Genetic polymorphisms and head and neck cancer risk (Review)

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Abstract. The aim of this report is to review and evaluate, in a comprehensive manner, the published data regarding the contribution of genetic polymorphisms to risk of head and neck cancer (HNC). All relevant studies available in MEDLINE and published before July 2007 were identified. Studies carried out in humans that compared HNC patients with at least 1 standard control group were considered for analysis. Two hundred and eighteen publications and 3 published meta-analyses were identified. Seventy-five (34%) studies were conducted in Asian, 72 (33%) in American, and 68 (31%) in European countries. The most widely studied gene was *GSTM1* (58 studies), followed by *GSTT1* (42 studies), *GSTP1* (codon 105, 22 studies) and *p53* (codon 72, 20 studies). *GSTM1*, *GSTT1*, GSTP1, *XRCC1* codons 194 and 399, and *CYP1A1* codon 462 were examined by meta-analyses, and significant relations were found between the *GSTM1*-null genotype and an increased risk for HNC. In addition, increased risk for HNC was associated consistently with the *ALDH2**1/*2, *p53* codon 72 Pro/Pro and *EPHX1* codon 113 Tyr/His and His/His genotypes. Cohort studies that simultaneously consider multiple genetic and environmental factors possibly involved in carcinogenesis of the head and neck are needed to ascertain not only the relative contribution of these factors to tumor development but also the contributions of their putative interactions.

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1. Introduction

Head and neck cancers (HNCs), including cancers of the oral cavity, pharynx and larynx, represent the 6 most frequent cancers and the seventh leading cause of cancer-related death worldwide. There are approximately 540,000 new cases and 271,000 deaths annually worldwide for a mortality of approximately 50% (1). HNCs represent approximately 3% of all cancers in the United States whereas these cancers are much more prevalent in other areas of the world, such as India, Thailand and Brazil (1,2). Standard therapeutic approaches, which focus on surgery, irradiation and chemotherapy (alone or in combination), have been modified over the last 30 years; however, the overall survival of HNC patients has not improved substantially. For patients affected by early-stage cancers with a high disease-specific survival rate, secondary tumors represent the most common cause of death (3). Furthermore, patients with advanced cancers have a high risk of primary treatment failure and death.

Development of HNC is a multifactorial process associated with a variety of risk factors. Major risk factors in developed countries include smoking tobacco and drinking alcohol, and chewing betel quid (4,5). For tobacco smoking, a dose-response trend has been reported. Relative risks of developing laryngeal and oropharyngeal cancers are 1.8 and 1.3, respectively, for persons who smoke ≤30 cigarettes per day and 7.7 and 2.9, respectively, for persons who smoke >30 cigarettes per day compared with non-smokers (6). Alcohol consumption is also linked to increased risk of HNCs. For persons who consume >4 drinks (=47.5 g of pure ethanol) per day, the relative risks of developing laryngeal and oropharyngeal cancers are 4.5 and 7.2, respectively, compared with non-drinkers (6). A synergistic effect was observed in persons who both smoke tobacco and drink alcohol. The relative risks of developing laryngeal and oropharyngeal cancers are 34.6 and 21.2, respectively, among those who smoke >30 cigarettes a day and consume >4 drinks per week.

Genetic factors as well as environmental factors play a role in development of HNC and of other cancers (7-13). Individual variations in cancer risk have been associated with specific variant alleles of different genes that are present in a significant proportion of the normal population. Recent studies have suggested that genetic polymorphisms may underlie some of the causes and events involved in carcinogenesis of the head and neck. A variety of genes may be associated with carcinogenesis, including genes involved in carcinogen

metabolism, alcohol metabolism, folate metabolism, DNA repair and cell-cycle control and oncogenes. Here we review and evaluate, in a comprehensive manner, the most recent published evidence regarding the relative contribution of genetics to susceptibility to HNC in humans.

We identified all studies related to the association of genetic polymorphisms with HNC risk published before July 2007 and listed in MEDLINE (National Library of Medicine). Only reviews published in English were considered. Studies of HNC patients with at least 1 standard control group were considered for analysis. Studies without control subjects or based only on serologic or histochemical assays were excluded. Studies that evaluated only the role of genetic factors as prognostic markers and those that described somatic mutations in tumor tissue were also excluded. Two hundred and eighteen publications (14-231) and 3 published meta-analyses (232-234) were identified. We extracted the first author, the year of publication, the country where the study was conducted, the size of each study, the selection and features of patients and control subjects, the availability and use of information on environmental factors (mainly smoking and alcohol) and the reported results.

Genes are named according to the HUGO Gene Nomenclature Committee (HGNC; http://www.gene.ucl.ac.uk/nomenclature/). Polymorphisms are termed according to the proposed nomenclature of Antonarakis *et al*. In short, a polymorphism designation that starts with a number refers to a nucleotide position, and subsequent letters indicate the nucleotide change. A polymorphism designation that starts with a letter (or 2 letters separated by a slash) indicates an amino acid substitution (single-letter amino acid code), and the number following it is the codon position. Metabolic gene allele nomenclature is according to that recommended by Garte *et al* (http://www.gsec.net).

2. Review of the studies

Of the 218 studies identified in our review, 75 (34%) were conducted in Asian countries, 72 (33%) in American countries, and 68 (31%) in European countries. For countries, 55 (25%) studies were conducted in the United States, 29 (13%) in China including Taiwan and Hong Kong and 15 (7%) each in Germany and Japan, respectively. The most intensively studied genes were those encoding enzymes involved in carcinogen metabolism. The most widely studied gene was *GSTM1* (58 studies) followed by *GSTT1* (42 studies), *GSTP1* (codon 105, 22 studies) and *p53* (codon 72, 20 studies). Summaries of genetic polymorphisms and risk of HNCs and meta-analyses are shown in Tables I-IX and X, respectively.

Carcinogen metabolic genes (Table I). Carcinogen metabolic enzymes, which are involved in the activation of carcinogens, convert endogenous and/or exogenous carcinogens into DNA-binding metabolites and can thereby influence intermediate effect markers, such as DNA adducts, and ultimately, risk for cancer. Accumulating data suggest that genetic polymorphisms in genes controlling carcinogen metabolism underlie individual variations in cancer risk (7,14-110,235). Most carcinogens undergo activation by Phase I enzymes, often as an oxidation reaction, and detoxification by Phase II enzymes. The cytochrome P450 enzyme superfamily, including CYP1A1, CYP2E1 and CYP2A6, constitutes the majority of Phase I enzymes, while the glutathione *S*-transferases (GSTs) and *N*-acetyltransferases (NATs) are primarily responsible for detoxification of xenobiotics.

CYP1A1. CYP1A1 is involved in the activation of major classes of tobacco procarcinogens, such as polyaromatic hydrocarbons and aromatic amines, and is present in many epithelial tissues (236). An Ile-Val substitution in codon 462 of *CYP1A1*, which is in the heme-binding region, results in a 2-fold increase in microsomal enzyme activity and, in Caucasians, is in complete linkage disequilibrium with the *CYP1A1 Msp*I polymorphism, which is also associated with increased catalytic activity (7).

We identified 15 studies (14-28) with data regarding the relation of the *CYP1A1* Ile-Val substitution at codon 462 to HNC. In 4 studies (14,19,22,24), the risk for HNC in subjects with the Ile/Val and/or Val/Val genotypes was significantly higher than that for subjects with the Ile/Ile genotype, suggesting that the Val allele may be associated with increased risk for HNC. A meta-analysis of studies that examined the association of the *CYP1A1* Ile-Val substitution with risk for HNC revealed that the Ile/Val and Val/Val genotypes tend to increase HNC risk with odds ratios (ORs) [95% confidence interval (CI)] compared with Ile/Ile of 1.32 (0.95-1.82) (232).

CYP2E1. CYP2E1 is primarily responsible for the metabolic activation of many low molecular weight carcinogens, including certain nitrosoamines, which may be involved in carcinogenesis of the esophagus (237,238). This enzyme is also believed to participate in the oxidation of other compounds, such as ethanol, to produce reactive free radicals that may initiate lipid peroxidation and consequently influence carcinogenesis (133). The variant c2 allele, which contains a novel *Rsa*I/*Pst*I site in the 5'-flanking region of the *CYP2E1* gene, appears to be associated with decreased enzyme activity.

Ten (15,17,18,27,28,35,40,43,46) of the 15 (67%) studies (15,17,18,27,28,35,39-44,46,47) suggested that the c1/c2 genotype of *CYP2E1* may increase risk for HNC compared with the c1/c1 genotype. Results of 6 (18,28,39-41,44) of 7 (86%) studies (17,18,28,39-41,44) suggested that the c2/c2 genotype may increase risk for HNC.

GSTs. GSTs are a family of multifunctional enzymes that metabolize a variety of xenobiotics with a large overlap in substrate specificity (239,240). Individuals who are homozygous for the null *GSTM1* or null *GSTT1* alleles lack the respective enzyme function. The null *GSTM1* genotype appears to be common in both Asians and Caucasians, whereas the frequency of the null *GSTT1* genotype varies among ethnicities. The null genotypes of *GSTM1* and *GSTT1* appear to be associated with increased risk of esophageal (235), gastric (241) and lung (242) cancers.

For HNCs, 36 (62%) ORs from 58 studies of the null *GSTM1* genotype vs. the positive genotype were >1, suggesting that the null *GSTM1* genotype may be associated with increased risk for HNC. Sixteen (28%) (30,35,55,58, 62,64,66-68,71,72,74,79,84-86) of the studies showed a significantly higher risk for HNC in subjects with the null

GSTM1 genotype than in subjects with the positive genotype. No studies showed a significantly lower risk in patients with the null *GSTM1* genotype than in those with the positive genotype. Two meta-analyses (232,233) of studies that examined the association of *GSTM1* with risk for HNC revealed that the null genotype significantly increases the risk with ORs (95% CI) of 1.23 (1.06-1.42) and 1.50 (1.21-1.87) compared with the positive genotype.

Twenty-three (55%) ORs from 42 studies of the null *GSTT1* genotype vs. the positive genotype were >1, and 7 studies (56,64,72,83,85,95,96) showed a significantly higher risk for HNC in subjects with the null genotype than in those with the positive genotype, suggesting that the null *GSTT1* genotype may be associated with increased risk for HNC. In contrast, only 1 study showed a significantly lower risk with the null *GSTT1* genotype than the positive genotype. A meta-analysis (232) of studies that examined the association of *GSTT1* with risk of HNC revealed that the null genotype tends to increase HNC risk with ORs (95% CI) of 1.17 (0.98-1.40) compared with positive genotype.

GSTP1 is a major GST isoform that eliminates thymidine and uracil propenal, products of DNA oxidation (243,244). An Ile to Val substitution at codon 105 (exon 5) has been identified. The 105Val form shows altered affinity and enzymatic activity for some substrates. Four (18%) (77,88-90) of the 22 studies (18,20,21,25,31,33,63,69,73,77,80,82,84, 87-94) showed a significantly higher risk for HNC in persons with the Ile/Val and/or Val/Val genotypes than in those with the Ile/Ile genotype. No studies showed a significantly lower risk with the Ile/Val and/or Val/Val genotypes than the Ile/Ile genotype. The 105Val allele might be associated with an increased risk for HNC. One meta-analysis revealed that the Ile/Val and Val/Val genotypes tend to increase HNC risk with ORs (95% CI) of 1.10 (0.92-1.31) compared with the positive genotype (232).

NATs. Two NAT isozymes, NAT1 and NAT2, are polymorphic and catalyze both *O*-acetylation (activation) and *N*-acetylation (usually detoxification) of aromatic and heterocyclic amine carcinogens. Molecular epidemiologic studies suggest that genetic polymorphisms in *NAT1* and *NAT2* modify risk of developing certain cancers (245). For HNC, all 7 (100%) ORs (18,23,33,42,97,100,101) for the slow *NAT2* genotype vs. the rapid genotype were >1, suggesting that the slow *NAT2* genotype may be associated with an increased risk for HNC.

EPHX1. The human microsomal epoxide hydrase (mEH), which is encoded by *EPHX1*, cleaves a range of alkene and arene oxides to form *trans*-dihydrodiols. For some polycyclic aromatic hydrocarbons, including benzo[a]pyrene, dihydrodiol derivatives are substrates for additional metabolic reactions that produce more highly reactive and carcinogenic compounds. Two amino acid-altering polymorphisms, Tyr113His and His139Arg, have been identified in *EPHX1* and both are associated with alterations in mEH activity. The *EPHX1* His113 variant shows a 40% decrease in EH activity, whereas the *EPHX1* Arg139 variant shows 25% increased enzyme activity (246). These polymorphic alleles have been linked to increases in risk for lung (247), colon (248) and ovarian (249) cancers.

Five (83%) ORs (73,92,103,104) from 6 studies (37,73,92, 103,104) of the *EPHX1* Tyr/His genotype vs. the Tyr/Tyr genotype were <1, and 3 studies (92,103) showed a significantly lower risk for HNC in subjects with the Tyr/His genotype than in those with the Tyr/Tyr genotype. Five (83%) ORs (73,92,103,104) from 6 studies (37,73,92,103,104) of the His/His genotype vs. Tyr/Tyr genotype were <1, and 1 study (92) showed a significantly lower risk for HNC in subjects with the His/His genotype than in those with the Tyr/Tyr genotype. These results suggest that the His allele at codon 113 may be associated with an increased risk for HNC.

ORs for the His/Arg genotype vs. the His/His genotype at codon 139 of *EPHX1* varied from 0.69 to 1.21. However, 5 (83%) ORs (37,92,103,104) from 6 studies (37,73,92, 103,104) of the Arg/Arg genotype vs. the His/His genotype were >1, suggesting that the Arg/Arg genotype at codon 139 may be associated with an increased risk for HNC.

Alcohol metabolic enzymes (Table II). Alcohol consumption is classified as a risk factor for HNC according to data from epidemiologic studies (6). Alcohol intake increases exposure to high levels of acetaldehyde, the principal metabolite of alcohol, which increases risk of cancers such as HNC. Acetoaldehyde is produced mainly from ethanol via oxidation by alcohol dehydrogenase (ADH) and is subsequently detoxified into acetate by aldehyde dehydrogenase (ALDH)-2.

ALDH2. *ALDH2* is a polymorphic gene, and an individual's genotype at this locus determines blood acetaldehyde concentrations after drinking. A single point alteration in *ALDH2* results in the *ALDH2**2 allele. The protein encoded by *ALDH2**2 has a Glu to Lys substitution at residue 487, resulting in an inactive subunit and the inability to metabolize acetaldehyde. The *ALDH2**2 allele is rare in Western populations but prevalent in East Asian populations including Chinese, Korean, Thai, and Japanese populations (250,251) *ALDH2**2/*2 homozygotes have serum acetaldehyde levels that are 13 times higher and heterozygotes have levels 4 times higher than those in *1*1 homozygotes (252). *ALDH2**2/*2 homozygotes are characterized by a facial flushing response after alcohol consumption with nausea, drowsiness, headache and other unpleasant symptoms.

Six studies (17,66,117-120) reported a relation between *ALDH2* polymorphisms and risk for HNC, and all were conducted in Japanese populations. Four (67%) studies (66,117,118,120) showed a significantly increased risk for HNC in *1/*2 heterozygotes compared with *1/*1 homozygotes. In contrast, 1 (119) of 2 (50%) studies (17,119) showed a lower risk for HNC in *2/*2 homozygotes than in *1/*1 homozygotes.

ADH3. ADH isoenzymes, which are primarily involved in ethanol oxidation, consist of subunits encoded by *ADH2* and *ADH3*. In contrast to *ADH2*, *ADH3* is highly polymorphic in Caucasians. Of the 2 allelic variants, the *ADH3**1 allele is associated with higher enzyme activity than the *ADH3**2 allele and occurs in Caucasians at frequencies of 55-63% (253).

In 5 (43,58,111-113) of 8 (63%) studies (43,58,111-116), *ADH3**2/*1 heterozygotes showed decreased risk for HNC compared with *2/*2 homozygotes. However, in 6 (43,58,

Table I. Studies on polymorphisms of carcinogen metabolic enzymes and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
CYP1A1 codon 462	OC	133	133	Ile/Val+Val/Val vs. Ile/Ile	2.6 (1.2-5.7)			Age, sex, ethnicity	14
CYP1A1 codon 462	OC, P, L	380	193	Ile/Val vs. Ile/Ile	1.08 (0.65-1.79)[d]	Val/Val vs. Ile/Ile	0.51 (0.07-3.66)[d]	-	15
CYP1A1 codon 462	OC, P, L, O	185	207	Ile/Val+Val/Val vs. Ile/Ile	1.15 (0.68-1.93)[d]			-	16
CYP1A1 codon 462	OC	92	147	Ile/Val vs. Ile/Ile	1.31 (0.71-2.42)	Val/Val vs. Ile/Ile	1.30 (0.38-4.50)	Age, sex, smoking	17
CYP1A1 codon 462	OC, P, L	145	164	Ile/Val vs. Ile/Ile	0.72 (0.44-1.20)[d]	Val/Val vs. Ile/Ile	2.35 (0.86-6.42)[d]	-	18
CYP1A1 codon 462	OC	142	142	Ile/Val vs. Ile/Ile	1.58 (0.96-2.62)	Val/Val vs. Ile/Ile	4.19 (1.59-11.1)	-	19
CYP1A1 codon 462	OC, P, L	172	193	Ile/Val vs. Ile/Ile	1.5 (0.6-3.6)	Val/Val vs. Ile/Ile	-	Age, sex, ethnicity	20
CYP1A1 codon 462	OC, P, L, O	139	121	Ile/Val vs. Ile/Ile	0.45 (0.19-1.06)[d]	Val/Val vs. Ile/Ile	-	-	21
CYP1A1 codon 462	OC	98	60	Ile/Val+Val/Val vs. Ile/Ile	5.28 (1.03-26.28)			-	22
CYP1A1 codon 462	OC	94	92	Ile/Val vs. Ile/Ile	0.64 (0.17-2.34)[d]	Val/Val vs. Ile/Ile	-	-	23
CYP1A1 codon 462	L	88	178	Ile/Val vs. Ile/Ile	2.28 (1.14-4.58)[d]	Val/Val vs. Ile/Ile	0.76 (0.08-7.44)[d]	-	24
CYP1A1 codon 462	OC, P, L	282	208	Ile/Val vs. Ile/Ile	0.81 (0.45-1.45)[d]	Val/Val vs. Ile/Ile	0.72 (0.14-3.61)[d]	-	25
CYP1A1 codon 462	OC	132	143	Ile/Val vs. Ile/Ile	0.94 (0.56-1.58)	Val/Val vs. Ile/Ile	0.52 (0.15-1.78)	-	26
CYP1A1 codon 462	OC	231	212	Ile/Val vs. Ile/Ile	1.09 (0.66-1.80)[d]	Val/Val vs. Ile/Ile	2.85 (0.50-29.16)[d]	-	27
CYP1A1 codon 462	OC	122	241	Ile/Val vs. Ile/Ile	0.61 (0.37-1.01)	Val/Val vs. Ile/Ile	0.97 (0.38-2.46)	Age, sex, smoking, alcohol	28
CYP1A1 MspI	OC, P, L	381	205	m1/m2 vs. m1/m1	1.82 (1.05-3.14)[d]	m2/m2 vs. m1/m1	0.29 (0.03-3.19)[d]	-	15
CYP1A1 MspI	OC, P, L, O	185	207	m1/m2+m2/m2 vs. m1/m1	1.14 (0.67-1.94)[d]			-	16
CYP1A1 MspI	OC	100	100	m1/m2 vs. m1/m1	3.42 (1.84-6.35)[d]	m2/m2 vs. m1/m1	3.63 (1.39-9.47)[d]	-	29
CYP1A1 MspI	OC	142	142	m1/m2 vs. m1/m1	0.9 (0.6-1.7)	m2/m2 vs. m1/m1	2.3 (1.1-4.7)	-	30
CYP1A1 MspI	NS	312	300	m1/m2 vs. m1/m1	1.17 (0.78-1.77)[d]	m2/m2 vs. m1/m1	0.49 (0.09-2.71)[d]	-	31
CYP1A1 MspI	OC	106	146	m1/m2 vs. m1/m1	0.87 (0.51-1.50)	m2/m2 vs. m1/m1	1.32 (0.6-3.1)	-	32
CYP1A1 MspI	P	172	218	m1/m2 vs. m1/m1	1.2 (0.7-1.8)	m2/m2 vs. m1/m1	1.4 (0.8-2.6)	Age, sex, smoking, ethnicity, education level	33
CYP1A1 MspI	OC, P, L, O	187	139	m1/m2 vs. m1/m1	1.49 (0.86-2.60)[d]	m2/m2 vs. m1/m1	-	-	34
CYP1A1 MspI	L	88	178	m1/m2 vs. m1/m1	0.90 (0.49-1.67)[d]	m1/m2 vs. m1/m1	-	-	24
CYP1A1 MspI	OC, P, L	103	102	m2/m2+m1/m2 vs. m1/m1	0.9 (0.53-1.66)			Age, sex	35
CYP1A1 MspI	OC	72	163	m1/m2 vs. m1/m1	0.8 (0.4-1.4)	m2/m2 vs. m1/m1	3.3 (1.4-10)	-	36
CYP1A1 MspI	OC, P, L, O	210	245	m1/m2 +m2/m2 vs. m1/m1	0.80 (0.51-1.27)			Age, sex	37
CYP1B1	NS	312	300	Val/Leu vs. Val/Val	1.56 (1.08-2.25)[d]	Leu/Leu vs. Val/Val	1.90 (1.21-3.00)[d]	-	31
CYP1B1	OC, P, L	724	1,226	Val/Leu vs. Val/Val	0.86 (0.70-1.07)	Leu/Leu vs. Val/Val	0.89 (0.68-1.16)	Age, sex, smoking, alcohol	38
CYP2E1 RsaI/PstI	P	48	50	c1/c2 vs. c1/c1	0.76 (0.30-1.9)	c2/c2 vs. c1/c1	7.7 (0.87-68)	-	39
CYP2E1 RsaI/PstI	OC	41[e]	122[e]	c1/c2 vs. c1/c1	1.8 (0.9-3.8)	c2/c2 vs. c1/c1	1.8 (0.3-10.7)	-	40
CYP2E1 RsaI/PstI	P	364	320	c1/c2 vs. c1/c1	0.79 (0.44-1.4)	c2/c2 vs. c1/c1	3.2 (0.69-15)	Age, sex, smoking, alcohol	41
CYP2E1 RsaI/PstI	OC, P, L	75	200	c1/c2 vs. c1/c1	0.75 (0.29-1.94)[d]	c2/c2 vs. c1/c1	-	-	42
CYP2E1 RsaI/PstI	OC, P, L	379	175	c1/c2 vs. c1/c1	1.07 (0.50-2.30)[d]	c2/c2 vs. c1/c1	-	-	15

Table I. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
CYP2E1 RsaI/PstI	OC	92	147	c1/c2 vs. c1/c1	1.52 (0.82-2.79)	c2/c2 vs. c1/c1	0.94 (0.17-5.10)	Age, sex, smoking	17
CYP2E1 RsaI/PstI	OC, P, L	145	164	c1/c2 vs. c1/c1	1.02 (0.63-1.66)[d]	c2/c2 vs. c1/c1	1.32 (0.46-3.78))[d]	-	18
CYP2E1 RsaI/PstI	OC, P	121	172	c1/c2 vs. c1/c1	2.07 (0.81-5.31)[d]	c2/c2 vs. c1/c1	-	-	43
CYP2E1 RsaI/PstI	L	129	172	c1/c2 vs. c1/c1	1.54 (0.58-4.10)[d]	c2/c2 vs. c1/c1	-	-	43
CYP2E1 RsaI/PstI	P	217	297	c1/c2 vs. c1/c1	0.94 (0.64-1.39)	c2/c2 vs. c1/c1	2.19 (0.62-8.68)	-	44
CYP2E1 RsaI/PstI	OC	160	365	other than c1/c1 vs. c1/c1	0.51 (0.22-1.20)			Age, sex, smoking, alcohol, ethnicity, site of subject recruitment	45
CYP2E1 RsaI/PstI	NS	312	297	c1/c2 vs. c1/c1	1.58 (0.56-4.49)	c2/c2 vs. c1/c1	-	Age, sex	46
CYP2E1 RsaI/PstI	L	288	323	c1/c2 vs. c1/c1	0.55 (0.24-1.24)	c2/c2 vs. c1/c1	-	-	47
CYP2E1 RsaI/PstI	P	103	553	c1/c2+c2/c2 vs. c1/c1	1.45 (0.79-2.65)			Age, sex, smoking, betel nut consumption, wood and formaldehyde exposure, and Guangdong and other salted fish consumption during childhood	48
CYP2E1 RsaI/PstI	OC	231	212	c1/c2 vs. c1/c1	1.16 (0.64-2.11)	c2/c2 vs. c1/c1	-	-	27
CYP2E1 RsaI/PstI	OC	122	241	c1/c2 vs. c1/c1	1.26 (0.76-2.07)	c2/c2 vs. c1/c1	3.38 (1.22-9.36)	Age, sex, smoking, alcohol	28
CYP2E1 RsaI/PstI	OC, P, L	103	102	c1/c2 vs. c1/c1	2.3 (0.84-6.34)	c2/c2 vs. c1/c1	-	Age, sex	35
CYP2E1 RsaI/PstI	OC, P, L, O	210	245	c1/c2+c2/c2 vs. c1/c1	0.72 (0.33-1.63)			Age, sex	37
CYP2E1 DraI	P	48	50	DC vs. DD	1.1 (0.45-2.7)	CC vs. DD	5.0 (0.95-16)	-	39
CYP2E1 DraI	P	364	320	DC vs. DD	1.1 (0.61-1.9)	CC vs. DD	0.81 (0.20-3.3)	Age, sex, smoking, alcohol	41
CYP2E1 DraI	OC, P, L	347	121	DC vs. DD	1.04 (0.57-1.88)[d]	CC vs. DD	0.17 (0.02-1.93)[d]	-	15
CYP2E1 DraI	OC, P	121	172	DC vs. DD	1.81 (0.94-3.47)[d]	CC vs. DD	3.15 (0.28-35.17)[d]	-	43
CYP2E1 DraI	L	129	172	DC vs. DD	1.83 (0.97-3.47)[d]	CC vs. DD	1.47 (0.09-23.70)[d]	-	43
CYP2E1 DraI	OC	122	241	DC vs. DD	0.97 (0.59-1.58)	CC vs. DD	2.28 (1.06-4.91)	Age, sex, smoking, alcohol	28
CYP2E1 DraI	OC, P, L, O	210	245	DC+CC vs. DD	0.87 (0.43-1.76)			Age, sex	37
CYP2E1 -71	NS	312	299	GT vs. GG	0.49 (0.25-0.98)	TT vs. GG	-	Age, sex	46
CYP2E1 1,532	OC, P, L	724	1,226	GC vs. GG	0.73 (0.49-1.10)	CC vs. GG	1.97 (0.39-9.86)	Age, sex, smoking, alcohol	38
CYP2E1 7,632	NS	262	236	TA vs. TT	1.02 (0.56-1.84)	AA vs. TT	-	Age, sex	46
CYP2D6	OC, P, L	75	200	HM vs. EM	0.69 (0.33-1.43)[d]	PM vs. EM	1.07 (0.27-4.29)[d]	-	42
CYP2D6	OC, P, L	385	191	HM vs. EM	0.95 (0.66-1.37)[d]	PM vs. EM	1.07 (0.50-2.26)[d]	-	15
CYP2D6	OC	100	467	HM vs. EM	0.87 (0.53-1.43)[d]	PM vs. EM	3.03 (1.44-6.39)[d]	-	49
CYP2D6	NS	25	36	HM vs. EM	1.96 (0.67-5.77)[d]	PM vs. EM	-	-	50
CYP2D6	NS	56	144	HM vs. EM	1.46 (0.72-2.95)[d]	PM vs. EM	0.94 (0.09-9.31)[d]	-	51
CYP2D6	OC, P, L, O	187	139	HM vs. EM	0.78 (0.49-1.25)[d]	PM vs. EM	1.29 (0.49-3.37)[d]	-	34

Table I. Continued.

Gene ·and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
CYP2D6	OC	286[f]	135	wt/vt+vt/vt vs. wt/wt	0.84 (0.55-1.27)[d]			-	52
CYP2D6	P	74	137	wt/vt+vt/vt vs. wt/wt	2.23 (1.19-4.44)			Sex	53
CYP17	OC	137	102	CC vs. TC	1.5 (0.85-2.66)	TT vs. TC	3.56 (1.56-8.13)	-	54
GSTM1	OC, P, L	186	42	Null vs. Positive	2.37 (1.20-4.67)			-	55
GSTM1	L	269	216	Null vs. Positive	0.84 (0.59-1.21)[d]			-	56
GSTM1	OC	40	577	Null vs. Positive	1.01 (0.53-1.92)[d]			-	57
GSTM1	P, L	39	37	Null vs. Positive	4.51 (1.60-12.70)[d]			-	58
GSTM1	OC	41[e]	123[e]	Null vs. Positive	1.0 (0.5-2.0)			-	40
GSTM1	OC, P, L, O	158	474	Null vs. Positive	1.29 (0.90-1.86)[d]			-	59
GSTM1	OC	133	133	Null vs. Positive	1.0 (0.6-1.7)			Age, sex, ethnicity	14
GSTM1	L	171	180	Null vs. Positive	0.7 (0.5-1.1)			-	60
GSTM1	L	129	172	Null vs. Positive	1.6 (1.0-2.8)			Age, sex, smoking, alcohol	61
GSTM1	OC, P, L	75	200	Null vs. Positive	1.34 (0.78-2.29))[d]			-	42
GSTM1	OC, P, L, O	185	207	Null vs. Positive	0.97 (0.65-1.44))[d]			-	16
GSTM1	OC, P	122	178	Null vs. Positive	1.2 (0.8-2.0)			Age, sex	15
GSTM1	L	264	178	Null vs. Positive	1.0 (0.7-1.5)			Age, sex	15
GSTM1	L	160	158	Null vs. Positive	1.9 (1.18-3.05)			-	62
GSTM1	OC, P	121	172	Null vs. Positive	0.9 (0.5-1.5)			Age, sex, smoking, alcohol	63
GSTM1	OC	100	100	Null vs. Positive	1.04 (0.59-1.83))[d]			-	29
GSTM1	NS	162	315	Null vs. Positive	1.50 (1.01-2.23)			Age, sex, smoking, alcohol, ethnicity	64
GSTM1	P	83	142	Null vs. Positive	1.9 (1.0-3.3)			Age, sex, smoking	65
GSTM1	OC	142	142	Null vs. Positive	2.2 (1.4-3.6)			-	30
GSTM1	OC	92	147	Null vs. Positive	1.81 (1.00-3.28)			Age, sex, smoking	17
GSTM1	OC, P, L	145	164	Null vs. Positive	0.94 (0.60-1.46))[d]			-	18
GSTM1	OC, P, L, O	147	129	Null vs. Positive	0.99 (0.62-1.59)			-	21
GSTM1	OC, P, L	172	193	Null vs. Positive	1.1 (0.7-1.7)			Age, sex, ethnicity	20
GSTM1	OC	114	33	Null vs. Positive	2.5 (1.1-5.4)			-	66
GSTM1	OC	101	212	Null vs. Positive	1.4 (0.68-2.8)			-	67
GSTM1	OC	63	132	Null vs. Positive	3.1 (1.1-8.5)			-	67
GSTM1	L	82[e]	63[e]	Null vs. Positive	3.53 (1.27-9.83)			Age, smoking	68
GSTM1	OC, P, L	151	264	Null vs. Positive	0.99 (0.64-1.5)			Age, smoking	69
GSTM1	OC	98	60	Null vs. Positive	1.34 (0.37-4.82)			-	22
GSTM1	NS	312	300	Null vs. Positive	1.03 (0.71-1.49)			Age, sex	31
GSTM1	L	20	20	Null vs. Positive	4.00 (0.98-16.27))[d]			-	70
GSTM1	OC	53	53	Null vs. Positive	3.0 (1.4-6.7)			-	71
GSTM1	OC	297	450	Null vs. Positive	3.2 (2.4-4.3)			Age	72
GSTM1	OC	286[f]	135	Null vs. Positive	1.43 (0.91-2.25)			-	52
GSTM1	L	204	203	Null vs. Positive	0.94 (0.61-1.47)			Age, sex, smoking	73
GSTM1	OC	94	92	Null vs. Positive	1.29 (0.72-2.31)[d]			-	23
GSTM1	P	314	337	Null vs. Positive	0.8 (0.6-1.1)			Age, sex, smoking, ethnicity, education level	33
GSTM1	L	36	35	Null vs. Positive	2.70 (1.02-7.14)[d]			-	74

Table I. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
GSTM1	OC, P, L, O	187	139	Null vs. Positive	0.78 (0.50-1.21)[d]			-	34
GSTM1	L	245	251	Null vs. Positive	0.94 (0.62-1.42)			Smoking, alcohol	75
GSTM1	L	42	47	Null vs. Positive	1.76 (0.74-4.17)			-	76
GSTM1	OC	256	259	Null vs. Positive	1.05 (0.7-1.5)			Age, sex, smoking	77
GSTM1	OC, P, L	282	208	Null vs. Positive	1.0 (0.7-1.5)			-	25
GSTM1	OC, P, L	149	180	Null vs. Positive	0.88 (0.50-1.5)			Age, sex, ethnicity	78
GSTM1	OC	70	82	Null vs. Positive	2.01 (1.04-3.88)			-	79
GSTM1	OC	132	143	Null vs. Positive	0.6 (0.3-1.0)			Age, sex, alcohol, raw vegetable and fruit intake	26
GSTM1	OC	310	348	Null vs. Positive	1.00 (0.72-1.38)[d]			-	80
GSTM1	L	292	321	Null vs. Positive	0.88 (0.64-1.21)			-	47
GSTM1	P	78	145	Null vs. Positive	1.7 (0.9-3.0)			-	81
GSTM1	OC	122	241	Null vs. Positive	0.87 (0.55-1.37)			Age, sex, smoking, alcohol	28
GSTM1	OC, P, L	103	102	Null vs. Positive	2.2 (1.24-3.79)			Age, sex	35
GSTM1	P, L, O	185	207	Null vs. Positive	0.96 (0.65-1.43)			-	82
GSTM1	OC	40	87	Null vs. Positive	2.2 (0.9-5.1)			-	83
GSTM1	OC, P, L	690	749	Null vs. Positive	1.29 (1.03-1.62)			Age, sex, smoking, alcohol, ethnicity	84
GSTM1	L	110[e]	197[e]	Null vs. Positive	1.78 (1.11-2.87)			-	85
GSTM1	OC, P, L	100	100	Null vs. Positive	3.35 (1.69-6.67)			Age, sex, smoking, alcohol	86
GSTM1	OC, P, L, O	210	245	Null vs. Positive	1.07 (0.75-1.56)			Age, sex	37
GSTM1	OC	72	221	Null vs. Positive	0.7 (0.4-1.3)			-	36
GSTM3	L	269	216	AB vs. AA	0.79 (0.52-1.20)[d]	BB vs AA	0.20 (0.07-0.63)[d]	-	56
GSTM3	OC, P, L	386	170	AB vs. AA	0.63 (0.42-0.95)[d]	BB vs AA	0.49 (0.18-1.35)[d]	-	15
GSTM3	L	129	172	AB vs. AA	1.79 (1.08-2.97)[d]	BB vs AA	1.28 (0.33-4.92)[d]	-	87
GSTM3	OC, P	121	172	AB vs. AA	0.98 (0.57-1.69)	BB vs AA	1.28 (0.33-4.93)	Age, sex, smoking, alcohol	63
GSTM3	OC	99	210	AB vs. AA	1.06 (0..64-1.74)[d]	BB vs AA	1.28 (0.33-4.94)[d]	-	67
GSTM3	OC	63	132	AB vs. AA	0.66 (0.26-1.63)[d]	BB vs AA	1.28 (0.33-4.95)[d]	-	67
GSTM3	OC	297	450	AB vs. AA	1.07 (0.7-1.8)	BB vs AA	1.28 (0.33-4.96)	Age	72
GSTM3	L	202	202	AB vs. AA	0.80 (0.49-1.31)	BB vs AA	1.28 (0.33-4.97)	Age, sex, smoking	73
GSTM3	OC	256	259	AB+BB vs. AA	0.7 (0.5-1.1)			Age, sex, smoking	77
GSTM3	OC	310	348	AB+BB vs. AA	0.71 (0.48-1.05)[d]			-	80
GSTM3	OC	231	212	AB vs. AA	1.37 (0.90-2.09)	BB vs AA	0.88 (0.47-1.66)	-	27
GSTP1 codon 105	OC, P	120	180	Ile/Val vs. Ile/Ile	2.04 (1.24-3.37)[d]	Val/Val vs. Ile/Ile	1.34 (0.63-2.87)[d]	-	88
GSTP1 codon 105	L	260	180	Ile/Val vs. Ile/Ile	1.30 (0.87-1.96)[d]	Val/Val vs. Ile/Ile	0.86 (0.46-1.61)[d]	-	88
GSTP1 codon 105	L	129	172	Ile/Val vs. Ile/Ile	1.13 (0.69-1.84))[d]	Val/Val vs. Ile/Ile	0.95 (0.45-1.97)[d]	-	87
GSTP1 codon 105	OC, P	121	172	Ile/Val vs. Ile/Ile	1.45 (0.88-2.40)[d]	Val/Val vs. Ile/Ile	1.33 (0.65-2.74)[d]	-	63
GSTP1 codon 105	OC, P, L	145	164	Ile/Val vs. Ile/Ile	0.67 (0.40-1.13)[d]	Val/Val vs. Ile/Ile	1.33 (0.65-2.75)[d]	-	18
GSTP1 codon 105	OC	157	260	Ile/Val vs. Ile/Ile	0.79 (0.47-1.3)	Val/Val vs. Ile/Ile	1.33 (0.65-2.76)	Smoking, alcohol, ethnicity	89
GSTP1 codon 105	OC	83	22	Ile/Val+Val/Val vs. Ile/Ile	1.93 (1.05-3.58)			Age, sex	90
GSTP1 codon 105	OC, P, L, O	146	124	Ile/Val vs. Ile/Ile	1.38 (0.83-2.30)[d]	Val/Val vs. Ile/Ile	0.84 (0.37-1.91)[d]	-	21

Table I. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
GSTP1 codon 105	OC, P, L	172	193	Ile/Val vs. Ile/Ile	1.4 (0.9-2.2)	Val/Val vs. Ile/Ile	0.6 (0.2-1.5)	Age, sex, ethnicity	20
GSTP1 codon 105	OC, P, L	151	264	Ile/Val vs. Ile/Ile	0.67 (0.43-1.02)[d]	Val/Val vs. Ile/Ile	1.07 (0.52-2.19)[d]	-	69
GSTP1 codon 105	NS	312	300	Ile/Val vs. Ile/Ile	0.79 (0.58-1.11)[d]	Val/Val vs. Ile/Ile	1.26 (0.76-2.10)[d]	-	31
GSTP1 codon 105	L	204	201	Ile/Val vs. Ile/Ile	1.17 (0.73-1.88)	Val/Val vs. Ile/Ile	0.78 (0.37-1.63)	Age, sex, smoking	73
GSTP1 codon 105	OC, P, L	87	51	Ile/Val vs. Ile/Ile	1.52 (0.72-3.24)[d]	Val/Val vs. Ile/Ile	1.34 (0.47-3.83)[d]	-	91
GSTP1 codon 105	P	137	99	Ile/Val vs. Ile/Ile	0.97 (0.54-1.75)[d]	Val/Val vs. Ile/Ile	1.03 (0.38-2.74)[d]	-	92
GSTP1 codon 105	P	264	323	Ile/Val vs. Ile/Ile	1.0 (0.6-1.4)	Val/Val vs. Ile/Ile	0.7 (0.2-2.3)	Age, sex, smoking, ethnicity, education level	33
GSTP1 codon 105	OC, P, L	235	285	Ile/Val vs. Ile/Ile	0.80 (0.55-1.16)[d]	Val/Val vs. Ile/Ile	0.80 (0.47-1.38)[d]	-	93
GSTP1 codon 105	OC, P, L	282	208	Ile/Val vs. Ile/Ile	1.22 (0.84-1.79)[d]	Val/Val vs. Ile/Ile	0.89 (0.48-1.63)[d]	-	25
GSTP1 codon 105	OC	256	259	Ile/Val+Val/Val vs. Ile/Ile	1.43 (1.01-2.02)[d]			Age, sex, smoking	77
GSTP1 codon 105	OC	310	348	Ile/Val+Val/Val vs. Ile/Ile	0.80 (0.59-1.09)[d]			-	80
GSTP1 codon 105	P, L, O	185	207	Ile/Val+Val/Val vs. Ile/Ile	1.01 (0.70-1.45)			-	82
GSTP1 codon 105	OC, P, L	294	333	Ile/Val vs. Ile/Ile	0.80 (0.57-1.12)[d]	Val/Val vs. Ile/Ile	0.73 (0.27-1.97)[d]	-	94
GSTP1 codon 105	OC, P, L	690	748	Ile/Val+Val/Val vs. Ile/Ile	1.04 (0.83-1.31)			Age, sex, smoking, alcohol, ethnicity	84
GSTP1 codon 114	OC	256	259	Ala/Val+Val/Val vs. Ala/Ala	1.2 (0.4-4.0)			Age, sex, smoking	77
GSTT1	OC, P, L	127	42	Null vs. Positive	1.47 (0.71-3.02)			-	55
GSTT1	O	34	509	Null vs. Positive	0.59 (0.20-1.71)[d]			-	57
GSTT1	L	269	216	Null vs. Positive	1.77 (1.08-2.89)[d]			-	56
GSTT1	OC	41[e]	123[e]	Null vs. Positive	1.2 (0.6-2.5)			-	40
GSTT1	L	129	172	Null vs. Positive	1.4 (0.7-2.9)			Age, sex, smoking, alcohol	61
GSTT1	L	171	180	Null vs. Positive	0.8 (0.5-1.3)			-	60
GSTT1	OC, P, L, O	185	207	Null vs. Positive	0.95 (0.58-1.56)[d]			-	16
GSTT1	OC, P	119	203	Null vs. Positive	1.5 (0.9-2.5)			Age, sex	15
GSTT1	L	263	203	Null vs. Positive	0.9 (0.5-1.4)			Age, sex	15
GSTT1	OC, P	121	172	Null vs. Positive	2.0 (1.0-4.0)			Age, sex, smoking, alcohol	63
GSTT1	NS	162	315	Null vs. Positive	2.27 (1.43-3.60)			Age, sex, smoking, alcohol, ethnicity	64
GSTT1	OC	92	147	Null vs. Positive	0.68 (0.38-1.22)			Age, sex, smoking	17
GSTT1	OC, P, L, O	142	109	Null vs. Positive	0.91 (0.47-1.74)			-	21
GSTT1	OC, P, L	172	193	Null vs. Positive	1.2 (0.7-2.3)			Age, sex, ethnicity	20
GSTT1	OC, P, L, O	46	44	Null vs. Positive	5.00 (1.66-15.1)			Smoking, alcohol	95
GSTT1	L	82[e]	63[e]	Null vs. Positive	1.83 (0.70-4.79)			Age, smoking	68
GSTT1	OC	98	60	Null vs. Positive	2.48 (0.28-21.71)			-	22
GSTT1	NS	312	300	Null vs. Positive	1.00 (0.64-1.60)			Age, sex	31
GSTT1	L	20	20	Null vs. Positive	0.71 (0.14-3.66)[d]			-	70
GSTT1	OC, P, L	151	264	Null vs. Positive	0.98 (0.6-1.7)			Age, smoking	69

Table I. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
GSTT1	OC	53	53	Null vs. Positive	0.6 (0.3-1.3)			-	71
GSTT1	OC	297	450	Null vs. Positive	1.6 (1.04-2.6)			Age	72
GSTT1	L	204	203	Null vs. Positive	0.61 (0.35-1.06)			Age, sex, smoking	73
GSTT1	OC, P, L, O	187	139	Null vs. Positive	1.07 (0.59-1.97)[d]			-	34
GSTT1	P	316	336	Null vs. Positive	1.0 (0.8-1.4)			Age, sex, smoking, ethnicity, education level	33
GSTT1	L	245	251	Null vs. Positive	1.34 (0.74-2.42)			Smoking, alcohol	75
GSTT1	L	42	47	Null vs. Positive	2.52 (1.0-6.4)			-	76
GSTT1	OC	256	259	Null vs. Positive	1.4 (0.9-2.4)			Age, sex, smoking	77
GSTT1	OC, P, L	283	208	Null vs. Positive	0.6 (0.4-0.9)			-	25
GSTT1	OC, P, L	149	180	Null vs. Positive	1.2 (0.55-2.5)			Age, sex, ethnicity	78
GSTT1	OC	132	143	Null vs. Positive	1.0 (0.5-1.9)			Age, sex, alcohol, raw vegetable and fruit intake	26
GSTT1	OC	310	348	Null vs. Positive	1.15 (0.76-1.74)4			-	80
GSTT1	OC	87	81	Null vs. Positive	7.20 (3.50-14.84)			-	96
GSTT1	L	290	316	Null vs. Positive	0.96 (0.64-1.44)			-	47
GSTT1	OC	122	241	Null vs. Positive	0.78 (0.49-1.23)			Age, sex, smoking, alcohol	28
GSTT1	OC, P, L	103	102	Null vs. Positive	1.5 (0.76-2.95)			Age, sex	35
GSTT1	P, L, O	185	207	Null vs. Positive	0.95 (0.57-1.56)			-	82
GSTT1	OC	40	87	Null vs. Positive	4.2 (1.6-10.9)			-	83
GSTT1	OC, P, L	690	750	Null vs. Positive	0.78 (0.59-1.04)			Age, sex, smoking, alcohol, ethnicity	84
GSTT1	L	110[e]	197[e]	Null vs. Positive	2.29 (1.31-4.01)			-	85
GSTT1	OC, P, L	100	100	Null vs. Positive	1.20 (0.64-2.26)			Age, sex, smoking, alcohol	86
GSTT1	OC, P, L, O	210	245	Null vs. Positive	0.97 (0.63-1.51)			Age, sex	37
NAT1	OC	62	122	Int. vs. wt/wt	3.7 (1.60-8.46)	Rapid vs. wt/wt	3.3 (1.31-8.56)	-	97
NAT1	OC, P	121	172	Rapid+Int. vs. wt/wt+Slow	0.8 (0.5-1.4)			Age, sex, smoking, alcohol	98
NAT1	L	129	172	Rapid+Int. vs. wt/wt+Slow	1.0 (0.6-1.7)			Age, sex, smoking, alcohol	98
NAT1	OC, P	143	300	Rapid+Int. vs. wt/wt+Slow	0.94 (0.61-1.45)[d]			-	99
NAT1	L	148	300	Rapid+Int. vs. wt/wt+Slow	1.22 (0.81-1.85)[d]			-	99
NAT1	L	88	172	Rapid+Int. vs. wt/wt	1.37 (0.79-2.39)			-	100
NAT2	OC	62	122	Int. vs. Rapid	1.3 (0.66-2.4)	Slow vs. Rapid	2.3 (0.8-7.2)	-	97
NAT2	OC, P, L	75	200			Slow vs. Rapid	2.63 (1.45-4.76)4	-	42
NAT2	OC, P	121	172	Slow vs. Rapid+Int.	1.7 (1.0-3.0)			Age, sex, smoking, alcohol	98
NAT2	L	129	172	Slow vs. Rapid+Int.	0.9 (0.5-1.6)			Age, sex, smoking, alcohol	98
NAT2	OC, P, L	145	164	Int. vs. Rapid	1.69 (1.04-2.75)[d]	Slow vs. Rapid	1.53 (0.73-3.19)4	-	18
NAT2	OC	341	552	Int. vs. Rapid	1.1 (0.6-2.0)	Slow vs. Rapid	1.2 (0.7-2.2)	Age, ethnicity	101
NAT2	L	88	172			Slow vs. Rapid	1.45 (0.84-2.51)	-	100

Table I. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
NAT2	OC	94	92	Int. vs. Rapid	1.78 (0.39-8.09)[d]	Slow vs. Rapid	1.73 (0.39-7.56)[d]	-	23
NAT2	P	279	325			Slow vs. Rapid	1.3 (0.8-2.0)	Age, sex, smoking, ethnicity, education level	33
NAT2	OC	231	212	4/11 vs. 11/11	0.79 (0.44-1.43)	4/4 vs. 11/11	1.95 (1.05-3.60)	-	27
NAT2	OC, P, L, O	210	245	Slow vs. Rapid+ Int	.0.98 (0.67-1.45)			Age, sex	37
*NAT2**14	L	45	104	wt/vt vs. wt/wt	0.68 (0.19-2.39)	vt/vt vs. wt/wt	13.87 (0.60-318.0)	-	102
*NAT2**5	L	45	104	wt/vt vs. wt/wt	0.71 (0.17-3.01)	vt/vt vs. wt/wt	7.34 (1.51-36.01)	-	102
*NAT2**6	L	45	104	wt/vt vs. wt/wt	3.85 (1.17-12.69)	vt/vt vs. wt/wt	38.31 (8.01-182.3)	-	102
*NAT2**7	L	45	104	wt/vt vs. wt/wt	0.20 (0.05-0.76)	vt/vt vs. wt/wt	4.45 (0.78-25.33)	-	102
EPHX1 codon 113	OC, P	121	172	Tyr/His vs. Tyr/Tyr	0.4 (0.2-0.7)	His/His vs. Tyr/Tyr	0.8 (0.4-1.8)	Age, sex, smoking, alcohol	103
EPHX1 codon 113	L	129	172	Tyr/His vs. Tyr/Tyr	0.4 (0.2-0.7)	His/His vs. Tyr/Tyr	0.5 (0.2-1.1)	Age, sex, smoking, alcohol	103
EPHX1 codon 113	P	137	99	Tyr/His vs. Tyr/Tyr	0.46 (0.24-0.86)[d]	His/His vs. Tyr/Tyr	0.19 (0.09-0.42)[d]	-	92
EPHX1 codon 113	L	204	203	Tyr/His vs. Tyr/Tyr	0.64 (0.41-1.02)	His/His vs. Tyr/Tyr	0.60 (0.24-1.47)	Age, sex, smoking	73
EPHX1 codon 113	OC, P, L	280	289	Tyr/His vs. Tyr/Tyr	0.83 (0.56-1.23)	His/His vs. Tyr/Tyr	0.89 (0.45-1.75)	Age, sex	104
EPHX1 codon 113	OC, L	142	213	Tyr/His+Tyr/Tyr vs. His/His	2.1 (1.0-4.0)			Age, sex, smoking, alcohol, region of subject recruitment	105
EPHX1 codon 113	OC, L	81	122	Tyr/His+Tyr/Tyr vs. His/His	2.4 (0.5-12.2)			Age, sex, smoking, alcohol, region of subject recruitment	105
EPHX1 codon 113	OC, P, L, O	210	245	Tyr/His vs. Tyr/Tyr	1.06 (0.70-1.60)	His/His vs. Tyr/Tyr	1.52 (0.86-2.69)	Age, sex	37
EPHX1 codon 139	OC, P	121	172	His/Arg vs. His/His	1.17 (0.70-1.95)[d]	Arg/Arg vs. His/His	2.27 (0.37-13.88)[d]	-	103
EPHX1 codon 139	L	129	172	His/Arg vs. His/His	1.21 (0.73-1.99)[d]	Arg/Arg vs. His/His	2.88 (0.52-16.09)[d]	-	103
EPHX1 codon 139	P	137	99	His/Arg vs. His/His	0.95 (0.50-1.81)[d]	Arg/Arg vs. His/His	1.47 (0.48-4.50)[d]	-	92
EPHX1 codon 139	L	204	203	His/Arg vs. His/His	0.95 (0.58-1.55)	Arg/Arg vs. His/His	0.27 (0.05-1.43)	Age, sex, smoking	73
EPHX1 codon 139	OC, P, L	280	289	His/Arg vs. His/His	0.75 (0.51-1.12)	Arg/Arg vs. His/His	1.38 (0.50-3.80)	Age, sex	104
EPHX1 codon 139	OC, L	142	213	His/Arg+Arg/ Arg vs. His/His	1.3 (0.8-2.2)			Age, sex, smoking, alcohol, region of subject recruitment	105
EPHX1 codon 139	OC, L	81	122	His/Arg+Arg/ Arg vs. His/His	1.3 (0.6-2.7)			Age, sex, smoking, alcohol, region of subject recruitment	105
EPHX1 codon 139	OC, P, L, O	210	245	His/Arg vs. His/His	0.69 (0.46-1.03)	Arg/Arg vs. His/His	1.21 (0.40-3.72)	Age, sex	37

Table I. Continued.

Gene ·and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
NQO1 465	OC, P, L, O	350	364	CT vs. CC	1.10 (0.60-2.05)	TT vs. CC	-	Age, sex	106
NQO1 465	OC, P, L	294	333	CT vs. CC	0.64 (0.29-1.43)[d]	TT vs. CC	-	-	94
NQO1 609	OC, P, L	724	1.226	CT vs. CC	0.89 (0.73-1.09)	TT vs. CC	1.56 (0.94-2.59)	Age, sex, smoking, alcohol	38
NQO1 609	OC, P, L, O	350	366	CT vs. CC	0.89 (0.64-1.23)	TT vs. CC	1.01 (0.43-2.36)	Age, sex	106
UGT1A10 codon 139	OC, L	113	115	Glu/Lys vs. Glu/Glu	0.20 (0.05-0.87)			Age, sex, smoking, alcohol	108
UGT1A10 codon 244	OC, L	115	111	Leu/Ile vs. Leu/Leu	0.94 (0.26-3.4)			Age, sex, smoking, alcohol	108
UGT1A7	OC, L	194	388	Int. vs. High	1.5 (0.78-2.7)	Low vs. High	3.7 (1.7-8.7)	Age, sex, smoking, alcohol, ethnicity, region of subject recruitment	109
SULT1A1	OC, P, L, O	123	247	Arg/His vs. Arg/Arg	1.26 (0.73-2.19)	His/His vs. Arg/Arg	3.60 (1.01-12.88)	Smoking, alcohol, fruits, vegetables, physical activity	110

[a]OC, oral cavity; P, pharynx; L, larynx; O, other; NS, not specified. [b]Int,, intermediate; wt, wild-type; vt, variant-type. [c]OR, odds ratio; 95% CI, 95% confidence interval. [d]OR and 95% CI were calculated from the genotype distribution. [e]Male. [f]Including premalignancies.

111,114-116) of 9 (67%) studies (43,58,111-116), ADH3*1/*1 homozygotes showed increased risk for HNC.

DNA repair genes (Table III). A wide variety of DNA damage may be induced by normal endogenous metabolic processes or by environmental carcinogens. If not repaired, such damage can lead to gene mutations and genomic instability, which in turn may cause malignant transformation of cells. Normal function of DNA repair enzymes is essential for removal of damage. It has been shown that reduced DNA repair capacity is associated with increased risk of cancer. Genetic polymorphisms in DNA repair genes that contribute to variations in DNA repair capacity may be related to risk of developing cancers, including esophageal cancer.

XRCC1. XRCC1, which is encoded by *X-ray repair cross complementary 1 (XRCC1)*, is involved in the core processes of single-strand break repair and base excision repair (254,255). Mutant hamster ovary cell lines that lack XRCC1 are hypersensitive to ionizing radiation, hydrogen peroxide and alkylating agents, which leads to a 10-fold increase in the frequency of spontaneous chromosome aberrations and deletions. Polymorphisms in *XRCC1*, including Arg194Trp, Arg280His and Arg399Gln, have been described. Although the biochemical and biologic characteristics of the variants have not been determined, it has been reported that individuals with the *XRCC1* 399Gln variant show increased sister chromatid exchange after treatment with a tobacco-specific carcinogen, NNK (256).

Four (57%) ORs (133,134,136,137) from 7 studies (80,133-138) of the Trp/Trp genotype vs. the Arg/Arg genotype at codon 194 were >1, whereas the remaining 3 (43%) (80,135,138) were not. Two (50%) ORs (80,136) from 4 studies (80,136,138,139) of the His/His genotype vs. the Arg/Arg genotype at codon 280 were >1, whereas the remaining 2 (50%) (135,139) were not. Six (55%) ORs (24,80,133,135,136,139) from 11 studies (24,80,131-140) of the Gln/Gln genotype vs. the Arg/Arg genotype at codon 399 were >1, whereas the remaining 5 (45%) (132,134,137, 138,140) were not. The results for the relations between *XRCC1* polymorphisms and HNC were inconsistent.

XPD. XPD, xeroderma pigmentosum complementary group D, is an evolutionarily conserved ATP-dependent helicase involved in the nucleotide excision repair pathway. XPD has 2 functions: nucleotide excision repair and basal transcription as part of the transcription factor complex, TFIIH (257). Polymorphisms, such as 22,541AC and 35,931CA, have been identified. Individuals homozygous for the variant genotype of *XPD* have suboptimal DNA repair capacity (258).

All 4 studies (137,138,142,145) of the genotype at nucleotide 22,541 of *XPD* and risk for HNC showed a decreased risk in AA homozygotes compared with CC homozygotes. Five (136,138,140,142,145) of 6 (83%) studies (136-138,140, 142,145) of the genotype at nucleotide 35,931 and HNC risk showed an increased risk in CC homozygotes ccompared with AA homozygotes.

Table II. Studies on polymorphisms of alcohol metabolic enzymes and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
ADH3	P, L	39[d,e]	37[d,e]	*2/*1 vs. *2/*2	0.26 (0.06-1.20)[c]	*1/*1 vs. *2/*2	1.36 (0.26-6.96)[c]	-	58
ADH3	OC	137	146	*2/*1 vs. *2/*2	0.91 (0.43-1.90)[c]	*1/*1 vs. *2/*2	1.39 (0.66-2.90)[c]	-	111
ADH3	OC, P	119	167	*2/*1 vs. *2/*2	0.7 (0.4-1.4)	*1/*1 vs. *2/*2	1.1 (0.6-2.2)	Age, sex, smoking, alcohol	43
ADH3	L	125	167	*2/*1 vs. *2/*2	1.0 (0.5-1.8)	*1/*1 vs. *2/*2	0.7 (0.4-1.4)	Age, sex, smoking, alcohol	43
ADH3	OC, P, L	173	194	*2/*1 vs. *2/*2	0.8 (0.4-1.7)	*1/*1 vs. *2/*2	0.9 (0.4-1.9)	Age, sex, ethnicity	112
ADH3	OC, P	229	575	*2/*1 vs. *2/*2	0.80 (0.53-1.21)[c]	*1/*1 vs. *2/*2	0.82 (0.52-1.29[c]	-	113
ADH3	OC	333	541	*2/*1 vs. *2/*2	1.3 (0.9-1.9)	*1/*1 vs. *2/*2	1.1 (0.7-1.6)	Age, sex, ethnicity	114
ADH3	OC	93	99			*1/*1 vs. *2/*2	1.1 (0.4-3.3)	Sex, smoking, alcohol, referring hospital	115
ADH3	OC, P, L	141	94	*2/*1 vs. *2/*2	1.11 (0.42-2.93)[c]	*1/*1 vs. *2/*2	1.25 (0.48-3.26)[c]	-	116
ALDH2	OC, P, L	34[d,e]	487[d,e]	*1/*2 vs. *1/*1	11.14 (5.09-24.36)	*2/*2 vs. *1/*1	-	Smoking, alcohol, age at admission	117
ALDH2	OC	92	147	*1/*2 vs. *1/*1	1.18 (0.65-2.13)	*2/*2 vs. *1/*1	1.35 (0.57-2.17)	Age, sex, alcohol	17
ALDH2	OC	114	33	*1/*2 vs. *1/*1	2.9 (1.1-7.8)	*2/*2 vs. *1/*1	-	-	66
ALDH2	OC, P, L	33[d,e]	526[d,e]	*1/*2 vs. *1/*1	18.52 (7.72-44.44)	*2/*2 vs. *1/*1	-	-	118
ALDH2	OC, P, L, O	192	192	*1/*2 vs. *1/*1	1.18 (0.78-1.79)[c]	*2/*2 vs. *1/*1	0.58 (0.19-1.79)[c]	-	119
ALDH2	OC, P	192	642	*1/*2 vs. *1/*1	1.55 (1.11-2.14)[c]	*2/*2 vs. *1/*1	-	-	120
ADH1C	L	245	251	*1/*2+*2/*2 vs. *1/*1	0.94 (0.62-1.43)			Smoking, alcohol	75
ADH1C	OC, P, L	87[f]	1036	*1/*2 vs. *1/*1	0.52 (0.27-1.04)[c]	*2/*2 vs. *1/*1	0.27 (0.10-0.71)[c]	-	121
ADH1C	OC, P, L, O	521	599	*1/*2 vs. *1/*1	1.1 (0.9-1.4)	*2/*2 vs. *1/*1	1.2 (0.9-1.8)	Age, sex, ethnicity	122
ADH1C	OC, P, L	84	525	*1/*2 vs. *1/*1	0.52 (0.31-0.88)[c]	*2/*2 vs. *1/*1	0.32 (0.15-0.66)[c]	-	123
ADH1C	OC, P	192	642	*1/*2 vs. *1/*1	2.09 (1.31-3.34)[c]	*2/*2 vs. *1/*1	-	-	120
ADH1B	L	245	251	*1/*2 vs. *1/*1	0.86 (0.41-1.82)	*2*/2 vs. *1/*1	-	Smoking, alcohol	75
ADH1B	OC, P	192	642	*1/*2 vs. *1/*1	0.20 (0.12-0.36)[c]	*2*/2 vs. *1/*1	0.21 (0.12-0.35)[c]	-	120
ADH2	OC, P, L	33[d,e]	526[d,e]	*1/*1 vs. *1/*2 +*2/*2	6.67 (2.78-16.7)			-	118

[a]OC, oral cavity; P, pharynx; L, larynx; O, other, [b]OR, odds ratio; 95% CI, 95% confidence interval. [c]OR and 95% CI were calculated from the genotype distribution. [d]Male. [e]Alcoholic. [f]Heavy drinker.

Cell-cycle control genes (Table IV)

p53. The *p53* tumor suppressor gene is frequently mutated in various human cancers including HNC (259-262). A G-to-C polymorphism in codon 72 of exon 4 results in an Arg-to-Pro substitution. Although both variants are morphologically wild-type, the Pro/Pro genotype is less effective in suppressing cellular transformation (263). Individuals with the Pro/Pro genotype showed a higher risk for HNC than individuals with the Arg/Arg genotype in 15 (153,154,156-159,161-167,169,170) of 20 (75%) studies (21,153-171). Two (10%) studies (169,170) showed a significantly higher risk for HNC in Pro/Pro homozygotes than in Arg/Arg homozygotes. These results suggest that the *p53* codon 72 polymorphism may play a role in susceptibility to HNC.

Cyclin D1. Cyclin D1 plays an important role in the multi-stage development of HNC (264). *Cyclin D1* mRNA is alternatively spliced to produce 2 transcripts, and the splicing pattern may be modulated by a common G870A polymorphism within the splice donor site in exon 4. This polymorphism increases the frequency of alternative splicing, leading to an altered protein. Six (67%) ORs (173-177, 179) from 9 studies (172-180) of the GA genotype vs. the GG genotype at nucleotide position 870 were <1, and 7 (78%) ORs (173-179) for the AA genotype vs. GG were <1. These results suggest that the A allele may be associated with decreased risk for HNC.

Others (Table V-IX). Relations between polymorphisms in other genes, such as folate metabolic and extracellular degra-

Table III. Studies on polymorphisms of DNA repair genes and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
XRCC1 codon 194	OC, P, L	98	161	Arg/Trp vs. Arg/Arg	1.3 (0.6-2.9)	Trp/Trp vs. Arg/Arg	-	Age, sex	132
XRCC1 codon 194	L	88	178	Arg/Trp vs. Arg/Arg	0.89 (0.37-2.13)[c]	Trp/Trp vs. Arg/Arg	-	-	24
XRCC1 codon 194	OC, P, L	120	145	Arg/Trp vs. Arg/Arg	2.46 (1.41-4.29)	Trp/Trp vs. Arg/Arg	2.21 (1.34-3.49)	Age, smoking, alcohol	133
XRCC1 codon 194	NS	95	98	Arg/Trp vs. Arg/Arg	1.97 (0.79-4.96)	Trp/Trp vs. Arg/Arg	1.69 (0.28-10.39)	-	134
XRCC1 codon 194	OC	310	348	Arg/Trp vs. Arg/Arg	1.16 (0.78-1.74)[c]	Trp/Trp vs. Arg/Arg	0.57 (0.14-2.31)[c]	-	80
XRCC1 codon 194	P	417	495	Arg/Trp vs. Arg/Arg	0.79 (0.60-1.05)	Trp/Trp vs. Arg/Arg	0.48 (0.27-0.86)	Age, sex, smoking	135
XRCC1 codon 194	OC	110	110	Arg/Trp vs. Arg/Arg	2.65 (1.40-5.04)	Trp/Trp vs. Arg/Arg	9.5 (1.14-79.47)	Age, sex, smoking, alcohol, betel quid chewing	136
XRCC1 codon 194	OC	106	164	Arg/Trp vs. Arg/Arg	2.26 (1.20-4.28)	Trp/Trp vs. Arg/Arg	1.97 (0.86-4.51)	betel quid chewing	137
XRCC1 codon 194	OC	309	387	Arg/Trp vs. Arg/Arg	0.9 (0.9-1.0)	Trp/Trp vs. Arg/Arg	0.9 (0.9-1.0)	Age, sex, smoking	138
XRCC1 codon 280	P	332	283	Arg/His vs. Arg/Arg	0.64 (0.43-0.97)	His/His vs. Arg/Arg	0.66 (0.09-4.7)	Age, sex, ethnicity	139
XRCC1 codon 280	OC, P, L	135	168	Arg/His vs. Arg/Arg	0.95 (0.50-1.83)	His/His vs. Arg/Arg	-	Age, smoking, alcohol	133
XRCC1 codon 280	OC	310	348	Arg/His vs. Arg/Arg	1.13 (0.79-1.61)[c]	His/His vs. Arg/Arg	1.16 (0.23-5.79)[c]	-	80
XRCC1 codon 280	OC	110	110	Arg/His vs. Arg/Arg	1.29 (0.70-2.36)	His/His vs. Arg/Arg	2.16 (0.92-24.4)	Age, sex, smoking, alcohol, betel quid chewing	136
XRCC1 codon 280	OC	307	387	Arg/His vs. Arg/Arg	1.0 (0.9-1.0)	His/His vs. Arg/Arg	1.0 (0.9-1.0)	Age, sex, smoking	138
XRCC1 codon 399	OC, P, L	98	161	Arg/Gln vs. Arg/Arg	0.8 (0.4-1.1)	Gln/Gln vs. Arg/Arg	0.1 (0.04-0.6)	Age, sex	132
XRCC1 codon 399	P	334	282	Arg/Gln vs. Arg/Arg	1.0 (0.74-1.5)	Gln/Gln vs. Arg/Arg	1.3 (0.72-2.4)	Age, sex, ethnicity	139
XRCC1 codon 399	L	88	178	Arg/Gln vs. Arg/Arg	1.08 (0.63-1.86)[c]	Gln/Gln vs. Arg/Arg	1.32 (0.57-3.08)[c]	-	24
XRCC1 codon 399	OC, P, L	129	157	Arg/Gln vs. Arg/Arg	0.84 (0.50-1.41)	Gln/Gln vs. Arg/Arg	1.22 (0.71-2.10)	Age, smoking, alcohol	133
XRCC1 codon 399	OC, P, L	525	757	Arg/Gln vs. Arg/Arg	0.91 (0.66-1.25)	Gln/Gln vs. Arg/Arg	0.40 (0.11-1.51)	Age, sex, smoking, alcohol, ethnicity, center	140
XRCC1 codon 399	OC	310	348	Arg/Gln vs. Arg/Arg	1.03 (0.74-1.42)[c]	Gln/Gln vs. Arg/Arg	1.39 (0.79-2.43)[c]	-	80
XRCC1 codon 399	NS	95	98	Arg/Gln vs. Arg/Arg	0.83 (0.45-1.52)	Gln/Gln vs. Arg/Arg	0.86 (0.35-2.10)	-	134
XRCC1 codon 399	P	425	501	Arg/Gln vs. Arg/Arg	0.82 (0.62-1.08)	Gln/Gln vs. Arg/Arg	1.20 (0.69-2.06)	Age, sex, smoking	135
XRCC1 codon 399	OC	110	110	Arg/Gln vs. Arg/Arg	2.31 (1.29-4.12)	Gln/Gln vs. Arg/Arg	6.35 (1.99-20.19)	Age, sex, smoking, alcohol, betel quid chewing	136

Table III. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
XRCC1 codon 399	OC	106	164	Arg/Gln vs. Arg/Arg	0.64 (0.35-1.16)	Gln/Gln vs. Arg/Arg	0.30 (0.10-0.88)	Betel quid chewing	137
XRCC1 codon 399	OC	309	385	Arg/Gln vs. Arg/Arg	0.9 (0.9-1.0)	Gln/Gln vs. Arg/Arg	0.9 (0.9-1.0)	Age, sex, smoking	138
XRCC1 26,304	OC, P, L	203	424	CT vs. CC	0.73 (0.43-1.22)[c]	TT vs. CC	-	-	141
XRCC1 28,152	OC, P, L	203	424	GA vs. GG	0.75 (0.52-1.08)[c]	AA vs. GG	1.34 (0.80-2.24)[c]	-	141
XRCC1 28,152	L	293	319	GA vs. GG	1.23 (0.87-1.74)	AA vs. GG	0.79 (0.47-1.32)	-	142
XRCC2 codon 188	OC, P	119	165	His/His+His/Arg vs. Arg/Arg	1.8 (1.0-3.5)			Age, sex, smoking, alcohol	143
XRCC2 codon 188	L	127	165	His/His+His/Arg vs. Arg/Arg	1.0 (0.5-2.0)			Age, sex, smoking, alcohol	143
XRCC3 codon 241	OC, P, L	367	354	Thr/Met vs. Thr/Thr	0.90 (0.66-1.24)	Met/Met vs. Thr/Thr	1.29 (0.81-2.03)	Age, sex, smoking, alcohol	144
XRCC3 codon 241	OC, P	119	166	Thr/Met vs. Thr/Thr	0.6 (0.4-1.1)	Met/Met vs. Thr/Thr	0.7 (0.3-1.4)	Age, sex, smoking, alcohol	143
XRCC3 codon 241	L	127	166	Thr/Met vs. Thr/Thr	0.7 (0.4-1.2)	Met/Met vs. Thr/Thr	0.7 (0.3-1.4)	Age, sex, smoking, alcohol	143
XRCC3 codon 241	OC, P, L	516	760	Thr/Met vs. Thr/Thr	1.01 (0.76-1.33)	Met/Met vs. Thr/Thr	1.04 (0.80-1.35)	Age, sex, smoking, alcohol, ethnicity, center	140
XRCC3 codon 241	OC	310	348	Thr/Met vs. Thr/Thr	0.88 (0.64-1.23)[c]	Met/Met vs. Thr/Thr	1.64 (0.66-4.10)[c]	-	80
XRCC3 codon 241	OC	106	164	Thr/Met vs. Thr/Thr	2.31 (1.09-4.91)	Met/Met vs. Thr/Thr	0.66 (0.04-10.92)	Betel quid chewing	137
XPD 22,541	OC, P, L	189	496	CA vs. CC	1.01 (0.70-1.63)	AA vs. CC	0.90 (0.52-1.56)	Age, sex, smoking, alcohol	145
XPD 22,541	L	286	319	CA vs. CC	0.61 (0.43-0.87)	AA vs. CC	0.62 (0.36-1.04)	-	142
XPD 22,541	OC	106	164	CA vs. CC	1.74 (0.94-3.22)	AA vs. CC	0.85 (0.30-2.37)	Betel quid chewing	137
XPD 22,541	OC	308	388	CA vs. CC	1.0 (0.9-1.0)	AA vs. CC	1.0 (0.9-1.0)	Age, sex, smoking	138
XPD 23,047	OC, P, L	180	400	CG+GG vs. CC	0.31 (0.04-2.57)[c]			-	146
XPD 23,591	OC, P, L	313	313	GA+AA vs. GG	1.28 (0.93-1.76)			Age, sex, smoking, alcohol	147
XPD 23,591	OC	305	387	GA vs. GG	1.0 (0.9-1.0)	AA vs. GG	1.0 (0.9-1.0)	Age, sex, smoking	138
XPD 35,931	OC, P, L	189	496	AC vs. AA	1.12 (0.77-1.62)	CC vs. AA	1.65 (0.98-2.77)	Age, sex, smoking, alcohol	145
XPD 35,931	L	293	320	AC vs. AA	0.61 (0.43-0.87)	CC vs. AA	1.53 (0.95-2.46)	-	142
XPD 35,931	OC, P, L	544	775	AC vs. AA	1.04 (0.80-1.37)	CC vs. AA	1.03 (0.69-1.52)	Age, sex, smoking, alcohol, ethnicity, center	140
XPD 35,931	OC	110	110	AC vs. AA	2.16 (1.20-3.86)	CC vs. AA	2.72 (1.07-6.91)	Age, sex, smoking, alcohol, betel quid chewing	136
XPD 35,931	OC	105	164	AC vs. AA	0.69 (0.35-1.39)	CC vs. AA	2.04 (0.19-21.66)	Betel quid chewing	137
XPD 35,931	OC	309	388	AC vs. AA	1.0 (0.9-1.0)	CC vs. AA	1.0 (0.9-1.0)	Age, sex, smoking	138
XPG	OC	200	921	His/Asp+His/His vs. Asp/Asp	2.08 (1.04-4.17)			Age, sex, smoking, alcohol, ethnicity, educational level	148

Table III. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
XPG	P	56	921	His/Asp+His/His vs. Asp/Asp	2.27 (0.71-7.14)			Age, sex, smoking, alcohol, ethnicity, educational level	148
XPG	L	73	921	His/Asp+His/His vs. Asp/Asp	2.17 (0.77-6.25)			Age, sex, smoking, alcohol, ethnicity, educational level	148
XPG	OC	122	241	His/Asp vs. Asp/Asp	1.01 (0.61-1.69)	HisHis vs. Asp/Asp	0.81 (0.42-1.58)	Age, sex, smoking, alcohol	28
XPC PAT	OC, P, L	287	311	Null/Positive vs. Null/Null	1.44 (1.01-2.05)	Positive/Positive vs. Null/Null	1.85 (1.12-3.05)	Age, sex, smoking, alcohol	149
XPC PAT	OC, P, L	73	82	Null/Positive vs. Null/Null	0.95 (0.48-1.88)[c]	Positive/Positive vs. Null/Null	0.89 (0.33-2.40)[c]	-	150
XPC PAT	OC	106	164	Null/Positive vs. Null/Null	0.83 (0.46-1.48)	Positive/Positive vs. Null/Null	1.60 (0.55-4.66)	Betel quid chewing	137
XPC exon 15	OC	106	164	CA vs. CC	0.87 (0.48-1.55)	AA vs. CC	1.35 (0.50-3.92)	Betel quid chewing	137
XPC intron 9	OC	122	241	Null/Positive vs. Null/Null	0.86 (0.52-1.42)	Positive/Positive vs. Null/Null	0.75 (0.36-1.55)	Age, sex, smoking, alcohol	28
XPA 5'-UTR	OC	122	241	AG vs. AA	2.15 (1.19-3.90)	GG vs. AA	1.88 (0.97-3.62)	Age, sex, smoking, alcohol	28
XPF 5'-UTR	OC	122	241	TA vs. TT	0.86 (0.53-1.38)	AA vs. TT	0.69 (0.28-1.69)	Age, sex, smoking, alcohol	28
MGMT codon 65	OC	106	164	Trp/Cys vs. Trp/Trp	-	Cys/Cys vs. Trp/Trp	-	Betel quid chewing	137
MGMT codon 84	OC, P, L	514	754	Leu/Phe vs. Leu/Leu	0.75 (0.56-1.02)	Phe/Phe vs. Leu/Leu	0.64 (0.26-1.60)	Age, sex, smoking, alcohol, ethnicity, center	140
MGMT codon 84	OC	106	164	Leu/Phe vs. Leu/Leu	1.11 (0.54-2.26)	Phe/Phe vs. Leu/Leu	0.37 (0.01-15.73)	Betel quid chewing	137
MGMT codon 143	OC, P, L	536	751	Ile/Val vs. Ile/Ile	0.72 (0.52-0.99)	Val/Val vs. Ile/Ile	0.66 (0.20-1.91)	Age, sex, smoking, alcohol, ethnicity, center	140
hOGG1 codon 326	OC, L	169	338	Ser/Cys vs. Ser/Ser	1.6 (1.04-2.6)	Cys/Cys vs. Ser/Ser	4.1 (1.3-13)	Age, sex, smoking, alcohol	151
hOGG1 codon 326	P	333	283	Ser/Cys vs. Ser/Ser	1.8 (1.1-2.9)	Cys/Cys vs. Ser/Ser	1.4 (0.86-2.4)	Age, sex, ethnicity	139
hOGG1 codon 326	NS	706	1,196	Ser/Cys vs. Ser/Ser	0.93 (0.76-1.14)	Cys/Cys vs. Ser/Ser	0.98 (0.65-1.48)	Age, sex, smoking, alcohol	152
ERCC1 8,092	OC, P, L	313	313	CA vs. CC	0.86 (0.62-1.19)[c]	AA vs. CC	0.94 (0.44-2.03)[c]	-	147
ERCC1 8,092	OC	122	241	CA vs. CC	0.56 (0.33-0.93)	AA vs. CC	1.56 (0.72-3.36)	Age, sex, smoking, alcohol	28
RAD51 135	OC, P, L	716	719	GC vs. GG	0.95 (0.69-1.30)	CC vs. GG	0.99 (0.06-16.70)	Age, sex, smoking, alcohol	153
RAD51 172	OC, P, L	716	719	GT vs. GG	0.96 (0.75-1.21)	TT vs. GG	0.64 (0.47-0.88)	Age, sex, smoking, alcohol	153

[a]OC, oral cavity; P, pharynx; L, larynx; NC, not specified, [b]OR, odds ratio; 95% CI, 95% confidence interval; [c]OR and 95% CI were calculated from the genotype distribution.

Table IV. Studies on polymorphisms of cell-cycle control genes and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
p53 codon 72	P	73	105	Arg/Pro vs. Arg/Arg	1.23 (0.58-2.60)[d]	Pro/Pro vs. Arg/Arg	2.02 (0.89-4.56)[d]	-	154
p53 codon 72	P	20	31	Arg/Pro vs. Arg/Arg	1.41 (0.39-5.13)[d]	Pro/Pro vs. Arg/Arg	0.63 (0.12-3.32)[d]	-	155
p53 codon 72	P	64	99	Arg/Pro vs. Arg/Arg	1.13 (0.52-2.48)	Pro/Pro vs. Arg/Arg	2.00 (0.86-4.67)	-	156
p53 codon 72	OC, P, L, O	140	120	Arg/Pro vs. Arg/Arg	0.96 (0.57-1.61)[d]	Pro/Pro vs. Arg/Arg	0.49 (0.19-1.26)[d]	-	21
p53 codon 72	OC, P, L, O	163	163	Arg/Pro vs. Arg/Arg	1.20 (0.77-1.89)[d]	Pro/Pro vs. Arg/Arg	1.08 (0.36-3.20)[d]	-	157
p53 codon 72	OC	190	308	Arg/Pro vs. Arg/Arg	1.03 (0.70-1.52)[d]	Pro/Pro vs. Arg/Arg	1.06 (0.56-2.01)[d]	-	158
p53 codon 72	OC	72	153	Arg/Pro vs. Arg/Arg	1.91 (0.73-4.99)[d]	Pro/Pro vs. Arg/Arg	1.66 (0.55-4.98)[d]	-	159
p53 codon 72	L	20	40	Arg/Pro vs. Arg/Arg	0.28 (0.08-0.96)[d]	Pro/Pro vs. Arg/Arg	0.18 (0.02-1.82)[d]	-	160
p53 codon 72	OC, P, L	304	333	Arg/Pro vs. Arg/Arg	1.04 (0.75-1.44)	Pro/Pro vs. Arg/Arg	1.01 (0.54-1.91)	Age, sex, smoking, alcohol	161
p53 codon 72	OC	82	164	Arg/Pro vs. Arg/Arg	1.06 (0.56-2.02)[d]	Pro/Pro vs. Arg/Arg	1.60 (0.41-6.20)[d]	-	162
p53 codon 72	OC	110	26	Arg/Pro vs. Arg/Arg	2.21 (0.89-5.51)[d]	Pro/Pro vs. Arg/Arg	4.40 (0.90-21.56)[d]	-	163
p53 codon 72	P	102	148	Arg/Pro vs. Arg/Arg	1.55 (0.85-2.83)[d]	Pro/Pro vs. Arg/Arg	1.93 (0.94-3.98)[d]	-	164
p53 codon 72	OC	97	97	Arg/Pro vs. Arg/Arg	0.71 (0.37-1.36)[d]	Pro/Pro vs. Arg/Arg	1.22 (0.58-2.56)[d]	-	165
p53 codon 72	OC	44	20	Arg/Pro vs. Arg/Arg	1.00 (0.28-3.58)[d]	Pro/Pro vs. Arg/Arg	1.67 (0.31-8.93)[d]	-	166
p53 codon 72	OC, P, L, O	50	142	Arg/Pro vs. Arg/Arg	0.51 (0.22-1.18)	Pro/Pro vs. Arg/Arg	3.27 (0.90-11.87)	-	167
p53 codon 72	OC, P, L, O	122	193	Arg/Pro vs. Arg/Arg	1.44 (0.90-2.30)[d]	Pro/Pro vs. Arg/Arg	0.13 (0.02-1.04)[d]	-	168
p53 codon 72	P	53	53	Arg/Pro vs. Arg/Arg	1.78 (0.62-5.14)	Pro/Pro vs. Arg/Arg	3.67 (1.16-11.56)	-	169
p53 codon 72	P	107	285	Arg/Pro vs. Arg/Arg	0.97 (0.58-1.64)	Pro/Pro vs. Arg/Arg	2.62 (1.10-6.30)	-	170
p53 codon 72	P	77	141	Arg/Pro vs. Arg/Arg	0.23 (0.09-0.53)	Pro/Pro vs. Arg/Arg	0.80 (0.23-2.59)	-	171
p53 codon 72	OC, P, L	716	719	Arg/Pro vs. Arg/Arg	0.92 (0.73-1.14)	Pro/Pro vs. Arg/Arg	1.10 (0.69-1.73)	Age, sex, smoking, alcohol	153
p53 duplication (intron 3)	P	73	105	dup(-)/dup(+) vs. dup(-)/dup(-)	4.97 (1.53-16.09)[d]	dup(+)/dup(+) vs. dup(-)/dup(-)	-	-	154
p53 intron 6	P	73	105	A1/A2 vs. A1/A1	2.86 (0.92-8.91)[d]	A2/A2 vs. A1/A1	-	-	154
cyclin D1 870	OC, P, L	233	248	GA vs. GG	1.15 (0.75-1.76)	AA vs. GG	1.77 (1.04-3.02)	Age, sex, smoking, alcohol	172
cyclin D1 870	P	84	91	GA vs. GG	0.84 (0.38-1.88)[d]	AA vs. GG	0.36 (0.15-0.88)[d]	-	173
cyclin D1 870	OC	70	93	GA vs. GG	0.83 (0.37-1.88)[d]	AA vs. GG	0.80 (0.32-1.98)[d]	-	174

Table IV. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
cyclin D1 870	OC, P, L	147	135	GA vs. GG	0.74 (0.44-1.26)[d]	AA vs. GG	0.75 (0.38-1.49)[d]	-	175
cyclin D1 870	L	66	110	GA vs. GG	0.37 (0.17-0.83)[d]	AA vs. GG	0.17 (0.07-0.42)[d]	-	176
cyclin D1 870	OC	174	155	GA vs. GG	0.65 (0.40-1.07)[d]	AA vs. GG	0.30 (0.14-0.64)[d]	-	177
cyclin D1 870	L	63	102	GA vs. GG	3.02 (1.39-6.56)	AA vs. GG	0.66 (0.24-1.79)	-	178
cyclin D1 870	P	94	187	GA vs. GG	0.43 (0.23-0.82)[d]	AA vs. GG	0.52 (0.25-1.05)[d]	-	179
cyclin D1 870	OC	176	142	GA vs. GG	1.29 (0.73-2.28)	AA vs. GG	1.20 (0.63-2.27)	Age, sex	180
cyclin D1 1,722	OC	176	142	GC vs. GG	1.20 (0.70-2.07)	CC vs. GG	0.91 (0.48-1.73)	Age, sex	180
p21 codon 31	P	76	66	Ser/Arg vs. Ser/Ser	1.13 (0.15-8.25)[d]	Arg/Arg vs. Ser/Ser	1.38 (0.16-11.94)[d]	-	184
p21 codon 31	NS	48	110	Ser/Arg+Arg/Arg vs. Ser/Ser	2.31 (0.87-6.11)[d]			-	185
p21 codon 31	P	47	119	CA vs. CC	1.25 (0.47-3.31)[d]	AA vs. CC	1.24 (0.44-3.51)[d]	-	186
p21 -2,298	NS	52	104	GA vs. GG	1.24 (0.54-2.86)[d]	AA vs. GG	-	-	181
p21 68	NS	52	104	CA vs. CC	1.65 (0.75-3.63)[d]	AA vs. CC	-	-	181
p21 70	OC, P, L	712	1,222	CT vs. CC	1.47 (1.12-1.93)	TT vs. CC	2.01 (0.64-6.31)	Age, sex, smoking, alcohol	182
p21 98	OC, P, L	712	1,222	CA vs. CC	1.32 (1.00-1.73)	AA vs. CC	2.50 (0.92-6.81)	Age, sex, smoking, alcohol	182
p21 codon 149	OC	30	50	Asp/Gly+Gly/Gly vs. Asp/Asp	3.56 (1.06-12.23)			-	183
PLUNC -1,888	P	232	282	TC vs. TT	1.2 (0.8-1.7)	CC vs. TT	3.3 (1.8-6.1)	Age, sex	187
PLUNC -2,128	P	239	281	TC vs. TT	0.9 (0.6-1.4)	CC vs. TT	2.8 (1.7-4.9)	Age, sex	187
PLUNC -3,348	P	233	279	AC vs. AA	1.3 (0.6-3.1)	CC vs. AA	1.5 (0.6-3.6)	Age, sex	187
p16 540	NS	208	224	CG vs. CC	1.01 (0.64-1.61)	GG vs. CC	0.74 (0.12-4.57)	Age, sex, smoking, alcohol	188
p16 580	NS	208	224	CT vs. CC	0.97 (0.58-1.64)	TT vs. CC	0.49 (0.04-5.49)	Age, sex, smoking, alcohol	188
p27 codon 109	OC, P, L	713	1,224	VG vs. VV	0.92 (0.75-1.12)	GG vs. VV	1.20 (0.81-1.77)	Age, sex, smoking, alcohol	189
p73 G4C14/A4T14	OC, P, L	708	1,229	GC/AT vs. GC/GC	1.36 (1.12-1.66)	AT/AT vs. GC/GC	1.11 (0.73-1.69)	Age, sex, smoking, alcohol	190
MDM -309	OC, P, L	157	185	wt/vt vs. wt/wt	0.74 (0.46-1.19)[d]	vt/vt vs. wt/wt	0.75 (0.39-1.43)[d]	-	191
FUS2	P	114	55	TA vs. TT	0.50 (0.25-1.01)[d]	AA vs. TT	0.49 (0.17-1.48)[d]	-	192
hCHK2	OC, P, L	215	229	AG vs. AA	0.40 (0.17-0.93)	GG vs. AA	-	Age, sex, smoking, alcohol	193
H-*ras* 81	OC	176	142	TC vs. TT	1.59 (0.98-2.56)	CC vs. GG	1.78 (0.67-4.74)	Age, sex	180
IFN-alpha	P	64	99	1-2 vs. 1-1	1.21 (0.51-2.83)	2-2 vs. 1-1	2.76 (1.13-6.73)	-	156

[a]OC, oral cavity; P, pharynx; L, larynx; O, other; NC, not specified. [b]dup, duplication; wt, wild-type; vt, variant-type. [c]OR, odds ratio; 95% CI, 95% confidence interval. [d]OR and 95% CI were calculated from the genotype distribution.

Table V. Studies on polymorphisms of folate metabolic enzymes and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
MTHFR 677	OC	135	146	CT vs. CC	0.6 (0.3-1.2)	TT vs. CC	0.5 (0.2-1.4)	Age, sex, smoking, alcohol, place of residence	124
MTHFR 677	NS	50	54	CT vs. CC	1.00 (0.44-2.26)[d]	TT vs. CC	-	-	231
MTHFR 677	OC, P, L	537	545	CT vs. CC	1.21 (0.9-1.6)	TT vs. CC	0.72 (0.5-1.2)	Age, sex, smoking, alcohol	125
MTHFR 677	P	65	100	CT vs. CC	1.43 (0.70-2.95)[d]	TT vs. CC	1.56 (0.63-3.82)[d]	-	126
MTHFR 677	OC	110	120	CT vs. CC	1.88 (1.06-3.34)[d]	TT vs. CC	0.96 (0.32-2.95)[d]	-	127
MTHFR 1,298	OC, P, L	537	545	AC vs. AA	0.69 (0.5-0.9)	CC vs. AA	0.28 (0.1-0.6)	Age, sex, smoking, alcohol	125
MTHFR 1,298	P	65	100	AC vs. AA	0.78 (0.41-1.49)[d]	CC vs. AA	1.42 (0.42-4.81)[d]	-	126
MTHFR 1,793	OC, P, L	537	545	GA vs. GG	1.35 (0.9-2.1)	AA vs. GG	-	Age, sex, smoking, alcohol	125
SHMT1 34,761	OC, P, L	721	1,234	CT vs. CC	0.99 (0.81-1.20)	TT vs. CC	1.22 (0.91-1.64)	Age, sex, smoking, alcohol	128
SHMT1 34,840	OC, P, L	721	1,234	CG vs. CC	1.03 (0.84-1.25)	GG vs. CC	1.05 (0.77-1.43)	Age, sex, smoking, alcohol	128
SHMT1 34,859	OC, P, L	721	1,234	CT vs. CC	1.11 (0.91-1.35)	TT vs. CC	1.10 (0.81-1.49)	Age, sex, smoking, alcohol	128
MTR 2,756	OC, P, L	721	1,442	AG vs. AA	1.31 (1.07-1.60)	GG vs. AA	1.00 (0.55-1.84)	Age, sex, smoking, alcohol	129
MTRR 66	OC, P, L	721	1,442	GA vs. GG	1.02 (0.82-1.26)	AA vs. GG	0.68 (0.52-0.90)	Age, sex, smoking, alcohol	129
TSER	OC, P, L	704	1,085	2R3R vs. 3R3R	1.23 (0.98-1.55)	2R2R vs. 3R3R	1.01 (0.77-1.33)	Age, sex, smoking, alcohol	130
Factror V	OC	102	120	wt/vt vs. wt/wt	0.98 (0.29-3.31)[d]	vt/vt vs. wt/wt	-	-	131
Prothrombin 20,210	OC	102	120	wt/vt vs. wt/wt	0.94 (0.25-3.59)[d]	vt/vt vs. wt/wt	-	-	131

[a]OC, oral cavity; P, pharynx; L, larynx; NC, not specified, [b]wt, wild-type; vt, variant-type. [c]OR, odds ratio; 95% CI, 95% confidence interval. [d]OR and 95% CI were calculated from the genotype distribution.

dation enzymes, apoptosis signaling and immune response factors, have been investigated. However, the number of studies was limited, and we found it difficult to draw conclusions.

3. Discussion

Molecular epidemiologic studies have provided evidence that individual susceptibility to cancer is mediated by both genetic and environmental factors. Interest in the role of genetic polymorphisms in HNC has increased recently, possibly due to advances in DNA analysis technologies or our knowledge of the human genome. The most intensively studied genes are those encoding enzymes that metabolize carcinogens and include *GSTM1*, *GSTT1* and *GSTP1*. This is likely because these variants are well characterized, and increased cancer risk associated with these variations is plausible.

A considerable amount of work has been done on these genes in relation to risk for HNC. One of the major problems of these studies is that many have a small sample size (<100 cases or <100 controls). Case-control studies with small sample size are reported to inflate ORs (232). To clarify the effect of genes on the risk of HNC, meta-analysis is useful because it is a statistical method to integrate and analyze previous research results. Therefore, the results of meta-analyses carry greater significance than the results of individual studies. At present, 23 studies describing meta-analyses of relations between genetic polymorphisms and risk of HNC have been published (232-234). The genetic polymorphisms examined were those in the *GSTM1*, *GSTT1*, *GSTP1*, *XRCC1* codons 194 and 399, and *CYP1A1* codon 462. Among these polymorphisms, a significant relation was observed between the *GSTM1*-null genotype and increased risk for HNC (Table II). When the studies on *GSTM1* were stratified as to Asians and Caucasians, the risk of HNC was more pronounced in Asian than in Caucasian populations (233). Polymorphisms in other genes, including *GSTT1*, *GSTP1*,

Table VI. Studies on polymorphisms of extracellular matrix degradation enzymes and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
MMP-1	OC, P	125[d]	249[d]	1G/2G vs. 1G/1G	0.7 (0.4-1.2)	2G/2G vs. 1G/1G	0.3 (0.1-0.6)	Age, smoking	194
MMP-1	OC, P, L, O	140	345	1G/2G vs. 1G/1G	0.53 (0.27-1.05)[c]	2G/2G vs. 1G/1G	0.91 (0.47-1.75)[c]	-	195
MMP-1	OC	121	147	1G/2G vs. 1G/1G	2.16 (0.95-4.93)[c]	2G/2G vs. 1G/1G	2.17 (0.96-4.93)[c]	-	196
MMP-1	OC	96	120	1G/2G vs. 1G/1G	1.91 (0.77-4.73)[c]	2G/2G vs. 1G/1G	4.19 (1.72-10.24)[c]	-	197
MMP-1	OC, P, L	300	300	1G/2G vs. 1G/1G	0.73(0.47-1.14)[c]	2G/2G vs. 1G/1G	1.89 (1.21-2.97)[c]	-	198
MMP-1	OC	156	141	1G/2G vs. 1G/1G	0.81 (0.42-1.56)	2G/2G vs. 1G/1G	0.56 (0.29-1.09)	Age	199
MMP-2	OC	121	147	CT vs. CC	0.62 (0.34-1.15)[c]	TT vs. CC	-	-	200
MMP-2	OC, P, L	239	250	CT vs. CC	0.54 (0.34-0.87)[c]	TT vs. CC	-	-	201
MMP-3	OC, P	125[d]	249[d]	5A/6A vs. 5A/5A	0.9 (0.5-1.6)	6A/6A vs. 5A/5A	0.5 (0.2-1.1)	Age, smoking	194
TIMP-2 -418	OC, P, L	239	250	CC+GC vs. GG	1.43 (0.98-2.08)			Age, sex, smoking, alcohol	201
TIMP-2 -418	OC	158	168	GC vs. GG	21.31 (9.82-46.21)	CC vs. GG	40.88 (2.24-744.4)	-	202
GPIa 807	OC	110	114	CT vs. CC	1.25 (0.56-2.77)[c]	TT vs. CC	3.50 (1.29-9.47)[c]	-	203
Urokinase 3'-UTR	OC	130	106	CT vs. CC	2.83 (1.35-5.96)			-	204

[a]OC, oral cavity; P, pharynx; L, larynx; O, other. [b]OR, odds ratio; 95% CI, 95% confidence interval. [c]OR and 95% CI were calculated from the genotype distribution. [d]Male.

Table VII. Studies on polymorphisms of apoptosis signaling factors and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
FAS -1,377	OC, P, L	721	1,234	GA vs. GG	0.91 (0.73-1.15)	AA vs. GG	2.23 (1.07-4.64)	Age, sex, smoking, alcohol	205
FAS -670	OC, P, L	721	1,234	AG vs. AA	1.21 (0.98-1.51)	GG vs. AA	1.29 (0.99-1.68)	Age, sex, smoking, alcohol	205
FAS -670	P	170	224	AG vs. AA	2.00 (1.19-3.33)	GG vs. AA	3.19 (1.76-5.77)	Age, sex	206
FASLG -844	OC, P, L	721	1.234	CT vs. CC	0.93 (0.76-1.13)	TT vs. CC	0.82 (0.61-1.11)	Age, sex, smoking, alcohol	205
FASLG IVS2nt -124	OC, P, L	721	1.234	AG vs. AA	0.97 (0.78-1.20)	GG vs. AA	0.83 (0.46-1.50)	Age, sex, smoking, alcohol	205
TRAIL-R1 422	NS	19	45	GA vs. GG	1.04 (0.23-4.71)[c]	AA vs. GG	6.00 (1.17-30.72)[c]	-	207
TRAIL-R1 422	NS	37	48	GA+AA vs. GG	4.52 (1.37-14.94)[c]			-	208
TRAIL-R2 626	NS	19	45	CG vs. CC	1.75 (0.39-7.91)[c]	GG vs. CC	4.50 (0.97-20.83)[c]	-	207
TRAIL-R2 626	NS	41	48	CG+GG vs. CC	4.72 (1.57-14.17)[c]			-	208

[a]OC, oral cavity; P, pharynx; L, larynx. [b]OR, odds ratio; 95% CI, 95% confidence interval; [c]OR and 95% CI were calculated from the genotype distribution.

XRCC1 (codon 399), and *CYP1A1* (codon 462), tend to be associated with an increased risk for HNC. One possible explanation for the lack of significant interaction is that gene-environment interactions are heterogeneous by ethnicity, in which case, pooling data from different ethnicities would dilute the interaction. Another possible explanation is that these gene-environment interactions are heterogeneous by tumor site. For instance, oral cancers may have different genetic backgrounds from those of laryngeal cancers. In addition, the genotype frequencies in controls vary among populations. In the Indian population, the prevalence of the *GSTM1*- and *GSTT1*-null genotypes is particularly low. It

Table VIII. Studies on polymorphisms of immune response factors and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
TNF-alpha -308	P	47	119	AG vs. AA	2.67 (1.03-6.92)[d]	GG vs. AA	-	-	186
TNF-alpha -308	P	140	274	GA vs. GG	0.77 (0.49-1.21)	AA vs. GG	1.38 (0.56-3.39)	-	209
TNF-alpha -308	OC	192	146	GA vs. GG	2.16 (1.10-4.24)	AA vs. GG	-	-	210
TNF-alpha -308	OC	137	102	GA vs. GG	0.60 (0.27-1.37)	AA vs. GG	-	-	54
TNF-alpha -308	P	23	50	GA vs. GG	0.8 (0.2-2.6)	AA vs. GG	-	-	211
TNF-alpha -1,031	P	23	50	TC vs. TT	0.9 (0.3-2.7)	CC vs. TT	-	-	211
TNF-alpha -238	OC	192	146	GA vs. GG	0.26 (0.08-0.8)	AA vs. GG	-	-	210
TNF-alpha -806	P	23	50	CT vs. CC	0.3 (0.0-2.9)	TT vs. CC	-	-	211
TNF-alpha -857	P	23	50	CT vs. CC	0.9 (0.3-2.8)	TT vs. CC	-	-	211
TNF-alpha -863	P	23	50	CA vs. CC	1.2 (0.4-3.6)	AA vs. CC	-	-	211
IL-1 beta	OC	153	711	TC vs. TT	1.21 (0.81-1.79)	CC vs. TT	0.87 (0.45-1.71)	Age, sex, smoking, alcohol, center	212
IL-1 beta	P	98	699	TC vs. TT	1.53 (0.94-2.49)	CC vs. TT	2.39 (1.19-4.81)	Age, sex, smoking, alcohol, center	212
IL-1 beta	L	288	699	TC vs. TT	1.08 (0.78-1.50)	CC vs. TT	1.06 (0.63-1.78)	Age, sex, smoking, alcohol, center	212
IL-1 -511	OC	130	105	CT vs. CC	1.32 (0.71-2.46)[d]	TT vs. CC	0.87 (0.41-1.83)[d]	-	213
IL-1 exon 5	OC	130	105	E1E2 vs. E1E1	0.54 (0.09-3.27)[d]	E2E2 vs. E1E1	-	-	213
IL-8	OC	153	725	TA vs. TT	0.96 (0.61-1.50)	AA vs. TT	1.10 (0.66-1.83)	Age, sex, smoking, alcohol, center	212
IL-8	P	107	725	TA vs. TT	1.02 (0.59-1.76)	AA vs. TT	1.38 (0.75-2.54)	Age, sex, smoking, alcohol, center	212
IL-8	L	313	725	TA vs. TT	0.66 (0.46-0.94)	AA vs. TT	0.82 (0.54-1.25)	Age, sex, smoking, alcohol, center	212
IL-8	OC	158	156	TA vs. TT	1.76 (1.11-2.79)	AA vs. TT	-	-	214
IL-10 -1,082	P	89	130	AG vs. AA	1.1 (0.7-2.8)	GG vs. AA	1.1 (0.8-2.8)	Age, sex, ethnicity	215
IL-10 -592	P	89	130	CA vs. CC	1.0 (0.5-3.1)	AA vs. CC	1.2 (0.5-3.4)	Age, sex, ethnicity	215
IL-10 -819	P	89	130	CT vs. CC	1.0 (0.5-3.1)	TT vs. CC	1.2 (0.5-3.4)	Age, sex, ethnicity	215
IL-4 -590	OC	130	105	TT vs. TC	1.8 (0.9-3.4)	CC vs. TC	6.0 (1.2-30.7)	-	213
IL-4 intron 3	OC	130	105	RP1/RP2 vs. RP1/RP1	0.63 (0.35-1.13)[d]	RP2/RP2 vs. RP1/RP1	0.41 (0.10-1.79)[d]	-	213
IL-18 -137	P	89	130	GC vs. GG	1.2 (0.5-3.0)	CC vs. GG	2.1 (0.4-4.3)	Age, sex, ethnicity	215
IL-18 -607	P	89	130	AC vs. AA	1.0 (0.7-2.6)	CC vs. AA	1.4 (0.9-3.3)	Age, sex, ethnicity	215
IL-6 -174	OC	162	156	GC vs. GG	3.74 (2.29-6.11)	CC vs. GG	7.39 (2.61-20.92)	Age, sex, ethnicity	216
TLR10 720	P	477	567	AC vs. AA	0.93 (0.70-1.24)	CC vs. AA	0.95 (0.67-1.34)	-	217
TLR10 891	P	477	570	GA vs. GG	0.87 (0.63-1.19)	AA vs. GG	0.23 (0.03-1.99)	-	217
TLR10 908	P	476	568	AG vs. AA	1.17 (0.88-1.56)	GG vs. AA	1.56 (0.61-4.00)	-	217
TLR10 976	P	479	569	TC vs. TT	0.92 (0.67-1.28)	CC vs. TT	0.39 (0.08-1.93)	-	217
TLR10 1.031	P	471	540	GT vs. GG	0.88 (0.68-1.14)	TT vs. GG	0.72 (0.48-1.09)	-	217
TLR10 1.104	P	475	547	AC vs. AA	0.85 (0.63-1.14)	CC vs. AA	0.99 (0.70-1.41)	-	217
TLR10 1.141	P	470	550	GA vs. GG	0.84 (0.65-1.09)	AA vs. GG	1.48 (0.89-2.46)	-	217
PTGS2	OC	153	711	TC vs. TT	1.07 (0.73-1.58)	CC vs. TT	0.65 (0.32-1.36)	Age, sex, smoking, alcohol, center	212
PTGS2	P	99	711	TC vs. TT	1.34 (0.82-2.17)	CC vs. TT	1.37 (0.62-3.06)	Age, sex, smoking, alcohol, center	212
PTGS2	L	281	711	TC vs. TT	0.88 (0.63-1.22)	CC vs. TT	0.60 (0.34-1.05)	Age, sex, smoking, alcohol, center	212
PIGR IVS3-156	P	175	317	Positive/Null vs. Positive/Positive	1.49 (0.98-2.26)[d]	Null/Null vs. Positive/Positive	1.31 (0.73-2.33)[d]	-	218

Table VIII. Continued.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1[b]	OR and 95% CI[c]	Result-2[b]	OR and 95% CI[c]	Covariates	Ref.
PIGR 1,093	P	175	317	GA vs. GG	1.08 (0.73-1.59)[d]	AA vs. GG	0.66 (0.34-1.30)[d]	-	218
PIGR 1,739	P	175	317	CT vs. CC	0.37 (0.24-0.56)[d]	TT vs. CC	0.45 (0.17-1.18)[d]	-	218
HLA-E 77	P	100	100	CT vs. CC	1.35 (0.74-2.44)[d]	TT vs. CC	2.24 (0.83-6.07)[d]	-	107
HLA-E 107	P	100	100	AG vs. AA	1.84 (0.72-4.66)[d]	GG vs. AA	3.55 (1.38-9.08)[d]	-	107
MPO -463	L	245	270	GA vs. GG	0.62 (0.42-0.91)	AA vs. GG	0.86 (0.24-3.02)	-	219
MPO -463	P	255	270	GA vs. GG	0.78 (0.54-1.13)	AA vs. GG	1.39 (0.49-4.00)	-	219
NFKbeta1	OC	212	201	del/ins vs. del/del	1.18 (0.73-1.88)	ins/ins vs. del/del	1.60 (0.93-2.77)	-	220
CCR5	L	34	267	wt/vt vs. wt/wt	0.59 (0.08-4.67)	vt/vt vs. wt/wt	-	-	221
CTLA-4	OC	118	147	AG vs. AA	1.89 (0.87-4.10)[d]	GG vs. AA	1.72 (0.78-3.79)[d]	-	222
HSP70-2	P	140	274	P1/P2 vs. P1/P1	1.24 (0.78-1.99)	P2/P2 vs. P1/P1	2.31 (1.26-4.22)	-	209
CR2 IVS-848	P	175	317	Positive/Null vs. Positive/Positive	0.76 (0.10-5.61)[d]	Null/Null vs. Positive/Positive	0.50 (0.07-3.56)[d]	-	218
Tx SNP3	P	82	80	GC vs. GG	2.76 (1.39-5.45)[d]	CC vs. GG	2.81 (1.03-7.68)[d]	-	223

[a]OC, oral cavity; P, pharynx; L, larynx. [b]del, deletion; ins, insertion; wt, wild-type; vt, variant-type. [c]OR, odds ratio; 95% CI, 95% confidence interval. [d]OR and 95% CI were calculated from the genotype distribution.

Table IX. Studies on polymorphisms of growth factors, vitamin and sex hormone, and risk of head and neck cancer.

Gene and polymorphic site	Tumor site[a]	Cases	Controls	Result-1	OR and 95% CI[b]	Result-2	OR and 95% CI[b]	Covariates	Ref.
Growth factor									
EGFR CA repeat	OC	124	138	one allele≤16 vs. both alleles>16	1.8 (0.9-3.5)	both alleles≤16 vs. both alleles>16	2.1 (0.9-5.2)	Age, sex, smoking, alcohol, fruit and vegetables consumption	224
IGF-2 Msp1	OC	60	45	AG vs. AA	9.11 (3.62-22.96)[c]	AA vs. GG	18.67 (2.07-168.1)[c]	-	225
IGFR2R	OC	93	94	167 bp/other vs. other/other	2.7 (1.16-6.48)	167 bp/167 bp vs. other/other	1.0 (0.18-5.69)	Age, sex, smoking, alcohol, hospital	226
INS 1127 Pst1	OC	60	45	TC vs. TT	0.72 (0.29-1.80)[c]	CC vs. TT	0.44 (0.07-2.82)[c]	-	225
TGFalpha	OC	131	132	c1/c2 vs. c1/c1	0.6 (0.2-1.3)	c2/c2 vs. c1/c1	-	Age, sex, smoking, alcohol, fruit and vegetables consumption	224
TGFbeta1 -509	P	108	120	CT vs. CC	1.31 (0.64-2.66)	TT vs. CC	2.48 (1.17-5.26)	-	227
TGFbeta1 869	P	108	120	TC vs. TT	1.51 (0.74-3.08)	CC vs. TT	2.78 (1.29-5.99)	-	227
VEGF -460	OC	137	230	TC vs. TT	0.02 (0.01-0.05)[c]	CC vs. TT	-	-	228
Vitamin									
VDR FokI	OC, P, L	719	821	Ff vs. FF	0.85 (0.68-1.06)	ff vs. FF	0.64 (0.47-0.87)	Age, sex, smoking, alcohol	229
VDR TaqI	OC, P, L	719	821	Tt vs. TT	0.97 (0.77-1.22)	tt vs. TT	0.72 (0.53-0.98)	Age, sex, smoking, alcohol	229
Sex hormone									
AR	OC, P, L	103[d]	100[d]	CAG repeat>20 vs. ≤20	2.54 (1.3-4.8)			-	230

[a]OC, oral cavity; P, pharynx; L, larynx. [b]OR, odds ratio; 95% CI, 95% confidence interval. [c]OR and 95% CI were calculated from the genotype distribution. [d]Male.

Table X. Summary of previous meta-analyses of genetic polymorphisms and head and neck cancer risk.

Gene and polymorphic site	Year	Result	Summary OR (95% CI)[a]	No. of included studies	Ref.
GSTM1	2003	Null vs. Positive	1.23 (1.06-1.42)	30	232
GSTT1	2003	Null vs. Positive	1.17 (0.98-1.40)	21	232
GSTP1	2003	Ile/Val+Val/Val vs. Ile/Ile	1.10 (0.92-1.31)	9	232
CYP1A1 codon 462	2003	Ile/Val+Val/Val vs. Ile/Ile	1.32 (0.95-1.82)	12	232
GSTM1	2006	Null vs. Positive	1.50 (1.21-1.87)	30	233
XRCC1 codon 194	2005	Arg/Trp+Trp/Trp vs. Arg/Arg	0.85 (0.59-1.23)	3	234
XRCC1 codon 399	2005	Gln/Gln vs. Arg/Arg	1.13 (0.81-1.58)	4	234

[a]OR, odds ratio; 95% CI, 95% confidence interval.

will be of interest to explore further whether these genotypes are more relevant in specific ethnic groups with respect to the risk for HNC. Additional data have been published since the last meta-analysis, and a meta-analysis that includes the most recent data should be conducted to clarify the role of these polymorphisms.

Alcohol consumption is a major risk factor for HNC as well as esophageal cancer, and dose-response trends have been reported (6). There are consistent findings that the *1/*2 genotype of *ALDH2* is associated with increased risk of HNC. In contrast, the *2/*2 genotype of the gene might be associated with decreased risk of HNC. The latter finding may seem somewhat confusing. A meta-analysis showed that the *1/*2 genotype of *ALDH2* is associated with increased risk and that the *2/*2 genotype is associated with a decreased risk of esophageal cancer (265). These findings may be due to markedly lower alcohol consumption in *2/*2 vs. *1/*1 homozygotes because *2/*2 homozygotes are alcohol intolerant and can have severe reactions following intake of small amounts of alcohol (250,265). Reduced consumption of alcohol may reduce the risk for HNC as well as the risk for esophageal cancer.

ADH2 influences serum concentrations of acetaldehyde after ingestion of alcohol. There has been only 1 study of the relation between *ADH2* polymorphisms and HNC risk. *ADH2**1/*1 homozygotes shows significantly increased risk for HNC (118). *ADH2**1/*1 homozygotes also show a significantly increased risk for esophageal cancer (10). Because HNC and esophageal cancer have similar etiologies, *ADH2**1*1 homozygotes may have increased risk for both HNC and esophageal cancer. To confirm this hypothesis, further studies needed to confirm the relation between *ADH2* polymorphisms and risk for HNC.

There have been consistent findings that the Tyr/His and His/His genotypes of *EPHX1* codon 113 are associated with increased risk of HNC. However, results for the relation between *EPHX1* codon 139 polymorphisms and risk of HNC are inconsistent. These results may be due to differences in activity between the *EPHX1* His113 variant and *EPHX1* Arg139 variant.

In addition to *ALDH2* and *EPHX1* codon 113, there are consistent findings that the *p53* codon 72 Pro/Pro genotype is associated with increased HNC risk. Several researchers reported significant associations between the *p53* codon 72 Pro/Pro genotype and lung (266), esophageal (10), gastric (2667) and skin (268) cancers. To confirm the degree to which the *p53* codon 72 polymorphism contributes to HNC, meta-analyses should be conducted.

We previously published a review of genetic polymorphisms and risk of esophageal cancer (10). HNC and esophageal cancer have similar etiologies, and the association between HNC and esophageal cancer is well known (269,270). For instance, in a median 29-month follow-up period, esophageal cancer was diagnosed in 7.4% of patients with HNC (269). Similar patterns of genetic polymorphisms between HNC and esophageal cancer risks are observed. The Val allele of *CYP1A1* codon 462, Pro/Pro genotype of *p53* codon 72 and the *1/*2 genotype of *ALDH2* may increase both risks for HNC and esophageal cancer. However, the *GSTM1*-null genotype significantly increases the risk of HNC compared with *GSTM1*-postive genotype, but it does not increase the risk of esophageal cancer (OR, 1.07; 95% CI, 0.76-1.51) according to the results of meta-analyses (232,233,265). Similarly, the *GSTT1*-null genotype may increase the risk of HNC (OR, 1.17; 95% CI, 0.98-1.40) compared with *GSTT1*-positive genotype, but it does not increase the risk of esophageal cancer (OR, 0.99; 95% CI, 0.80-1.22) (232,265). In contrast to HNC, the occurrence of esophageal cancer shows a remarkable geographic bias. Most patients with esophageal cancer live in the 'esophageal cancer belt', which stretches from North-Central China westward through Central Asia to Northern Iran. Environmental risk factor(s) other than tobacco smoking, alcohol consumption and betel quid chewing may affect the geographic bias, and differences in genetic polymorphisms may also affect the bias.

Most genetic association studies use a case-control design. One important factor is the number of cases available to study. There are some advantages to increasing the number of control subjects (that is, having >1 matched control for each case). In practice 2:1 matching of control subjects to cases often provides the most efficient design for relatively common diseases. The size of the population required to determine a relative risk of a polymorphism is dependent on the allele frequency of the polymorphism. For example, with 90% power,

750 cases and the same number of controls are necessary to calculate an OR of >1.5 and a minor allele frequency of 0.4. Six hundred cases and the same number of controls are necessary for the same effect size and a minor allele frequency of 0.2 (271). Programs for estimating required sample size are available [http://hydra.usc.edu/gxe/ (272) and http://Statgen.iop.kcl.ac.uk/gpc (273)].

The best scientific evidence for associations of genetic factors with risk for HNC will come from large cohort studies that consider simultaneously the different factors potentially involved in carcinogenesis of the head and neck, including genetic polymorphisms and environmental factors, such as drinking alcohol and smoking tobacco. Identification of genetic factors that modify the impacts of environmental factors will depend on direct exploration of interactions between genes and environment (274). Furthermore, simultaneous analysis of multiple polymorphic genes should be done to address the possibility of identifying gene-gene interactions. The results of such studies will allow us to estimate the relative contribution of individual genetic variations to overall HNC risk.

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