotes (OR = 1.0, 95% CI = 0.5–2.1), compared with *ADH1C*2* homozygotes (Table 5).[107] Similarly, mild and statistically nonsignificant risk associations were seen with the presence of the *ADH1C*1* allele in 2 other studies of oral squamous-cell carcinoma. However, on additional analysis stratified by the amount of alcohol consumed, the data suggest that subjects possessing the *ADH1C*2* allele, with a slower rate of enzyme activity, may have a greater susceptibility to the carcinogenic effect of alcohol.[110,111] This is in agreement with the findings by Peters et al,[112] in which heavy drinkers with the *ADH1C*2* homozygous genotype had a significantly elevated risk for SCCHN (OR = 7.1, 95% CI = 2.3–22.0).

In 3 other case-control studies of SCCHN, no significant difference in *ADH1C* genotype distribution was seen between cases and control subjects.[39,109,112] A large matched case-control investigation on American whites with oral and pharyngeal squamous carcinoma similarly found no significant risk correlation with *ADH1C* genotype polymorphisms.[108] Interestingly, the study again found that the *ADH1C*2* homozygous genotype was associated with a mildly increased risk for oral and pharyngeal carcinoma, which could be explained by the possible link between *ADH1C*2* allele and alcoholism.[115] It has been hypothesized that those individuals with the *ADH1C*1* allele, hence the isoenzyme with higher metabolic activity, are less likely to become alcoholics because they are more prone to the adverse reactions from alcohol consumption, secondary to a faster accumulation of the toxin acetaldehyde. Finally, no risk association was seen between SCCHN and the *ADH1C*1* heterozygous genotype (OR = 1.0, 95% CI = 0.8–1.2) and only a weak association for

the *ADH1C*1* homozygous genotype (OR = 1.1, 95% CI = 0.9–1.4) in a recent HuGE review.[116] In summary, the available data on *ADH1C* polymorphisms do not provide convincing evidence that this polymorphism plays a major role in SCCHN; however, a modest association is possible (Figure 4).

ADH1B (ADH2). ADH1B is also polymorphic, and the polymorphic allele *ADH1B*2* (Arg47His) is highly prevalent among East Asians, being reported to be present in 93% of Japanese and in less than 20% of whites or Africans.[117] The polymorphic allele encodes a highly active ADH1B subunit in which the *ADH1B*2* homozygous genotype has a V_{max} 40 times higher than that of the *ADH1B*1* homozygous genotype.[118] The role of the *ADH1B*2* polymorphic allele has been extensively investigated in esophageal carcinoma, demonstrating that the less-active *ADH1B*1* homozygous genotype is an independent risk factor, with ORs ranging from 2.0 to 6.2. This has been reviewed by Yokoyama and Omori.[119] With regard to SCCHN, a case-control study involving alcoholic Japanese men similarly showed increased risk for the *ADH1B*1* homozygous genotype in oropharyngolaryngeal carcinoma (OR = 6.7), oral cavity/oropharyngeal carcinoma (OR = 5.5), and hypopharyngeal/epilaryngeal carcinoma (OR = 6.6). However, this was a small study, with only 33 case subjects.[114] More recently in a large multicenter case-control trial, Hashibe et al[106] similarly demonstrated a decreased risk for upper aerodigestive tract cancers in subjects possessing the homozygous and heterozygous *ADH1B*2* genotypes (OR = 0.5, 95% CI = 0.3–0.7), particularly in the oral cavity and esophagus (OR = 0.5 and 0.2, respectively). Given the limited data available, larger studies are needed to confirm the protective effect of the *ADH1B*2* SNP in SCCHN.

Aldehyde Dehydrogenase. Aldehyde dehydrogenase (ALDH) plays a key role in alcohol metabolism by catalyzing the conversion of acetaldehyde to acetate. Most of the acetaldehyde produced during alcohol metabolism in vivo is eliminated by ALDH2, the major human liver mitochondrial ALDH located on chromosome 12q24.2. ALDH2 is expressed in various human tissues, including the liver and stomach,[120] although only a relatively low level of ALDH2 enzyme activity is detectable in the esophagus and oral cavity.[102,121] The *ALDH2* gene contains an *ALDH2*2* allele secondary to substitution of lysine for glutamine at codon 487, which is considered to be inactive.[119,122] The presence of this allele results in a considerably decreased enzyme activity, leading to accumulation of acetaldehyde, which is an established animal carcinogen. Nearly all whites possess the functional *ALDH2*1/*1* genotype; however, the mutant *ALDH2*2* allele is prevalent among East Asians, with approximately 30% heterozygotes and 5% to 10% homozygotes.[115,118,123] After consuming alcohol, individuals with inactive ALDH2 experience the "flushing response" secondary to acetaldehyde accumulation, which includes facial flushing, drowsiness, and other unpleasant symptoms. It has been hypothesized that the presence of the *ALDH2*2* allele, and thus inactive ALDH2, prevents many East Asians from drinking heavily and developing alcoholism.

A statistically significant risk association was seen with the *ALDH2*1/*2* genotype in a study of Japanese patients with oropharyngeal carcinoma (OR = 18.5, 95% CI = 7.7–44.4) (Table 5). Combined *ALDH2*2* and *ADH1B*2* polymorphisms produced a synergistic increase in cancer risk. However, the series was small with only 33 cases.[114] An increased risk association was also observed for the *ALDH2*1/*2* genotype in a case-control study of Japanese patients with oral squamous carcinoma (OR = 2.9, 95% CI = 1.1–7.8).[63] However, no statistically significant risk association was seen for the *ALDH2*2* allele in another similar study of Japanese patients with oral squamous carcinoma.[113] Although it is possible that ALDH2 polymorphisms may influence SCCHN risk in Asian populations, the results are in part conflicting and further studies are needed, including greater exploration of the interaction between polymorphisms of the activating (*ADH*) and detoxifying (*ALDH*) genes.

CONCLUSION

In this article, we have briefly reviewed some of the available evidence regarding the association between various xenobiotic-metabolizing enzymes and SCCHN, including CYPs, GSTs, NATs, NQO1, ADH, and ALDH2. The results have been largely inconsistent among the published investigations that examined the risk association between these polymorphic genotypes of carcinogen-metabolizing enzymes and SCCHN.

New evidence has emerged since the publication of the review by Lazarus and Park[16] in 2000 on carcinogen-metabolizing enzyme genotypes and upper aerodigestive tract cancer risk. More

evidence has surfaced to support the mild to moderate risk association between CYP1A1 Ile462Val polymorphism and SCCHN. This is also true for GSTM1 and GSTT1 null polymorphisms. Despite the availability of new data on the risk association between NAT polymorphisms and SCCHN, their contributions remain unclear. More data have also become available on ADH polymorphisms, particularly for the ADH1C genotype. The available evidence to date does not appear to support an association between SCCHN and the investigated ADH1C SNPs. For the newly reviewed NQO1 polymorphism no definitive conclusion can be drawn, given the limited data available. However, given its association with other cancer types, further investigations are warranted.

In addition to the common confounding variables such as age, sex, and ethnicity, which were often controlled for in the studies reviewed, certain possible additional confounding factors should also be considered in determining the sources of heterogeneity among the study results. For instance, although the studies reviewed have not shown convincing evidence for a significant risk correlation of ADH and ALDH2 polymorphisms with SCCHN, it should be taken into consideration that subjects with nonfunctional enzyme secondary to the null genotype are likely to consume less or no alcohol, given the unpleasant reaction they experience. This may partially explain why heterozygous genotypes sometimes demonstrate a higher risk association than do homozygous genotypes. Therefore, the risk associated with carcinogen-metabolizing polymorphisms is confounded by the amount of exposure, and further adjustment or subgroup analyses are needed along with larger sample sizes. A similar concern applies to tobacco exposure as well. Second, the process of carcinogen metabolism is complex, and the regulation of xenobiotic-metabolizing enzyme expression can differ according to variations in general control of gene expression and sites. For instance, relative to other GSTs, higher levels of GSTP1 has been observed in the oral and pharyngeal mucosa when compared with levels of GSTM1, which has been observed in greater concentration in the larynx.[15]

Finally, while the polymorphic variants in individual carcinogen-metabolizing genes may be mild to moderate risk factors, there is a certain functional redundancy associated with various detoxification enzymes. This may explain why no statistically significant risk elevation was seen in many of the studies involving single enzyme deficiencies. This may also explain the dramatically elevated risk seen in studies involving the simultaneous deficiency of multiple detoxification enzymes (eg, CYP1A 1 and GSTM1). Future directions should include larger studies that focus on assessing the association between several genes simultaneously, with attention on subgroups (ethnicity, site, and exposure levels). On the basis of combined analyses of the existing literature, the GSTM1 and GSTT1 null genotypes and CYP1A1 Ile462Val polymorphic allele seem to confer a modest risk for SCCHN, while the ADH1C genotypes do not seem to be a major influence on SCCHN risk. The success of such combined studies is encouraging to the developing effort of the INHANCE (INternational Head And Neck Cancer Epidemiology) Consortium. This group of large molecular epidemiology programs is planning pooled analyses of such genotyping data to allow sample sizes large enough to investigate the role of these polymorphisms on SCCHN risk with appropriate subgroup analyses, multivariate adjustment, and combined genotype effects.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106–130.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
3. Hsu TC, Spitz MR, Schantz SP. Mutagen sensitivity: a biological marker of cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1991;1:83–89.
4. Yu GP, Zhang ZF, Hsu TC, Spitz MR, Schantz SP. Family history of cancer, mutagen sensitivity, and increased risk of head and neck cancer. Cancer Lett 1999;146:93–101.
5. Copper MP, Jovanovic A, Nauta JJ, et al. Role of genetic factors in the etiology of squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1995;121:157–160.
6. Foulkes WD, Brunet JS, Kowalski LP, Narod SA, Franco EL. Family history of cancer is a risk factor for squamous cell carcinoma of the head and neck in Brazil: a case-control study. Int J Cancer 1995;63:769–773.
7. Foulkes WD, Brunet JS, Sieh W, Black MJ, Shenouda G, Narod SA. Familial risks of squamous cell carcinoma of the head and neck: retrospective case-control study. BMJ 1996;313:716–721.
8. Schulte PA, Waters M. Using molecular epidemiology in assessing exposure for risk assessment. Ann NY Acad Sci 1999;895:101–111.
9. Chen YC, Hunter DJ. Molecular epidemiology of cancer. CA Cancer J Clin 2005;55:45–54; quiz 57.
10. Sturgis EM, Wei Q. Genetic susceptibility—molecular epidemiology of head and neck cancer. Curr Opin Oncol 2002;14:310–317.
11. Friedlander PL. Genomic instability in head and neck cancer patients. Head Neck 2001;23:683–691.
12. Huang MF, Lin WL, Ma YC. A study of reactive oxygen species in mainstream of cigarette. Indoor Air 2005;15: 135–140.
13. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 1999;91:1194–1210.

14. Hashibe M, Brennan P, Strange RC, et al. Meta- and pooled analyses of *GSTM1*, *GSTT1*, *GSTP1*, and *CYP1A1* genotypes and risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev 2003;12:1509–1517.
15. Geisler SA, Olshan AF. *GSTM1*, *GSTT1*, and the risk of squamous cell carcinoma of the head and neck: a mini-HuGE review. Am J Epidemiol 2001;154:95–105.
16. Lazarus P, Park JY. Metabolizing enzyme genotype and risk for upper aerodigestive tract cancer. Oral Oncol 2000;36:421–431.
17. Nelson DR, Koymans L, Kamataki T, et al. P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 1996;6:1–42.
18. Nelson DR, Kamataki T, Waxman DJ, et al. The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. DNA Cell Biol 1993;12:1–51.
19. Nebert DW. Role of genetics and drug metabolism in human cancer risk. Mutat Res 1991;247:267–281.
20. Kimura S, Gonzalez FJ, Nebert DW. The murine Ah locus. Comparison of the complete cytochrome P1-450 and P3-450 cDNA nucleotide and amino acid sequences. J Biol Chem 1984;259:10705–10713.
21. Phillips DH. Fifty years of benzo (a) pyrene. Nature 1983;303:468–472.
22. Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of *CYP* genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomarkers Prev 2000;9:3–28.
23. Nakachi K, Hayashi S, Kawajiri K, Imai K. Association of cigarette smoking and *CYP1A1* polymorphisms with adenocarcinoma of the lung by grades of differentiation. Carcinogenesis 1995;16:2209–2213.
24. Kawajiri K, Nakachi K, Imai K, Yoshii A, Shinoda N, Watanabe J. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P450IA1 gene. FEBS Lett 1990;263:131–133.
25. Tanimoto K, Hayashi S, Yoshiga K, Ichikawa T. Polymorphisms of the *CYP1A1* and *GSTM1* gene involved in oral squamous cell carcinoma in association with a cigarette dose. Oral Oncol 1999;35:191–196.
26. Sato M, Sato T, Izumo T, Amagasa T. Genetic polymorphism of drug-metabolizing enzymes and susceptibility to oral cancer. Carcinogenesis 1999;20:1927–1931.
27. Oude Ophuis MB, van Lieshout EM, Roelofs HM, Peters WH, Manni JJ. Glutathione s-transferase M1 and T1 and cytochrome P4501A1 polymorphisms in relation to the risk for benign and malignant head and neck lesions. Cancer 1998;82:936–943.
28. Gronau S, Koenig-Greger D, Jerg M, Riechelmann H. Gene polymorphisms in detoxification enzymes as susceptibility factor for head and neck cancer? Otolaryngol Head Neck Surg 2003;128:674–680.
29. Ko Y, Abel J, Harth V, et al. Association of CYP1B1 codon 432 mutant allele in head and neck squamous cell cancer is reflected by somatic mutations of p53 in tumor tissue. Cancer Res 2001;61:4398–4404.
30. Gajecka M, Rydzanicz M, Jaskula-Sztul R, Kujawski M, Szyfter W, Szyfter K. *CYP1A1, CYP2D6, CYP2E1, NAT2, GSTM1* and *GSTT1* polymorphisms or their combinations are associated with the increased risk of the laryngeal squamous cell carcinoma. Mutat Res 2005;574(1/2):112–123.
31. Morita S, Yano M, Tsujinaka T, et al. Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to head-and-neck squamous-cell carcinoma. Int J Cancer 1999;80:685–688.
32. Park JY, Muscat JE, Ren Q, et al. *CYP1A1* and *GSTM1* polymorphisms and oral cancer risk. Cancer Epidemiol Biomarkers Prev 1997;6:791–797.
33. McWilliams JE, Evans AJ, Beer TM, et al. Genetic polymorphisms in head and neck cancer risk. Head Neck 2000;22:609–617.
34. Sato M, Sato T, Izumo T, Amagasa T. Genetically high susceptibility to oral squamous cell carcinoma in terms of combined genotyping of *CYP1A1* and *GSTM1* genes. Oral Oncol 2000;36:267–271.
35. Olshan AF, Weissler MC, Watson MA, Bell DA. *GSTM1, GSTT1, GSTP1, CYP1A1*, and *NAT1* polymorphisms, tobacco use, and the risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev 2000;9:185–191.
36. Evans AJ, Henner WD, Eilers KM, et al. Polymorphisms of *GSTT1* and related genes in head and neck cancer risk. Head Neck 2004;26:63–70.
37. Li G, Liu Z, Sturgis EM, Chamberlain RM, Spitz MR, Wei Q. *CYP2E1 G1532C*, *NQO1* Pro187Ser, and *CYP1B1* Val432Leu polymorphisms are not associated with risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 2005;14: 1034–1036.
38. Gonzalez MV, Alvarez V, Pello MF, Menendez MJ, Suarez C, Coto E. Genetic polymorphism of *N*-acetyltransferase-2, glutathione s-transferase-M1, and cytochromes P450IIE1 and P450IID6 in the susceptibility to head and neck cancer. J Clin Pathol 1998;51:294–298.
39. Bouchardy C, Hirvonen A, Coutelle C, Ward PJ, Dayer P, Benhamou S. Role of alcohol dehydrogenase 3 and cytochrome P-4502E1 genotypes in susceptibility to cancers of the upper aerodigestive tract. Int J Cancer 2000;87:734–740.
40. Liu S, Park JY, Schantz SP, Stern JC, Lazarus P. Elucidation of CYP2E1 5′ regulatory RsaI/PstI allelic variants and their role in risk for oral cancer. Oral Oncol 2001;37:437–445.
41. De Vivo I, Hankinson SE, Li L, Colditz GA, Hunter DJ. Association of *CYP1B1* polymorphisms and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2002; 11:489–492.
42. Lee KM, Abel J, Ko Y, et al. Genetic polymorphisms of cytochrome P450 19 and 1B1, alcohol use, and breast cancer risk in Korean women. Br J Cancer 2003;88: 675–678.
43. Watanabe J, Shimada T, Gillam EM, et al. Association of *CYP1B1* genetic polymorphism with incidence to breast and lung cancer. Pharmacogenetics 2000;10:25–33.
44. Shimada T, Watanabe J, Kawajiri K, et al. Catalytic properties of polymorphic human cytochrome P450 1B1 variants. Carcinogenesis 1999;20:1607–1613.
45. Port JL, Yamaguchi K, Du B, et al. Tobacco smoke induces CYP1B1 in the aerodigestive tract. Carcinogenesis 2004;25:2275–2281.
46. Hanna IH, Dawling S, Roodi N, Guengerich FP, Parl FF. Cytochrome P450 *1B1* (*CYP1B1*) pharmacogenetics: association of polymorphisms with functional differences in estrogen hydroxylation activity. Cancer Res 2000;60: 3440–3444.
47. Li DN, Seidel A, Pritchard MP, Wolf CR, Friedberg T. Polymorphisms in P450 *CYP1B1* affect the conversion of estradiol to the potentially carcinogenic metabolite 4-hydroxyestradiol. Pharmacogenetics 2000;10:343–353.
48. Raunio H, Husgafvel-Pursiainen K, Anttila S, Hietanen E, Hirvonen A, Pelkonen O. Diagnosis of polymorphisms in carcinogen-activating and inactivating enzymes and cancer susceptibility—a review. Gene 1995;159:113–121.
49. Clapper ML. Genetic polymorphism and cancer risk. Curr Oncol Rep 2000;2:251–256.
50. Crespi CL, Penman BW, Gelboin HV, Gonzalez FJ. A tobacco smoke-derived nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, is activated by multiple human cytochrome P450s including the polymorphic human cytochrome P4502D6. Carcinogenesis 1991;12: 1197–1201.

51. Ayesh R, Idle JR, Ritchie JC, Crothers MJ, Hetzel MR. Metabolic oxidation phenotypes as markers for susceptibility to lung cancer. Nature 1984;312:169–170.
52. Benhamou S, Bouchardy C, Paoletti C, Dayer P. Effects of CYP2D6 activity and tobacco on larynx cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:683–686.
53. Guengerich FP, Kim DH, Iwasaki M. Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 1991; 4:168–179.
54. Hayashi S, Watanabe J, Kawajiri K. Genetic polymorphisms in the 5′-flanking region change transcriptional regulation of the human cytochrome P450IIE1 gene. J Biochem (Tokyo). 1991;110:559–565.
55. Parl FF. Glutathione s-transferase genotypes and cancer risk. Cancer Lett 2005;221:123–129.
56. Piipari R, Nurminen T, Savela K, Hirvonen A, Mantyla T, Anttila S. Glutathione s-transferases and aromatic DNA adducts in smokers' bronchoalveolar macrophages. Lung Cancer 2003;39:265–272.
57. Bauer M, Herbarth O, Aust G, et al. Expression patterns and novel splicing variants of glutathione-s-transferase isoenzymes of human lung and hepatocyte cell lines. Cell Tissue Res 2006;324:423–432.
58. Hayes JD, Strange RC. Glutathione s-transferase polymorphisms and their biological consequences. Pharmacology 2000;61:154–166.
59. Garte S, Gaspari L, Alexandrie AK, et al. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev 2001;10:1239–1248.
60. McWilliams JE, Sanderson BJ, Harris EL, Richert-Boe KE, Henner WD. Glutathione s-transferase M1 (GSTM1) deficiency and lung cancer risk. Cancer Epidemiol Biomarkers Prev 1995;4:589–594.
61. Trizna Z, Clayman GL, Spitz MR, Briggs KL, Goepfert H. Glutathione s-transferase genotypes as risk factors for head and neck cancer. Am J Surg 1995;170:499–501.
62. Jahnke V, Matthias C, Fryer A, Strange R. Glutathione s-transferase and cytochrome-P-450 polymorphism as risk factors for squamous cell carcinoma of the larynx. Am J Surg 1996;172:671–673.
63. Nomura T, Noma H, Shibahara T, Yokoyama A, Muramatusu T, Ohmori T. Aldehyde dehydrogenase 2 and glutathione s-transferase M 1 polymorphisms in relation to the risk for oral cancer in Japanese drinkers. Oral Oncol 2000;36:42–46.
64. Cheng L, Sturgis EM, Eicher SA, Char D, Spitz MR, Wei Q. Glutathione-s-transferase polymorphisms and risk of squamous-cell carcinoma of the head and neck. Int J Cancer 1999;84:220–224.
65. Park LY, Muscat JE, Kaur T, et al. Comparison of GSTM polymorphisms and risk for oral cancer between African-Americans and Caucasians. Pharmacogenetics 2000;10:123–131.
66. Oude Ophuis MB, Roelofs HM, van den Brandt PA, Peters WH, Manni JJ. Polymorphisms of the glutathione s-transferase P1 gene and head and neck cancer susceptibility. Head Neck 2003;25:37–43.
67. Jourenkova-Mironova N, Voho A, Bouchardy C, et al. Glutathione S-transferase *GSTM3* and *GSTP1* genotypes and larynx cancer risk. Cancer Epidemiol Biomarkers Prev 1999;8:185–188.
68. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 2003;33: 177–182.
69. Tripathy CB, Roy N. Meta-analysis of glutathione s-transferase M1 genotype and risk toward head and neck cancer. Head Neck 2006;28:217–224.
70. Pemble S, Schroeder KR, Spencer SR, et al. Human glutathione *s*-transferase θ (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. Biochem J 1994;300(Part 1):271–276.
71. Terrier P, Townsend AJ, Coindre JM, Triche TJ, Cowan KH. An immunohistochemical study of pi class glutathione s-transferase expression in normal human tissue. Am J Pathol 1990;137:845–853.
72. Ali-Osman F, Akande O, Antoun G, Mao JX, Buolamwini J. Molecular cloning, characterization, and expression in *Escherichia coli* of full-length cDNAs of three human glutathione s-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem 1997;272:10004–10012.
73. Hein DW, Doll MA, Rustan TD, et al. Metabolic activation and deactivation of arylamine carcinogens by recombinant human NAT1 and polymorphic NAT2 acetyltransferases. Carcinogenesis 1993;14:1633–1638.
74. Boukouvala S, Sim E. Structural analysis of the genes for human arylamine *N*-acetyltransferases and characterisation of alternative transcripts. Basic Clin Pharmacol Toxicol 2005;96:343–351.
75. Smith G, Stanley LA, Sim E, Strange RC, Wolf CR. Metabolic polymorphisms and cancer susceptibility. Cancer Surv 1995;25:27–65.
76. Lang NP, Butler MA, Massengill J, et al. Rapid metabolic phenotypes for acetyltransferase and cytochrome P4501A2 and putative exposure to food-borne heterocyclic amines increase the risk for colorectal cancer or polyps. Cancer Epidemiol Biomarkers Prev 1994;3:675–682.
77. Evans DA, Eze LC, Whibley EJ. The association of the slow acetylator phenotype with bladder cancer. J Med Genet 1983;20:330–333.
78. Drozdz M, Gierek T, Jendryczko A, Pilch J, Piekarska J. *N*-Acetyltransferase phenotype of patients with cancer of the larynx. Neoplasma 1987;34:481–484.
79. Bell DA, Stephens EA, Castranio T, et al. Polyadenylation polymorphism in the acetyltransferase 1 gene (*NAT1*) increases risk of colorectal cancer. Cancer Res 1995;55:3537–3542.
80. Bell DA, Badawi AF, Lang NP, Ilett KF, Kadlubar FF, Hirvonen A. Polymorphism in the *N*-acetyltransferase 1 (NAT1) polyadenylation signal: association of NAT1*10 allele with higher N-acetylation activity in bladder and colon tissue. Cancer Res 1995;55:5226–5229.
81. Katoh T, Kaneko S, Boissy R, Watson M, Ikemura K, Bell DA. A pilot study testing the association between *N*-acetyltransferases 1 and 2 and risk of oral squamous cell carcinoma in Japanese people. Carcinogenesis 1998; 19:1803–1807.
82. Fronhoffs S, Bruning T, Ortiz-Pallardo E, et al. Real-time PCR analysis of the *N*-acetyltransferase NAT1 allele *3,*4,*10,*11,*14 and *17 polymorphism in squamous cell cancer of head and neck. Carcinogenesis 2001;22:1405–1412.
83. Varzim G, Monteiro E, Silva R, Pinheiro C, Lopes C. Polymorphisms of arylamine *N*-acetyltransferase (NAT1 and NAT2) and larynx cancer susceptibility. ORL J Otorhinolaryngol Relat Spec 2002;64:206–212.
84. Chen C, Ricks S, Doody DR, Fitzgibbons ED, Porter PL, Schwartz SM. *N*-acetyltransferase 2 polymorphisms, cigarette smoking and alcohol consumption, and oral squamous cell cancer risk. Carcinogenesis 2001;22: 1993–1999.
85. Begleiter A, Norman A, Leitao D, et al. Role of NQO1 polymorphisms as risk factors for squamous cell carcinoma of the head and neck. Oral Oncol 2005;41:927–933.
86. Thier R, Bruning T, Roos PH, et al. Markers of genetic susceptibility in human environmental hygiene and toxicology: the role of selected *CYP*, *NAT* and *GST* genes. Int J Hyg Environ Health 2003;206:149–171.
87. Jaiswal AK. Human NAD(P)H:quinone oxidoreductase (NQO1) gene structure and induction by dioxin. Biochemistry 1991;30:10647–10653.

88. Jaiswal AK. Human NAD(P)H:quinone oxidoreductase 2 gene structure, activity, and tissue-specific expression. J Biol Chem 1994;269:14502–14508.
89. Winski SL, Koutalos Y, Bentley DL, Ross D. Subcellular localization of NAD(P)H:quinone oxidoreductase 1 in human cancer cells. Cancer Res 2002;62:1420–1424.
90. Belinsky M, Jaiswal AK. NAD(P)H:quinone oxidoreductase1 (DT-diaphorase) expression in normal and tumor tissues. Cancer Metastasis Rev 1993;12:103–117.
91. Ross D, Traver RD, Siegel D, Kuehl BL, Misra V, Rauth AM. A polymorphism in NAD(P)H:quinone oxidoreductase (NQO1): relationship of a homozygous mutation at position 609 of the NQO1 cDNA to NQO1 activity. Br J Cancer 1996;74:995–996.
92. Kelsey KT, Ross D, Traver RD, et al. Ethnic variation in the prevalence of a common NAD(P)H quinone oxidoreductase polymorphism and its implications for anti-cancer chemotherapy. Br J Cancer 1997;76:852–854.
93. Traver RD, Siegel D, Beall HD, et al. Characterization of a polymorphism in NAD(P)H: quinone oxidoreductase (DT-diaphorase). Br J Cancer 1997;75:69–75.
94. Lafuente MJ, Casterad X, Trias M, et al. NAD(P)H:quinone oxidoreductase-dependent risk for colorectal cancer and its association with the presence of K-ras mutations in tumors. Carcinogenesis 2000;21:1813–1819.
95. Schulz WA, Krummeck A, Rosinger I, et al. Increased frequency of a null-allele for NAD(P)H:quinone oxidoreductase in patients with urological malignancies. Pharmacogenetics 1997;7:235–239.
96. Zhang JH, Li Y, Wang R, et al. *NQO1* C609T polymorphism associated with esophageal cancer and gastric cardiac carcinoma in North China. World J Gastroenterol 2003;9:1390–1393.
97. Gaedigk A, Tyndale RF, Jurima-Romet M, Sellers EM, Grant DM, Leeder JS. NAD(P)H:quinone oxidoreductase: polymorphisms and allele frequencies in Caucasian, Chinese and Canadian Native Indian and Inuit populations. Pharmacogenetics 1998;8:305–313.
98. Pan SS, Han Y, Farabaugh P, Xia H. Implication of alternative splicing for expression of a variant NAD(P)H: quinone oxidoreductase-1 with a single nucleotide polymorphism at 465C≫T. Pharmacogenetics 2002;12:479–488.
99. Grafstrom RC, Curren RD, Yang LL, Harris CC. Aldehyde-induced inhibition of DNA repair and potentiation of *N*-nitrosocompound-induced mutagenesis in cultured human cells. Prog Clin Biol Res A 1986;209:255–264.
100. Singh NP, Khan A. Acetaldehyde: genotoxicity and cytotoxicity in human lymphocytes. Mutat Res 1995;337: 9–17.
101. Duester G, Farres J, Felder MR, et al. Recommended nomenclature for the vertebrate alcohol dehydrogenase gene family. Biochem Pharmacol 1999;58:389–395.
102. Dong YJ, Peng TK, Yin SJ. Expression and activities of class IV alcohol dehydrogenase and class III aldehyde dehydrogenase in human mouth. Alcohol 1996;13:257–262.
103. Edenberg HJ. Regulation of the mammalian alcohol dehydrogenase genes. Prog Nucleic Acid Res Mol Biol 2000;64:295–341.
104. Hoog JO, Heden LO, Larsson K, Jornvall H, von Bahr-Lindstrom H. The γ1 and γ2 subunits of human liver alcohol dehydrogenase. cDNA structures, two amino acid replacements, and compatibility with changes in the enzymatic properties. Eur J Biochem 1986;159: 215–218.
105. Iron A, Groppi A, Fleury B, Begueret J, Cassaigne A, Couzigou P. Polymorphism of class I alcohol dehydrogenase in French, Vietnamese and Niger populations: genotyping by PCR amplification and RFLP analysis on dried blood spots. Ann Genet 1992;35:152–156.
106. Hashibe M, Boffetta P, Zaridze D, et al. Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev 2006;15:696–703.
107. Olshan AF, Weissler MC, Watson MA, Bell DA. Risk of head and neck cancer and the alcohol dehydrogenase 3 genotype. Carcinogenesis 2001;22:57–61.
108. Sturgis EM, Dahlstrom KR, Guan Y, et al. Alcohol dehydrogenase 3 genotype is not associated with risk of squamous cell carcinoma of the oral cavity and pharynx. Cancer Epidemiol Biomarkers Prev 2001;10:273–275.
109. Wang D, Ritchie JM, Smith EM, Zhang Z, Turek LP, Haugen TH. Alcohol dehydrogenase 3 and risk of squamous cell carcinomas of the head and neck. Cancer Epidemiol Biomarkers Prev 2005;14:626–632.
110. Schwartz SM, Doody DR, Fitzgibbons ED, Ricks S, Porter PL, Chen C. Oral squamous cell cancer risk in relation to alcohol consumption and alcohol dehydrogenase-3 genotypes. Cancer Epidemiol Biomarkers Prev 2001;10:1137–1144.
111. Zavras AI, Wu T, Laskaris G, et al. Interaction between a single nucleotide polymorphism in the alcohol dehydrogenase 3 gene, alcohol consumption and oral cancer risk. Int J Cancer 2002;97:526–530.
112. Peters ES, McClean MD, Liu M, Eisen EA, Mueller N, Kelsey KT. The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. Cancer Epidemiol Biomarkers Prev 2005;14:476–482.
113. Katoh T, Kaneko S, Kohshi K, et al. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and oral cavity cancer. Int J Cancer 1999;83: 606–609.
114. Yokoyama A, Muramatsu T, Omori T, et al. Alcohol and aldehyde dehydrogenase gene polymorphisms and oropharyngolaryngeal, esophageal and stomach cancers in Japanese alcoholics. Carcinogenesis 2001;22:433–439.
115. Thomasson HR, Edenberg HJ, Crabb DW, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am J Hum Genet 1991;48: 677–681.
116. Brennan P, Lewis S, Hashibe M, et al. Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. Am J Epidemiol 2004;159:1–16.
117. Higuchi S, Matsushita S, Murayama M, Takagi S, Hayashida M. Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism. Am J Psychiatry 1995;152:1219–1221.
118. Bosron WF, Li TK. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. Hepatology 1986;6:502–510.
119. Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. Alcohol 2005;35:175–185.
120. Yin SJ, Liao CS, Wu CW, et al. Human stomach alcohol and aldehyde dehydrogenases: comparison of expression pattern and activities in alimentary tract. Gastroenterology 1997;112:766–775.
121. Yin SJ, Chou FJ, Chao SF, et al. Alcohol and aldehyde dehydrogenases in human esophagus: comparison with the stomach enzyme activities. Alcohol Clin Exp Res 1993;17:376–381.
122. Yoshida A, Huang IY, Ikawa M. Molecular abnormality of an inactive aldehyde dehydrogenase variant commonly found in orientals. Proc Natl Acad Sci U S A 1984;81:258–261.
123. Goedde HW, Agarwal DP, Fritze G, et al. Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 1992;88:344–346.