Review

Genetic Polymorphism of *CYP* Genes, Alone or in Combination, as a Risk Modifier of Tobacco-related Cancers[1]

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Abstract

Tobacco use is causally associated with cancers of the lung, larynx, mouth, esophagus, kidneys, urinary tract, and possibly, breast. Major classes of carcinogens present in tobacco and tobacco smoke are converted into DNA-reactive metabolites by cytochrome P450 (CYP)-related enzymes, several of which display genetic polymorphism. Individual susceptibility to cancer is likely to be modified by the genotype for enzymes involved in the activation or detoxification of carcinogens in tobacco and repair of DNA damage. We summarize here the results of case-control studies published since 1990 on the effects of genetic variants of *CYP1A1, 1A2, 1B1, 2A6, 2D6, 2E1, 2C9, 2C19, 17,* and *19* alone or in combination with detoxifying enzymes as modifiers of the risk for tobacco-related cancers. The results of studies on gene-gene interactions and the dependence of smoking-related DNA adducts on genotype were also analyzed. Some *CYP* variants were associated with increased risks for cancers of the lung, esophagus, and head and neck. The risk was often increased in individuals who also had *GSTM1* deficiency. For breast cancer in women, a few studies suggested an association with *CYPs* related to metabolism of tobacco carcinogens and steroidal hormones.

The overall effects of common *CYP* polymorphisms were found to be moderate in terms of penetrance and relative risk, with odds ratios ranging from 2 to 10. Some *CYP1A1/GSTM1* 0/0 genotype combinations seem to predispose the lung, esophagus, and oral cavity of smokers to an even higher risk for cancer or DNA damage, requiring, however, confirmation. Future strategies in molecular cancer epidemiology for identifying such susceptible individuals are discussed with emphasis on well-designed larger studies.

Introduction

Epidemiological and human genetic studies have identified different types of population "at risk," one consisting of individuals with heavy exposure to carcinogens, such as smokers and exposed workers, and the other consisting of carriers of cancer-predetermining germ-line mutations in genes that because of high penetrance confer a very high risk for cancer *per se* (1). There is also another group of predisposing polymorphic, low-penetrance genes, *i.e.,* those involved in carcinogen metabolism and DNA repair, which modestly increase the risk for cancer in exposed individuals, perhaps at low doses of carcinogens (2, 3). In the latter case, the proportion of cancers attributable to such genetic traits may be high, because the frequency of "at risk" alleles in the population is high.

Drug-metabolizing enzymes, which often display genetic polymorphism, convert many tobacco carcinogens into DNA-binding metabolites in target cells and can thereby modulate intermediate effect markers such as DNA adducts and ultimately, the risk for cancer. The development of simple assays based on the PCR has allowed identification of individual genotypes for a variety of metabolic polymorphisms and studies on the modulation of cancer risk by environmental exposures, such as tobacco smoke, which are the subject of this review. Given the great number of carcinogen-activating and -detoxifying enzymes, the variation in their expression, and the complexity of exposures to tobacco carcinogens, assessment of a single polymorphic enzyme or genotype may not be sufficient to assess their role in carcinogenesis (reviewed in Ref. 4). Tobacco smoking is the major cause of lung cancer and is associated with risks for cancers of the larynx, mouth, esophagus, urinary bladder, and kidney (5). Breast cancer in women is at best weakly associated with cigarette smoking. We have included this site because recent studies suggested that postmenopausal women who are carriers of the *CYP1A1* or *NAT2* variant alleles may be at increased risk for breast cancer in a smoking-dose-related manner (6, 7).

Because major classes of tobacco carcinogens are converted to DNA-reactive metabolites by the oxidative, mainly CYP[4]-related enzymes, we have summarized studies of the effect of genetic polymorphism of *CYP*s in humans, alone or in combination with phase II enzymes, as risk modifiers of some major tobacco-related cancers. Our analysis includes case-control studies published from 1990 to May 1999 on cancers of the

Received 8/10/99; revised 11/2/99; accepted 11/2/99.

[1] Supported by the following sources, fellowships, or grants: Deutsches Krebsforschungszentrum (DKFZ)/International Agency for Research on Cancer (to U. N.), Deutsche Forschungsgemeinschaft and Verein zur Förderung der Krebsforschung (to A. R.), DKFZ (to M. R.), and the European Commission and Gottlieb Daimler-Carl Benz Stiftung (to H. W.).

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[4] The abbreviations used are: *CYP,* cytochrome P-450; PAH, polycyclic aromatic hydrocarbon; TSNA, tobacco-specific nitrosamine; B[*a*]P, benzo[*a*]pyrene; BPDE, benzo[*a*]pyrene diolepoxide; *GST,* glutathione *S*-transferase; NNK, 4-methylnitrosamino-1,3-pyridyl-1-butanone; NNN, *N*′-nitrosonornicotine; *NAT, N*-acetyltransferase; ROS, reactive oxygen species; Ah, aromatic hydrocarbon; OR, odds ratio; PM, poor metabolizer; UM, ultraploid metabolizer; EM, extensive metabolizer; HEM, heterozygous EM; RFLP, restriction fragment length polymorphism.

upper aerodigestive tract, urinary tract, and breast. To be included, a study had to have been published in a full article in English, cited in MedLine, and have involved a case-control design and adequate methods for analysis of *CYP* genotype. When several overlapping reports on one study population were available, we included the most recent publication, which usually covered a larger number of study subjects. To obtain insights into mechanisms, we also briefly reviewed studies of gene-gene interactions and the dependence of the formation of smoking-related PAH-DNA adducts on genotype. Because of space limitations, the references cited are not exhaustive, and the reader is referred to review articles marked in the text.

Tobacco Carcinogenesis, Major Causative Agents, Role of Metabolism, and DNA Adducts

These subjects have been reviewed by Hoffmann and Hecht (8, 9), McClellan (10), and Bergen and Caporaso (11). Processed tobacco contains over 3000 compounds including 30 carcinogens. The mainstream and sidestream smoke generated when tobacco in cigarettes is burnt contains more than 4000 constituents including about 50 carcinogens. The diversity of carcinogenic and toxic compounds in tobacco smoke leads to ambiguity about which are the most important; however, studies on the mechanisms of tobacco carcinogenesis and dosimetry in smokers and tobacco chewers indicate that three major classes of carcinogens, PAHs, TSNAs, and aromatic amines, play important roles in tobacco-associated cancers.

PAHs

The mechanism by which PAHs such as B[*a*]P interact with DNA, activate oncogenes, and initiate the carcinogenic process involves the formation of bay-region diolepoxides as the major ultimate carcinogens. B[*a*]P is converted into phenolic metabolites and B[*a*]P-7,8-diol by a CYP-mediated process. Secondary metabolism, mainly involving epoxide hydrolase and other CYP isoforms, leads to the formation of the highly reactive (+)-*anti*-BPDE. Several carcinogens present in tobacco smoke are inactivated by GSTs. The most frequently studied carcinogenic PAH diolepoxide, BPDE, is a relatively good substrate for *GSTM1*, *M2*, and *M3* and better still for *GSTP1* (12).

Sensitive detection methods have been used to demonstrate the presence of smoking-related bulky (PAH)-DNA adducts in virtually all target organs of tobacco carcinogenesis. The amounts of (+)-*anti*-BPDE bound to DNA can be quantified by high-performance liquid chromatography with fluorescence detection by measuring the release of B[a]P-tetrols both from lung tissue and lymphocyte DNA (13). Subsequently, the complex interrelationship between PAH-DNA adduct levels, daily or total smoking dose, genotype, and cancer risk was studied (reviewed in Ref. 14).

TSNAs

This topic has been reviewed by McClellan (10) and Hecht (9, 15). NNK and NNN are the most important TSNAs. They originate mostly from unburned tobacco and are also pyrosynthesized during smoking. The exposure of smokers to TSNAs is much higher than that to other environmental nitrosamines. The evidence that TSNAs are causative in tobacco-induced cancers of the upper aerodigestive tract in humans is highly suggestive: NNK is a powerful lung carcinogen in all species tested; human exposure is comparable with the dose that causes tumors in laboratory animals; and the metabolic activation pathways of NNK are similar in humans and laboratory animals. NNK and NNN require metabolic activation to bind to DNA and express their carcinogenic effects. The metabolism of NNK includes α-methylhydroxylation, α-methylenehydroxylation, pyridine-*N*-oxidation by CYP-mediated reactions, and reduction to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its conjugation as glucuronide (reviewed in Refs. 9 and 15). The last compound can be detected in human urine and is a good indicator of exposure to NNK. *N*- and *O*-methylated DNA bases have been detected in many exposed tissues. In addition, pyridyl-oxobutylation of DNA and globin occurs after exposure to NNK or NNN. The keto alcohol released from globin or DNA after hydrolysis allows sensitive human dosimetry of these TSNAs in tobacco users. NNK-derived DNA adducts in humans have been characterized only partially (15).

Aromatic Amines

4-Aminobiphenyl and other aromatic amines are the components of smoke that appear to be primarily responsible for urinary bladder cancer in smokers. The key reactions by which the compounds are metabolized and produce DNA adducts in the bladder epithelium involve *N*-hydroxylation (CYP1A2) and *N*-acetylation (NAT1 and NAT2). The resulting hydroxylamine also reacts with hemoglobin to form 4-aminobiphenyl-hemoglobin adducts in smokers or may be further activated by *O*-acetylation to *N*-acetoxyarylamines, reactions that are also catalyzed by NAT1 and NAT2. Molecular dosimetry in smokers of black (air-cured) and blond (flue-cured) tobacco provided further evidence that aromatic amines induce bladder cancer in smokers. Smokers of black tobacco, who have a risk for bladder cancer that is two to three times that of smokers of blond tobacco, have 2-fold higher 4-aminobiphenyl-hemoglobin adduct levels and excrete twice as much mutagens in their urine (reviewed in Ref. 16). The 4-aminobiphenyl-DNA guanine adduct was detected as a major smoking-related adduct in biopsy samples from bladder cancer patients and in exfoliated urothelial cells of volunteers. The levels of adducts of 4-aminobiphenyl with hemoglobin and with DNA in the bladder were correlated, and both were related to recent cigarette smoking. The metabolic phenotypes of rapid or slow *N*-acetylator and rapid or slow *N*-oxidizer, *CYP1A2*, significantly affected the levels of 4-aminobiphenyl-hemoglobin and 4-aminobiphenyl-DNA adducts in the urothelium of smokers. Studies in aromatic amine-exposed workers and in smokers have shown previously that the slow acetylator phenotype (slow NAT2) is at higher risk for developing bladder cancer than those with the fast phenotype (reviewed in Ref. 17).

Oxidative and Lipid Peroxidation-induced DNA Damage

Like preformed carcinogens, tobacco smoke contains ROS and reactive nitrogen species that impose oxidative stress on smokers' tissue. As a consequence, oxidative DNA-base damage has been detected in respiratory tract tissue of smokers, with lipid peroxidation products such as malondialdehyde, crotonaldehyde, and *trans*-4-hydroxy-2-nonenal, the last of which can be further epoxidized by CYP-mediated reactions. These reactive aldehydes have been shown to form promutagenic exocyclic DNA adducts in human tissues (18, 19) and thus could contribute to carcinogenesis in the upper aerodigestive tract (20). Chewing of tobacco alone or with betel quid is causally associated with oral cancer; because chewing of betel quid generates large amounts of ROS in the mouth, TSNAs and ROS are the major genotoxic agents implicated in oral cancer related to chewing (reviewed in Ref. 21).

Table 1 Overview of CYP1A1 nomenclature

Historical nomenclature of polymorphism	Point mutations	Systematic nomenclature for mutations from Cascorbi *et al.* (26), 1996	Systematic nomenclature for alleles from Cascorbi *et al.* (26), 1996	Nomenclature proposed by IARC (84), 1999	Nomenclature proposed by Nebert *et al.* (86), 1999
Wild-type allele, *m1*	None	wt[a]	*1	*1	*1
*Msp*I Allele 3′ non-coding region, m2	6235 T → C	m1	*2A	*2	*2A
Ile → Val, exon 7, codon 462	4889 A → G	m2	*2B (*m1* + *m2*[b])	*3 (*m2*)	*2B (*m1* + *m2*) *2C (*m2*)
African-American specific allele, intron 7	5639 T → C	m3	*3	*4	*3
Thr → Asn, exon 7, codon 461	4887 C → A	m4	*4	*5	*4

[a] wt, wild type.
[b] Mutation *m2* is in strict linkage disequilibrium with mutation *m1* in Caucasians.

Because tobacco carcinogens, ROS, and lipid peroxidation products are likely to be substrates for *GSTT1* or *M1*, the extent of DNA damage and ultimately the cancer risk may be affected by polymorphic CYPs and GST detoxifying enzymes (reviewed in Refs. 17 and 22).

Environmental Tobacco Smoke and Exposure to Low Doses of Carcinogens

Epidemiological studies have incriminated environmental tobacco smoke as a risk factor for lung cancer in nonsmokers. The concentrations of carcinogenic agents in such smoke appear to be low overall in comparison with those in undiluted mainstream smoke. Involuntary inhalation of tobacco smoke can occur over several hours/day. When comparing the ratio of concentration in sidestream and in mainstream smoke, relatively large amounts of carcinogenic, volatile nitrosamines and aromatic amines are released into sidestream smoke, as reflected by the concentrations of cotinine, a crude marker for uptake of tobacco carcinogens, in body fluids of passive smokers, which are about two orders of magnitude lower than those in active cigarette smokers (8). However, some data suggest that people with certain "at risk" genotypes are particularly susceptible to low doses of carcinogens (Ref. 2; reviewed in Ref. 3). This important health issue should be resolved by properly designed studies that would show whether passive smokers who have developed lung cancer are particularly susceptible.

Polymorphic Human *CYP* Genes Associated with Metabolism of Tobacco Carcinogens: Modulation of Cancer Risk

Molecular Basis for Enzyme Polymorphisms

Some of the principal ways in which genetic polymorphism can affect the expression of gene products or the catalytic activity of the respective enzyme can be summarized as follows:

(*a*) Nucleotide variations in the coding region of the gene result in amino acid substitution and alter enzyme activity or substrate binding (*e.g., CYP2D6*).

(*b*) Deletions in (of) the coding region lead to an inactive enzyme or lack of protein synthesis (*e.g., CYP2A6*, *CYP2D6*, and *GSTM1*).

(*c*) Polymorphisms in the noncoding region affect transcriptional control elements involved in basal enzyme expression and induction (*e.g., CYP1A1*).

(*d*) Variations in the polyadenylation signal of a gene affect transcript half-life and thus the quantity of enzyme (*e.g., NAT1*).

(*e*) Gene amplification increases the quantity of enzyme (*e.g., CYP2D6*).

(*f*) Complex interactions of polymorphic genes and/or their enzyme catalysis products (*e.g., GSTM1*-deficient subjects or cells have greater induction of *CYP1A1* and *1A2*, probably because of greater bioavailability of inducer compounds).

Allelic CYP *Variants and Effect on Cancer Risk in Tobacco Users*

The role of particular human CYP450 in the metabolism of carcinogens has been reviewed (23–25). In the following, we evaluate case-control studies on the effect of polymorphic CYPs on the tobacco smoke-associated risk of cancers of the lung, larynx, mouth, esophagus, kidneys, urinary tract, and female breast. The past and recent systematic nomenclature for *CYP1A1* polymorphisms is given in Table 1. For the purpose of clarity, we have referred to *CYP1A1* mutations by the system of Cascorbi *et al.* (26).[5]

CYP1A1. The human enzyme CYP1A1, which is well conserved, is involved in the activation of major classes of tobacco procarcinogens, like PAHs and aromatic amines, and is present in many epithelial tissues. About 10% of the Caucasian population has a highly inducible form of the CYP1A1 enzyme (termed B[a]P-hydroxylase or previously arylhydrocarbon hydroxylase), which is associated with an increased risk for bronchial, laryngeal, and oral cavity tumors in smokers (reviewed in Ref. 27).

The induction of *CYP1A1* is initiated by the specific binding of aromatic inducer compounds to the Ah receptor. An Ah receptor nuclear translocator (*Arnt*) gene is further involved in the *CYP1A1* induction pathway. Thus far, no relationship has been found between Ah receptor polymorphism and lung cancer risk (28, 29).

Beginning in 1973 with the pioneering work by Kellerman *et al.* (30) on B[a]P hydroxylase inducibility and bronchogenic carcinoma, studies on the association of the genetic polymorphism of CYP1A1 and cancer started after cosegregation of the CYP1A1 high inducibility phenotype and polymorphism of the *Msp*I restriction site (31).

The *CYP1A1* Ile-Val (*m2*) mutation in the heme-binding region results in a 2-fold increase in microsomal enzyme activity and is in complete linkage disequilibrium in Caucasians with the *CYP1A1 Msp*I (*m1*) mutation, which has also been

[5] A complete description of *CYP* alleles is given at http://www.imm.ki.se./CYPalleles/.

associated experimentally with increased catalytic activity (32). Although the Ile-Val mutation in the *CYP1A1* allele did not increase activity *in vitro* (33, 34), it might be linked to other functional polymorphisms, for example in the regulatory region important for *CYP1A1* inducibility. Smokers with the exon 7 Ile-Val mutation were found to have more PAH-DNA adducts in their WBCs than smokers without the variant (35). The amount of these adducts is also elevated in cord blood and placenta of newborns with the *CYP1A1-Msp*I polymorphism (36). In lung parenchymal tissue of smokers, the concentrations of BPDE and bulky (PAH)-DNA adducts were positively correlated with CYP1A1 enzyme activity (13). Significant ethnic differences in the frequency of homozygous *CYP1A1 Msp*I alleles have been observed, and both the *Msp*I and *Val* alleles are rarer in Caucasian than in Japanese populations (26).

A proposal has been made for a mechanism whereby the *CYP1A1* genotype and *GSTM1* 0/0 gene-gene interactions result in a greater-than-additive risk for DNA damage and cancer; in human cells, deletion of *GSTM1* is associated with strong inducibility of *CYP1A1* gene transcription by 2,4,7,8-tetrachlorodibenzo-*para*-dioxin (37). When BPDE-DNA adduct levels were measured in lung tissue of smokers, a significant interaction between deficiency of the *GSTM1* phenotype and high *CYP1A1* inducibility or *CYP1A1* allelic variants was observed (38, 39), leading to very high adduct levels in Caucasians with *CYP1A1/Msp*I/*Msp*I-*GSTM1* 0/0 [see "*CYP1A1-GSTM1* Genotype Dependence of Bulky (PAH)-DNA Adduct Levels and of Other Effect Markers in Smokers"]. These data suggest that this "at risk" genotype combination predisposes to an increased risk for tobacco-associated DNA damage and lung cancer.

Lung Cancer. The relationship between *CYP1A1* variants and lung cancer risk in various ethnic populations has been examined in more than 20 studies. Early Japanese studies pointed to an increased risk for lung cancer in association with both the m1 (Table 2, study nos. 1 and 10) and m2 mutations (Table 2, study 4); the *CYP1A1* genotype was particularly important at a low level of smoking and in the development of squamous cell carcinoma (Table 2, study 3). These findings were not confirmed in studies conducted in Norway (Table 2, study 2), Finland (Table 2, study 5), the United States (Table 2, study 6), and Sweden (Table 2, study 8), perhaps because of the much lower prevalence of the *m1* allele in Caucasians. Larger studies in mixed American populations (Table 2, study nos. 16, 17, 18, and 20) do point to an increased risk for lung cancer among carriers of *m1* alleles, whereas in Caucasian smokers in France, no significant association was observed for either *m1* or *m2* (Table 2, study 19). In two Brazilian populations, the presence of the *m2* allele was significantly associated with an increased risk for lung cancer (Table 2, study 12). The African-American-specific *m3* (*3) mutation was not associated with an increased risk for lung cancer overall in three studies (Table 2, study nos. 9, 13, and 21); however, in one of them, a significantly increased risk for adenocarcinoma was seen for carriers of the *m3* mutation (Table 2, study 21), and the OR for lung cancer was 8.4 for the genotype *m1/m1,m2* (*2A/*2B). In Chinese, the *m1* and *m2* mutations were not correlated with either allele or lung cancer risk (Table 2, study 24), whereas results from the Republic of Korea surprisingly showed a significantly decreased risk for lung cancer among carriers of the *m2* allele (Table 2, study 25). A recently described *m4* mutation in close proximity to *m1* has thus far been investigated in only one study of Caucasians, in which it did not correlate with an increased risk for lung cancer (Table 2, study 14). It is possible that individuals carrying the *m4* mutation were misclassified as carriers of the *m2* mutation in earlier studies, in which allele-specific primers were used. The combined *CYP1A1* variants (either *m2* or *m1*) and *GSTM1* 0/0 genotype have been associated with a significantly increased risk for lung cancer (Table 2, study nos. 4, 7, and 11), especially squamous cell carcinoma (Table 2, study nos. 4 and 20) in Japanese populations.

Head and Neck Cancer. The CYP1A1 enzyme is present in oral tissue (40), and *CYP1A1* variants and cancer risk at these sites have been investigated in 11 studies. There was overrepresentation of the *CYP1A1* Ile-Val variant among Caucasian patients with oral cancer, but the prevalence of the Ile-Val variant was significantly higher in nonsmokers than smokers, although the number of nonsmokers was low (Table 3, study 2). Similarly, an increased prevalence of *CYP1A1* Val-Val variant was found among Japanese patients with head and neck cancers and especially those with pharyngeal cancer (Table 3, study 5). Individuals with the homozygous *CYP1A1 Msp*I (*m1/m1*) variant were at significantly increased risk for oral squamous cell carcinoma, in particular after exposure to low concentrations of PAH. The combination of homozygous *CYP1A1 Msp*I (*m1/m1*) variant and *GSTM1* 0/0 further increased the risk. The buccal mucosa and upper gingiva appear to be the most susceptible tissues in carriers of the risk genotype (Table 3, study 6). The highest prevalence of *p53* mutation was observed in oral tumors from patients with the *CYP1A1*(Val)/*GSTM1* active genotype (41).

Esophageal Cancer. Studies in Caucasians and Japanese showed no association with esophageal cancer. Esophageal cancer patients in China who were heavy smokers had a 3-fold higher frequency of the *CYP1A1* Val-Val variant. The risk was further increased in patients with the combination of *CYP1A1* Val-Val and *GSTM1* 0/0 genotypes (Table 4, study 4).

Urinary Tract Cancer. Two studies of Japanese and Caucasians showed no significant associations (Table 5, study nos. 1 and 2). High *CYP1A1* expression, as determined by immunohistochemistry, correlated with the grade of urinary bladder tumor (42).

Breast Cancer. None of four studies of the effect of the *m2* allele in Caucasian populations found a significant association overall (Table 6, study nos. 1–4), but a significant increase in risk was found among postmenopausal women who were light smokers and carried the *m2* allele (Table 6, study 2). These results were not confirmed in a smaller study of Caucasians, but an increased risk for breast cancer was found among African-American women with the homozygous *m1/m1* genotype (Table 6, study 3). Bailey *et al.* (Ref. 43; Table 6, study 4), investigating *m1, m2, m3,* and *m4* in Caucasian and African-American women, found no significant association, nor did the largest study, nested within the Nurses' Health Study (Table 6, study 5), although in the latter study an increased risk was found for smoking at a young age and the presence of *m1* and/or *m2*. A recent study of the *m2* allele in postmenopausal women (Table 6, study 2) showed a significant correlation between above-median serum concentrations of polychlorinated biphenyls, the *m2* allele, and breast cancer risk (Table 6, study 6).

Taken together, there is increasing evidence that the homozygous *CYP1A1* (*Msp*I and Ile-Val) genotypes are at higher risk for contracting smoking-associated lung (squamous cell carcinoma), head and neck, and esophageal cancers, as particularly seen in Asian study populations where these "at risk" allele frequencies are 8–18 times higher than in Caucasians. The cancer risk was further increased in the combined "at risk" *CYP1A1-GSTM1* 0/0 genotypes. The underlying mechanism of

Table 2 CYP1A1 and lung cancer

Study no.	Gene	Mutations/ allele	Major cancer subtypes[a](*n*)	Country/ ethnicity[b]	Cases/controls (*n*)	Genotype frequencies[c] (% in cases/ controls)	Significance[d] OR (95% CI)	Comments	References
1	*CYP1A1*	*m1*	SCC (23) AC (21) SCLC (18) LCLC (6)	Japanese	68/104	*m1/m1:* 23.5/10.6 *wt/wt:* 35.3/49.0	S *m1/m1 vs. wt/wt* + LC: 3.1 (CI not given) + SCC: 4.6 (CI not given)		Kawajiri *et al.* (87), 1990
2	*CYP1A1*	*m1*	SCC (80) SCLC (55) AC (46) LCLC (27)	Norwegian	221/212	*m1/m1:* <1/<1 *wt/wt:* 77.8/78.8	NS *m1/m1* and *m1/wt vs. wt/wt* and LC: 1.05 (0.67–1.67)	Histological type, smoking habits and family history investigated; no association with *m1*	Tefre *et al.* (88), 1991
3	*CYP1A1*	*m1*	SCC (57) AC (60) SCLC (24) LCLC (10)	Japanese	151/375	*m1/m1:* 21.2/10.6 *wt/wt:* 40.4/44.3	NS but SCC, low doseof smoking and *m1/m1* S: 7.31 (2.13–25.12)	Patients with susceptible genotypes contracted carcinoma after fewer cigarettes, but no difference at high smoking dose	Nakachi *et al.* (89), 1991
4	*CYP1A1*	*m2*	SCC (67) AC (96)	Japanese	212/358	*m2/m2:* 12.3/4.7 *wt/wt:* 56.6/65.1	S *m2/m2:* LC: 2.97 (1.59–5.57) SCC: 3.34 (1.49–7.52) AC: 2.54 (1.48–4.34)	*m2/m2* + *GSTM1* 0/0: LC: OR, 5.83 (CI, 2.28–13.3) SCC: OR, 9.07 (CI, 3.38–24.4)	Hayashi *et al.* (90), 1992
5	*CYP1A1*	*m2*	SCC (57) AC (37) SCLC (8)	Finnish	106/122	*m2/m2:* 0/1.6 *wt/wt:* 78.3/78.7	NS		Hirvonen *et al.* (91), 1992; study population overlapping with Hirvonen *et al.* (92), 1992 and Hirvonen *et al.* (93), 1993
6	*CYP1A1*	*m1*	SCC (29) AC (18) LCLC (4) SCLC (5)	A-A (28/23) and Caucasian-Americans (28/25)	56/48	*m1/m1:* 3.5/6.2 *wt/wt:* 76.8/68.8	NS *m1/m1* and *m1/wt vs. wt/wt* LC: 0.7 (0.3–1.6)		Shields *et al.* (94), 1993
7	*CYP1A1*	*m1, m2*	SCC only	Japanese	85/170	*m1:* *m1/m1:* 22.4/8.8 *wt/wt:* 38.8/48.2 *m2:* *m2/m2:* 10.6/3.5 *wt/wt:* 58.8/64.7	S *m1/m1:* lower smoking dose: 6.55 (2.49–17.24); higher smoking dose 8.32 (2.34–29.62) *m2/m2:* lower smoking dose 8.46 (2.48–28.85); higher smoking dose 8.46 (1.68–42.73)	*GSTM1* null + *CYP1A1 m1/m1:* OR, 16 (CI, 3.76–68.02) *GSTM1* null + *CYP1A1 m2/m2:* OR, 41 (CI, 8.68–193.61) each at low smoking dose	Nakachi *et al.* (95), 1993
8	*CYP1A1*	*m1, m2*	SCC (107) AC (84) SCLC (58)	Swedish	296/329 healthy controls + 79 hospital controls	*m1:* *m1/m1:* 1.3/0.3 *wt/wt:* 83.8/83.9 *m2: m2/m2:* 0/0 *wt/wt:* 94.6/93.0	NS	OR for SCC before age 66, for *m1/wt* among *GSTM1* 0/0 OR, 3.0 (CI, 1.2–7.2)	Alexandrie *et al.* (96), 1994
9	*CYP1A1*	*m3*	Newly diagnosed, previously untreated LC, no histological restrictions	A-A in USA	72/97	*m3/m3:* 1.4/2.1 *wt/wt:* 83.3/76.3	NS *m3/m3* and *m3/wt vs. wt/wt* 0.64 (0.3–1.4)		Kelsey *et al.* (97), 1994
10	*CYP1A1*	*m1*	SCC (86) AC (147) SCLC (8) LCLC (21)	Japanese	267/151	*m1/m1:* 16.9/10.6 *wt/wt:* 36.7/44.3	S *m1/m1* and *m1/wt:* 1.71 (1.07–2.69)	Same control group as Nakachi *et al.* (89), 1991	Okada *et al.* (98), 1994
11	*CYP1A1*	*m1, m2*	SCC (71) SCLC (47)	Japanese	118/331 (185 smoking controls)	*m1: m1/m1:* 16.5/17.8[e] *wt/wt:* 37.1/43.8[e] *m2:* *m2/m2:* 5.3/6.0[e] *wt/wt:* 61.1/55.5[e]	NS	For *m2/m2* and *GSTM1* 0/0 OR, 21.9 (CI, 4.68–112.7)	Kihara *et al.* (78), 1995

Table 2 Continued

Study no.	Gene	Mutations/ allele	Major cancer subtypes[a] (*n*)	Country/ ethnicity[b]	Cases/controls (*n*)	Genotype frequencies[c] (% in cases/ controls)	Significance[d] OR (95% CI)	Comments	References
12	CYP1A1	m1, m2	Newly diagnosed and histologically confirmed LC	Black, white, and mullato Brazilians	110/112	*m1: m1/m1:* 8/8 *wt/wt:* 63/63 *m2: m2/m2:* 2/2 *m2/wt:* 27/14 *wt/wt:* 71/84	S *m2/m2 + m2/wt:* 2.26 (1.14–4.47) *m2/m2 + m2/wt* in white Brazilians: 2.4 (1.15–4.98)		Sugimura *et al.* (99), 1995; Hamada *et al.* (100), 1995; study population overlapping with Sugimura *et al.* (101), 1994
13	CYP1A1	m3	AC (51) SCC (35) SCLC (14)	A-A	144/230	*m3/m3* and *m3/wt:* 16.7/15.2 *wt/wt:* 83.3/84.8	NS *m3/m3* and *m3/wt vs. wt/wt* LC: 1.3 (0.7–2.4)	Strongest association with SCC, but NS	London *et al.* (102), 1995
14	CYP1A1	m1, m2, m3, m4	LC	Caucasian	157/314	*m3:* 0/0 *m4:* 2.87/2.87	S *m2:* 3.01 (1.29–7.26) NS for *m1, m3, m4*		Cascorbi *et al.* (26), 1996 study population overlapping with Drakoulis *et al.* (103), 1994
15	CYP1A1	m1	SCC (13)	AC (15) SCLC (8)	European	44/81 *m1/m1:* 2.3/2.5 *wt/wt:* 84.1/79.0	NS *m1/m1* and *m1/wt vs. wt/wt* LC: 0.71 (0.27–1.87)	*CYP1A1* inducibility Significant association with risk for AC OR, 5.29 (CI, 1.27–22.00); for LC OR, 3.41 (CI, 1.19–9.75)	Jacquet *et al.* (104), 1996
16	CYP1A1	m1	AC (110) SSC (67)	Mixed: Caucasian and "non-Caucasian"	207/283	*m1/m1:* 1.0/0.7 *m1/wt:* 16.9/17.0 *wt/wt:* 82.1/82.3	S for *m1/wt + m1/m1:* for LC 2.08 (1.15–3.73)[f]; for light smokers with AC: 2.25 (1.13–4.48)[f]	Positive association for each subtype of LC	Xu *et al.* (105), 1996
17	CYP1A1	m1	AC (225) SSC (116) SCLC (18) LCLC (23)	Mostly white American	412/442	*m1/m1:* 1.0/1.0 *m1/wt:* 18.0/16.3 *wt/wt:* 81.0/82.7	S *m1/wt* and LC: 1.5 (1.0–2.3)[f]	Includes data from Xu *et al.* (105), 1996 OR for *m1/wt* and *GSTM1* null: OR, 1.9 (CI, 1.0–3.4)	Garcia Closas *et al.* (106), 1997
18	CYP1A1	m1, m2, m3	LC	A-A and M-A	171/295	A-A: *m1: m1/m1:* 1.8/5.8 *wt/wt:* 60.6/63.5 *m2: m2/wt:* 3.7/3.7 *wt/wt:* 96.3/96.3 *m3: m3/m3:* 1.1/1.9 *wt/wt:* 81.5/77.9 M-A: *m1: m1/m1:* 16.1/17.1 *wt/wt:* 40.3/42.4 *m2: m2/m2:* 11.5/12.7 *wt/wt:* 44.3/46.2	NS A-A: OR for "presence of": *m1:* 1.54 (0.78–3.03)[f] *m2:* 0.72 (0.11–4.79)[f] *m3:* 0.63 (0.24–1.62)[f] M-A: *m1:* 0.85 (0.4–1.78)[f] *m2:* 1.34 (0.63–2.84)[f] But *m1/m1* and *m1/wt* in light smokers (≤30 PY) S: 2.03 (1.03–4.01)[f]		Ishibe *et al.* (107), 1997
19	CYP1A1	m1, m2	SCC (98) SCLC (52)	Caucasian (in France)	150/171	*m1/m1:* 0.7/0 *m1/wt:* 12.0/10.5 *m1,m2/wt:* 5.3/8.7 *m1,m2/m1,m2:* 1.3/0 *wt/wt:* 80.7/80.7	NS *m1/m1* and *m1/wt vs. wt/wt* 0.9 (0.5–1.8)[f] *m2/m2* and *m2/wt vs. wt/wt* 0.8 (0.3–1.9)[f]		Bouchardy *et al.* (108), 1997

Table 2 Continued

Study no.	Gene	Mutations/ allele	Major cancer subtypes[a] (*n*)	Country/ ethnicity[b]	Cases/controls (*n*)	Genotype frequencies[c] (% in cases/ controls)	Significance[d] OR (95% CI)	Comments	References
20	CYP1A1	m1, m2	SCC (74) AC (162) SCLC (51)	Caucasian, Japanese, Hawaian	341/456	*m1:* *m1/m1:* 10.3/9.7 *m1/wt:* 35.7/35.2 *wt/wt:* 54.0/55.1 *m2:* *m2/m2:* 1.8/2.9 *wt/wt:* 78.0/74.0	NS *m1/m1 vs. wt/wt* 1.2 (0.6–2.2)[f] *m1/wt vs. wt/wt* 1.3 (0.9–1.9)[f] *m2/m2 vs. wt/wt* 0.7 (0.2–2.3)[f] *m2/wt vs. wt/wt* 1.0 (0.6–1.5)[f] but *m1/m1* and *m1/wt* and SCC: S: 2.4 (1.2–4.7)	*m1/m1* and *m1/wt* + *GSTM1* null + SCC: OR, 3.1 (CI, 1.2–7.9)[f]	Le Marchand *et al.* (109), 1998
21	CYP1A1	*m1, m2, m3*	SCC (37) AC (41) LCLC (8) SCLC (7)	A-A	96/278	*m1/m1:* 6.2/6.0 *m1/wt:* 20.8/27.0 *m1/m3:* 5.2/3.6 *m1/m2:* 0/4.7 *m1/m1,m2:* 3.0/0.4 *m1/m3,m3:* 1.0/0 *m1/m2,m3:* 1.0/0 *m2/m2:* 1.0/0 *m2/wt:* 3.0/1.1 *m3/m3:* 0/0.4 *m3/wt:* 10.5/10.4 *wt/wt:* 47.9/46.4	NS *m1/wt vs. wt/wt:* 1.2 (0.7–2.2)[f] *m1/m1 vs. wt/wt:* 1.3 (0.5–3.5)[f] ORs for "presence of": *m2:* 1.1 (0.4–2.7)[f] *m3:* 1.5 (0.7–3.2)[f] but *m3/m3* and *m3/wt* + AC: S: 2.8 (1.3–6.5)[f]	*m1/m1* and *m2/wt:* OR, 8.4 (CI, 1.6–43.2)[f]	Taioli *et al.* (110), 1998; study population overlapping with Taioli *et al.* (111), 1995
22	CYP1A1	m2	SCC (122) SCLC (28) AC (78)	Japanese from Okinawa	247/185	*m2/m2:* 11.3/3.8 *m2/wt:* 38.1/45.4 *wt/wt:* 50.6/50.8	S *m2/m2* + LC: 3.3 (1.3–8.6)[f] + SCC: 4.9 (1.4–16.3)[f] + SCLC: 9.4 (2.1–42.0)[f]		Sugimura *et al.* (112), 1998
23	CYP1A1	m1, m2	SCC (30) AC (56) SCLC (16) LCLC (6)	Japanese	108/95	*m1:* *m1/m1:* 22.2/10.5 *wt/wt:* 36.1/na *m2:* *m2/m2:* 16.7/6.3 *wt/wt:* 53.7/na	S *m1/m1* and LC: 2.93 (1.26–6.84)[f] *m2/m2* and LC: 3.45 (1.29–9.25)[f]		Kiyohara *et al.* (113), 1998
24	CYP1A1	m1, m2	AC (38) SCLC (18) SCC (14)	Chinese	76/122	*m1:* *m1/m1:* 12/11 *wt/wt:* 43/44 *m2:* *m2/m2:* 8/4 *wt/wt:* 66/65	NS *m1/wt vs. wt/wt:* 0.84 (0.44–1.60) *m1/m1 vs. wt/wt:* 0.99 (0.37–2.61) *m1,m2/wt vs. wt/wt:* 0.83 (0.44–1.59) *m1,m2/m1,m2 vs. wt/wt* 1.81 (0.58–5.71)	Combined analysis of *CYP1A1* variants and GSTM1 "0": NS	Persson *et al.* (114), 1999
25	CYP1A1	m1, m2	SCC (27) SCLC (15) AC (28)	Korean	85/63	*m1:* *m1/m1:* 7/5 *wt/wt:* 40/46 *m2:* *m2/m2:* 1/2 *m2/wt:* 80/95 *wt/wt:* 19/3	S *m2/m2* or *m2/wt:* 0.14 (0.03–0.64)	Combined analysis of *CYP1A1 m1* alleles and *GSTM1* "0": NS Very high frequency of *m2/wt-m2* distribution not in Hardy-Weinberg equilibrium *m1* and *m2* mutations are not in complete linkage disequilibrium	Hong *et al.* (115), 1998

[a] SCC, squamous cell carcinoma; AC, adenocarcinoma; SCLC, small cell lung cancer; LCLC, large cell lung cancer; LC, lung cancer.
[b] A-A, African-American.
[c] wt, wild type; M-A, Mexican-American.
[d] S, significant; NS, not significant; CI, confidence interval; PY, pack years.
[e] Values for smoking controls ($n = 185$).
[f] Data adjusted for confounding factors such as smoking, age, gender, and others (for details, refer to original publication).

Table 3 CYPs and head and neck cancers

Study no.	Gene	Mutation/ allele	Cancer site[a](*n*)	Country/ ethnicity	Cases/controls (*n*)	Genotype frequencies (% cases/controls)	Significance[b] OR (95% CI)	Comments	References
1	*CYP1A1*	*m1*	Upper aerodigestive tract cancer	French Caucasians	96/202	Allele frequencies *m1:* 0.12/0.12	NS	Alcoholic controls NS alcoholic controls (202) *vs.* normal controls (260) 0.12/0.087	Lucas *et al.* (145), 1996
2	*CYP1A1*	*m2*	Oral cancer SCC (112) Larynx (23)	United States Caucasians	131/131	*wt/m2 + m2/m2* All: 17.6/7.6 M: 12.9/7.1 F: 26.1/8.7	S All: 2.6 (1.2–5.7) F: 3.7 (1.1–12.5)	Higher prevalence of *wt/m2 + m2/m2* in nonsmoker cases *vs.* smoker cases; OR, 0.3 (CI, 0.1–1.0)	Park *et al.* (146), 1997
3	*CYP1A1*	*m1 m2*	Upper aerodigestive tract. Oral/pharynx (126) Larynx (272) (Total cases)	German Caucasians	398/219	*m1/m1:* 0.3/1.0 *wt/wt:* 84/89.8 *m2/m2:* 0.5/1.0 *wt/wt:* 85/85.5	NS *m1/m1 + m1wt/wtwt* Oral/ pharynx 0.6 (0.3–1.3)[c] Larynx 0.6 (0.3–1.1)[c] *m2m2 + m2wt/ wtwt* Oral/pharynx 1.3 (0.6–2.6)[c] Larynx 0.8 (0.5–2.6)[c]	No interaction between *CYP1A1* and *GSTM1* or *CYP1A1* and smoking.	Matthias *et al.* (147), 1998
4	*CYP1A1*	*m1 m2*	SCC (185) Larynx (73) Oral and oropharynx (76) Other subsites (36)	Dutch Caucasians	185/207	Allele frequencies *m1:* 0.178/0.159 *wt:* 0.822/0.841 *m2:* 0.184/0.164 *wt:* 0.816/0.836	NS $P = 0.71$	NS: in combination with *GSTM1* and *GSTT1*	Oude Ophuis *et al.* (148), 1998
5	*CYP1A1*	m2	SCC Larynx (69) Hypo/oropharynx (45) Tongue (22) Oral cavity (12)	Japanese	145/164	All: $n = 145$ *m2/m2:* 9/3.7 *wt/m2:* 25/33 *wt/wt:* 66/63 Pharynx: $n = 45$ *m2/m2:* 13/3.7 *wt/m2:* 31/33 *wt/wt:* 56/63	*m2/m2 vs. m2/wt + wt/wt* S SCC 4.1 (1.1–15) $P = 0.038$ S Pharynx 5.7 (1.1–28) $P = 0.034$	NS Logistic regression analysis of cases with multiple *vs.* single tumors; with age, gender, smoking, ethanol, CYP1A1, CYP2E1, GSTM1, GSTP1 and NAT2 as covariates	Morita *et al.* (149), 1999
6	*CYP1A1*	m1	Oral SCC Lower gingiva (30) Tongue (29) Floor of the mouth (21) Buccal mucosa (11) Upper gingiva (9)	Japanese	100/100	*m1/m1:* 15/8 *wt/wt:* 32/62	S: *m1/m1* in cases *vs.* controls 3.6 (1.4–9.5)	*m1/m1* and *GSTM1* 0/0 S: 4.3 (1.0–17.4) S: in cases, smoking dose for *m1/m1* was significantly less than smoking dose for *wt/wt* S: *m1/m1* in combination with *GSTM1* 0/0; 4.3 (1.0–17.4) S: for various subsites of oral cancer except floor of the mouth ORs ranging from 2.3 (tongue) to 46.5 (buccal mucosa)	Tanimoto *et al.* (150), 1999
7	*CYP2D6*	*4	Pharynx (35) Larynx (35) Mouth-floor (5)	Spanish Caucasians	75/200	PM: 4/3 EM: 82/76	NS	Cases all male NS: Control 150 M *vs.* 50 F NS: Pharynx *vs.* larynx	Gonzalez *et al.* (151), 1998
8	*CYP2D6*	*3 *4	Upper aerodigestive tract. Oral/pharynx (126) Larynx (272)	German Caucasians	398/219	PM: 6.2/5.8 EM: 59/58.1	NS Oral/pharynx PM: 0.7 (0.2–2.1)[c] EM: 1-1 (0.7–1.8)[c] Larynx PM: 1.1 (0.5–2.6)[c] EM: 1.1 (0.8–1.7)[c]		Matthias *et al.* (147), 1998
9	*CYP2D6*	*3, *4, *5	Oral SCC	British Caucasians	100/467	PM: 13/4.5 EM: 66/63	S: PM in cases *vs.* controls 3.2 (1.6–6.5) $P = 0.001$	S: in cases <65 yr PM greater and EM less than in cases >65 yr $P = 0.009$ Time to lymph node metastasis shorter in PM compared with EM Alcohol or smoking had no effect.	Worrall *et al.* (152), 1998

Table 3 Continued

Study no.	Gene	Mutation/ allele	Cancer site[a] (*n*)	Country/ethnicity	Cases/ controls (*n*)	Genotype frequencies (% cases/controls)	Significance[b] OR (95% CI)	Comments	References
10	CYP2E1	*Rsa*I*Dra*I	Upper aerodigestive tract cancer	French Caucasians	96/202	Allele frequency *c2:* 0.040/0.044 *C:* 0.141/0.114	NS	Alcoholic controls S: alcoholic controls (202) *vs.* normal controls (260) *C:* 0.141/0.079; $P < 0.01$ NS: but lower frequency of *C* allele in <45 yr cases (protective effect!)	Lucas *et al.* (145), 1996
11	CYP2E1	*Rsa*I	Oral cancer	Taiwan Chinese: 71% Fukienese; 7% Hakka; and 22% mainland	41/123	*c2/c2:* 5/3 *c1/c2:* 46/34 *c1/c1:* 49/62	NS *c1/c2 + c2/c2/c1/c1* 1.8 (0.9–3.9)[c] but among nonchewers only *c1/c2* and *c2/c2 vs. c1/c1* S: 4.7 (1.1–20.2)[c] $n = 7/40$	Cases all male. Age and ethnicity adjusted; alcohol and betel-quid chewing investigated NS: combination with *GSTM1* and/ or *GSTT1*	Hung *et al.* (153), 1997
12	CYP2E1	*Pst*I	Pharynx (35) Larynx (35) Mouth floor (5)	Spanish Caucasians	75/200	*c2/c2:* 2/0 *c1/c1:* 90/90	NS		Gonzalez *et al.* (151), 1998
13	CYP2E1	*Pst*I, *Rsa*I*Dra*I	Upper aerodigestive tract. Oral/pharynx (126) Larynx (272)	German Caucasians	398/219	*c2/c2:* 0.3/0 *c1c1:* 93.7/94.3 *CC:* 0.3/1.7 *DD:* 85/84.3	NS *c1/c2 + c2/c2/c1/c1* Oral/ Pharynx 0.9 (0.3–2.7)[c] Larynx 0.8 (0.3–1.9)[c] *CD + DD/DD* Oral/pharynx 1.2 (0.6–2.5)[c] Larynx 1.3 (0.7–2.6)[c]	Alcohol had no effect.	Matthias *et al.* (147), 1998
14	CYP2E1	*Pst*I, *Rsa*I	SCC Larynx (69) Hypo/ oropharynx (45) Tongue (22) Oral cavity (12)	Japanese	145/164	*c2/c2:* 5.5/4.3 *c1/c1:* 62.8/64	NS All cases $P = 0.4$ Larynx $P = 0.12$ Pharynx $P = 0.9$	NS Logistic regression analysis of cases with multiple *vs.* single tumors; with age, gender, smoking, ethanol, CYP1A1, CYP2E1, GSTM1, GSTP1, and NAT2 as covariates.	Morita *et al.* (149), 1999

[a] SCC, squamous cell carcinoma.
[b] NS, not significant; S, significant.
[c] Data adjusted for confounding factors such as smoking, age, gender, and others (for details, refer to original publication).

Table 4 CYPs and esophageal cancers

Study no.	Gene	Mutation/allele	Cancer site	Country/ethnicity	Cases/controls (*n*)	Genotype frequencies (% cases/controls)	Significance[a] OR (95% CI)	Comments	References
1	*CYP1A1*	*m1*	Esophageal cancer	French Caucasians	62/202	Allele frequency *m1:* 0.12/0.14	NS	Alcoholic controls NS: Alcoholic controls (202) *vs.* normal controls (260) 0.12/0.087	Lucas *et al.* (145), 1996
2	*CYP1A1*	*m1 m2*	Esophageal cancer	Japanese	94/70	*m1:* *m1/m1:* 11.7/21.4 *wt/wt:* 35.1/41.4 *m2:* *m2/m2:* 2.2/4.3 *wt/wt:* 57.1/60.0	NS		Hori *et al.* (154), 1997
3	*CYP1A1*	*m2*	Esophagus SCC[b]	Japanese	53/132	*m2: m2/m2:* 1.9/2.3 *wt/wt:* 60.4/60.6	NS *m2/m2* + *m2/wt vs. wt/wt* 1.0 (0.5–1.9)	NS: Genotype distribution in male smokers or alcohol drinkers NS: Multiple regression analysis of *CYP2E1*, *CYP1A1*, and *GSTM1* with age alcohol and gender as covariates	Morita *et al.* (155), 1997
4	*CYP1A1*	*m2*	Esophageal carcinoma	Chinese	89/137	*m2: m2/m2:* 15/5 *wt/wt:* 56/67	S *m2/m2* cases *vs.* controls $P < 0.05$	S: *m2/m2* and high smoking dose OR, 6.63 (CI, 1.86–23.7) $P < 0.01$ S: *m2/m2* and *GSTM1* 0/0 and high smoking dose OR, 12.7 (CI, 1.97–81.8) $P < 0.01$	Nimura *et al.* (156), 1997
5	*CYP1A1*	*m1 m2*	Esophageal carcinoma AC: 21 SCC: 13	Dutch Caucasians	AC: 21/247 SCC: 13/247	AC: *m1:* *m1/m1:* 0/1 *wt/wt:* 67/84 *m2:* *m2/m2:* 0/1 *wt/wt:* 86/84 SCC: *m1:* *m1/m1:* 0/1 *wt/wt:* 61/84 *m2:* *m2/m2:* 0/1 *wt/wt:* 61/84	NS	Very few cases	Van Lieshout *et al.* (157), 1999
6	*CYP2E1*	*Rsa*I *Dra*I	Esophageal cancer	French Caucasians	62/202	Allele frequency *c2:* 0.040/0.00 *C:* 0.141/0.09	NS	Alcoholic controls S: Alcoholic controls (202) *vs.* normal controls (260). *C:* 0.141/0.079 NS but lower frequency of *C* allele in <45 yr cases (protective effect ?)	Lucas *et al.* (145), 1996
7	*CYP2E1*	*Pst*I, *Rsa*I	Esophageal cancer	Japanese	94/70	*c2/c2:* 7.6/1.4 *c1/c1:* 62/64.3	NS	Also shown that S: ADH2/ADH2[b] OR, 6.2 (CI, 2.6–14.7) S: ALDH2[b]/ALDH2 OR, 4.4 (CI 2.5–7.7) S: Combination of two OR, 17.9 ($P < 0.001$)	Hori *et al.* (154), 1997
8	*CYP2E1*	*Pst*I, *Rsa*I	Esophagus SCC	Japanese	53/132	*c2/c2:* 1.9/3.8 *c1/c1:* 64.2/64.4	NS *c2c2* + *c2c1 vs. c1c1* 1.0 (0.5–2.0)	NS: Genotype distribution in male smokers and alcohol drinkers NS: Multiple regression analysis of *CYP2E1*, *CYP1A1*, and *GSTM1* with age alcohol and gender as covariates	Morita *et al.* (155), 1997
9	*CYP2E1*	*Rsa*I *Dra*I	Esophagus SCC or AC	Chinese	45/46	*c2/c2:* 7/7 *c1/c2:* 13/49 *c1/c1:* 80/44 *DD:* 9/7 *CC:* 55/42	S *c2/c2*and*c1/c2 vs. c1/c1* OR, 4.8 (CI,1.8–12.4) but NS for *Dra*I *CD* + DD/*CC* 1.5 (0.5–3.6)[c]	Small study size S: 45 hyperplasia and dysplasia cases *c2/c2*and *c1/c2 vs. c1/c1* OR, 6 (CI,2.3–16) S: 62 cancer + advanced dysplasia *c2/c2* and *c1/c2 vs. c1/c1* OR, 4 (CI, 1.8–12.4)	Lin *et al.* (158), 1998

[a] NS, not significant; S, significant.
[b] SCC, squamous cell carcinoma; AC, adenocarcinoma; ADH2, alcohol dehydrogenase 2; ALDH2, aldehyde dehydrogenase 2.
[c] Data adjusted for confounding factors such as smoking, age, gender, and others (for details, refer to original publication).

Table 5 CYPs and urinary tract cancer

Study no.	Gene	Cancer site	Mutation/ allele	Country/ ethnicity (*n*)	Cases/ controls (*n*)	Genotype/allele frequencies (% cases/controls)	Significance[a] (OR and 95% CI)	Comments	References
1	*CYP1A1*	Bladder, renal pelvis, and ureter	*m2*	Japanese	83/101	*m2/m2:* 3.6/5.0 *wt/wt:* 60.3/56.4	NS		Katoh *et al.* (159), 1995
2	*CYP1A1*	Bladder	*m1, m2*	German Caucasians	374/373	*m1/m1:* 0.8/0.6 *wt/wt:* 83.7/83.9 *m2/m2:* 0.3/0 *wt/wt:* 95.6/94.4	NS *m1wt + m1m1:* 0.9 (0.6–1.4)[b] *m2wt + m2m2:* 0.7 (0.3–1.4)[b]	Effect on LC risk not modified by smoking or histological type	Brockmöller *et al.* (160), 1996
3	*CYP1A2*	Bladder	Intron 1	German Caucasians	220/137	Data not given	NS but for smokers borderline OR, 1.7 (CI not given)	*CYP1A2 + NAT* slow; OR, 2.2 (CI not given)	Brockmöller *et al.* (17), 1998
4	*CYP2D6*	Bladder	*4	British Caucasians	184/720	PM: 4.4/4.3 HEM: 41.8/29.6 EM: 53.8/66.1	S $P = 0.005$ only for HEM *vs.* EM		Smith *et al.* (116), 1992
5	*CYP2D6*	Bladder	*3, *4, *5	British Caucasians	126/132	PM: 10/6 HEM: 34/27 EM: 56/67	NS $P = 212$	Controls: non-bladder cancer outpatients	Spurr *et al.* (161), 1995
6	*CYP2D6*	Bladder	*3, *4, *5	Egyptian	22/21	PM: 31.8/52.3 HEM: 22.7/19.0 EM: 45.5/28.6	NS EM: 2.4 (0.7–9.9)	*GSTM1* 0/0 and *CYP2D6* EM: OR, 14.0 (CI, 1.3–151)	Anwar *et al.* (162), 1996
7	*CYP2D6*	Bladder	*3, *4, *5, *16, *2xn	Caucasians in Germany	374/373	PM: 5.6/8.9 EM: 51.4/51.7	NS[b]	Effect on LC[c] risk not modified by histological type or tumor grade or stage	Brockmöller *et al.* (160), 1996
8	*CYP2E1*	Bladder	*Pst*I	Egyptian	22/21	*c2c2:* 0/0 *c1c1:* 100/95.3	NS $P = 0.48$		Anwar *et al.* (162), 1996
9	*CYP2E1*	Bladder	*Pst*I, *Rsa*I, *Taq*I	German Caucasians	374/373	*Pst*I: *c2c2:* 0/0 *c1c1:* 96.2/94.3 *Dra*I: *CC:* 1.8/0.3 *DD:* 85.6/87.3 *Taq*I: *A1A1:* 0.8/0.3 *A2A2:* 77.6/74.1	NS[a]	Effect on LC risk not modified by smoking or histological type	Brockmöller *et al.* (160), 1996
10	*CYP2E1*	Renal and urothelial	*Dra*I, *Pst*I	German Caucasians	187 renal + 38 urothelial cancer patients/304	Renal: *Dra*I: *CC:* 1.1/0.7 *DD:* 84.0/86.2 *Pst*I: *c2c2:* 0.5/0.0 *c1c1:* 93.0/95.1 Urothelial: *Dra*I: *CC:* 0.0/0.7 *DD:* 86.8/86.2 *Pst*I: *c2c2:* 0/0.0 *c1c1:* 97.4/95.1	Renal: NS *c1c2:* 1.3 (0.6–2.9)[b] but females S c1c2: 8.0 (1.6–39.2)[b] & C/D: 2.6 (1.3–5.3)[b] Urothelial: NS[b]		Farker *et al.* (163), 1998
11	*CYPC19*	Bladder	*2	German Caucasians	374/373	*2/*2: 1.7/3.5 *1A/*1A: 67.9/71.5	NS *1A*1A + *1A*2: OR, 2.7 (CI, 0.9–7.7)[b]	Effect on LC risk not modified by smoking or histological type	Brockmöller *et al.* (160), 1996

[a] NS, not significant; S, significant.
[b] Data adjusted for confounding factors such as smoking, age, gender, and others (for details, refer to original publication).
[c] LC, lung cancer.

Table 6 CYPs and breast cancer in women

Study no.	Gene	Mutation/ allele	Country/ ethnicity[a]	Cases/controls[b] (*n*)	Genotype frequency (% cases/controls)	Significance[c] OR (95% CI)	Comments	References
1	*CYP1A1*	*m2*	Caucasian	96/126	Allele frequency *m2:* 0.01/0	**NS**		Rebbeck *et al.* (164), 1994
2	*CYP1A1*	*m2*	United States Caucasian	216/282	*m2/m2:* 2/1 *wt/wt:* 80/85	**NS** *m2/m2* and *m2/wt vs. wt/wt* 1.61 (0.94–2.75)[d] but for light smokers (up to 29 py) and m2/wt or m2/m2: **S:** 5.22 (1.16–23.56)[d]	Postmenopausal women only	Ambrosone *et al.* (6), 1995
3	*CYP1A1*	*m1, m2, m3*	Caucasian and A-A	30/183 Cauc.; 21/86 A-A	Cauc.: *m1:* *m1/m1:* 0/2.7 *wt/wt:* 73.3/79.8 *m2:* *m2/m2:* 0/1.1 *wt/wt:* 82.8/82.9 A-A: *m1:* *m1/m1:* 19.0/3.5 *wt/wt:* 33.4/60.0 *m2:* *m2/wt:* 0/6.0 *wt/wt:* 100/94.0 *m3:* *m3/wt:* 19.0/16.2 *wt/wt:* 81.0/83.7	**S** m1/m1 in A-A: 9.7 (2.0–47.9)		Taioli *et al.* (165), 1995
4	*CYP1A1*	*m1, m2, m3, m4*	Caucasian and A-A	164/164 Cauc.; 59/59 A-A	Cauc.: *m1:* *m1/m1:* 2.4/3.0 *wt/wt:* 79.3/84.0 *m2:* *m2/wt:* 9.1/7.4 *wt/wt:* 90.9/92.6 *m4:* *m4/m4:* 0.6/0.6 *wt/wt:* 93.3/92.0 A-A: *m1:* *m1/m1:* 3.4/5.1 *wt/wt:* 71.1/55.9 *m2:* *m2/wt:* 1.7/0 *wt/wt:* 98.3/100 *m3:* *m3/m3:* 1.7/0 *wt/wt:* 79.7/76.3 *m4:* *m4/wt:* 1.7/0 *wt/wt:* 98.3/100	**NS** Cauc: *m1:* 1.37 (0.78–2.41) *m2:* 1.38 (0.62–3.11) *m4:* 0.82 (0.36–1.90) A-A: *m1:* 0.51 (0.24–1.10) *m2:* 1.02 (0.98–1.05) *m3:* 0.82 (0.34–1.96) *m4:* 1.02 (0.98–1.05)		Bailey *et al.* (43), 1998
5	*CYP1A1*	m1, m2	United States registered nurses	466/466	*m1:* *m1/m1* or *m1/wt:* 18.7/17.2 *wt/wt:* 81.3/82.8 *m2: m2/m2* or *m2/wt:* 13.1/14.0 *wt/wt:* 86.9/86	NS RR (*m1*): 1.05 (0.74–1.50) RR (*m2*): 0.88 (0.58–1.33)	Prospective study nested within "Nurses' Health Study" Suggested increased risk for early smoking and *m1* or *m2*	Ishibe *et al.* (166), 1998
6	*CYP1A1*	m2	Postmenopausal women in United States	154/192	*m2/m2:* 83/88 *wt/m2* or *wt/wt:* 17/12	NS *m2/m2* and *m2/wt vs. wt/wt* 1.79 (0.91–3.55)[d] but for women with serum PCB[e] levels above median of distribution in control group: S: *m2/m2* or *m2/wt:* 2.93 (1.17–7.36)[d]	Patients are subset of another study [Ambrosone *et al.* (6), 1995]	Moysich *et al.* (167), 1999

Table 6 Continued

Study no.	Gene	Mutation/ allele	Country/ ethnicity[a]	Cases/controls[b] (*n*)	Genotype frequency (% cases/controls)	Significance[c] OR (95% CI)	Comments	References
7	CYP1B1	Val432Leu (*m1*) Asn[453]Ser (m2)	Caucasians, A-A	164/164 Cauc. 59/59 A-A	Cauc.: codon 432: *leu/leu:* 31.7/29.9 *val/val:* 16.5/11.6 codon 453: *ser/ser:* 3.0/2.4 *asn/asn:* 67.7/67.7 A-A: codon 432: *leu/leu:* 8.4/5.1 *val/val:* 45.8/44.1 codon 453: *asn/ser:* 5.1/6.8 *asn/asn:* 94.9/93.2	**NS** Cauc: codon 432: *val/leu vs. val/val:* RR, 0.6 (0.3–1.3)[d] *leu/leu vs. val/val:* RR, 0.7 (0.4–1.5)[d] codon 453: *asn/ser vs. asn/asn* RR, 0.9 (0.6–1.6)[d] *ser/ser vs. asn/asn* RR, 1.3 (0.3–4.8)[d] A-A: codon 432: *val/leu vs. val/val:* RR, 0.9 (0.4–1.8)[d] *leu vs. val/val:* RR, 1.6 (0.4–2.9)[d] codon 453: *asn/ser vs. asn/asn* RR, 0.7 (0.2–3.4)[d]	Caucasian patients with codon 432 val/val genotype have more estrogen receptor-positive and progesterone receptor-positive breast cancers	Bailey *et al.* (51), 1998
8	CYP2D6	*3, *4, *5	United States Caucasian	167/114	*m/m:* 7.2/6.1 *wt/wt:* 62.3/69.3	**NS**		Buchert *et al.* (168), 1993
9	CYP2D6	*3, *4, *9	Spanish	151/187	PMs: 2.7/3.8 HEM: 31.0/19.9 EM: 65.2/77.4	**S** HEM 1.81 (1.06–3.11) also: *4/wt and *4/*4 1.7 (1.14–3.13)	*3 and *4 are non-functioning *9 and wt are functioning alleles *4 allele most prevalent in postmenopausal women and those with non-ductal-infiltrating carcinomas	Ladona *et al.* (169), 1996
10	CYP2E1	*Dra*I	Caucasians	166/221	DC and CC: 13.3/14.0 DD: 86.7/86.0	**NS** *C/C* and *D/C vs. D/D* premenopausal women: 1.04 (0.48–2.24)[d] postmenopausal women: 1.01 (0.55–1.84)[d] but *C/C* and *CD* in premenopausal smokers: **S:** 11.1 (1.5–81.4)		Shields *et al.* (170), 1996
11	CYP17	A2	Women from Hawaii and Los Angeles; A-A, Latino, Japanese	174/285	*A2/A2* and *A2/A1:* 71.8/66.3 *A1/A1:* 28.2/33.7	**NS** 1.32 (0.87–2.00)[d] but *A2/A2* and *A2/A1* and regional/metastatic disease: **S:** 2.5 (1.07–5.94)	*A1/A1* genotype had lower age at menarche	Feigelson *et al.* (171), 1997
12	CYP17	A2	Women from East Anglia	835/591	*A2/A2:* 15.6/14.4 *A1/A1:* 36.3/38.7	**NS** **OR for** *A2* allele carriers 1.1 (0.89–1.37)		Dunning *et al.* (172), 1998
13	CYP17	A2	Primarily Americans of European descent	109/113	*A2/A2:* 19.2/15.9 *A1/A1:* 37.6/32.7	**NS** *A2/A1 vs. A1/A1* 0.61 (0.33–1.14) *A2/A2 vs. A1/A1* 0.89 (0.41–1.95)		Helzlsouer *et al.* (173), 1996
14	CYP17	A2	Women in New York City: 224 Caucasian 55 A-A 84 Hispanic	123/240 (76/148 Cauc.; 20/35 A-A; 27/57 Hispanic)	*A2/A2:* 17/15 *A1/A1:* 37/38	**NS**		Weston *et al.* (174), 1998
15	CYP17	A2	United States registered nurses	463/618	*A2/A2:* 16/15 *A1/A1:* 38/35	**NS** OR for *A2* allele carriers: 0.85 (0.65–1.12)	Case-control study nested within Nurses' Health Study	Haiman *et al.* (175), 1999

Table 6 Continued

Study no.	Gene	Mutation/ allele	Country/ ethnicity[a]	Cases/ controls[b] (*n*)	Genotype frequency (% cases/controls)	Significance[c] OR (95% CI)	Comments	References
16	CYP19	TTTA repeat (intron 5), alleles found with 7, 8, 9, 11, and 12 repeats	Swedish and Norwegian	182 sporadic and 185 familial cases, 252 controls	Allele frequencies: *A1* (7xTTTA): 0.037/0.016 *A2* (8xTTTA): 0.339/0.329 *A3* (9xTTTA): 0.011/0.014 *A4* (11xTTTA): 0.091/0.119 *A5* (12xTTTA): 0.522/0.522	S *A1* allele carriers and breast cancer: 2.42 (1.03–5.80)	Higher frequency of *A1* allele in patients with estrogen/ progesterone receptor-positive tumors	Kristensen *et al.* (176), 1998
17	CYP19	6 common and 2 rare alleles	United States Caucasians	348/145	171-bp allele homozygotes: 3.78/0.70 Allele frequencies: *A1* (168 bp): 0.327/0.334 *A2* (171 bp): 0.185/0.134 *A3* (175 bp): 0.118/0.116 *A4* (183 bp): 0.019/0.018 *A5* (187 bp): 0.335/0.345 *A6* (191 bp): 0.016/0.053	S 171-bp allele overrepresented in cases RR, 5.4; $P = 0.019$		Siegelmann Danieli and Buetow (177), 1999

[a] A-A, African-American.
[b] Cauc., Caucasian.
[c] NS, not significant; S, significant; RR, relative risk.
[d] Data adjusted for confounding factors such as smoking, age, gender, and others (for details, refer to original publication).
[e] PCB, polychlorinated biphenyl.

this genetic predisposition in these "at risk" smokers is supported by a higher prevalence of *p53* mutations and B[*a*]P-DNA adducts (see "*CYP1A1-GSTM1* Genotype Dependence of Bulky (PAH)-DNA Adduct Levels and of Other Effect Markers in Smokers"). For breast cancer risk, the available studies conducted on *CYP1A1* variants mostly in Caucasians did not reveal an overall association.

CYP1A2. This isoform activates many dietary and tobacco procarcinogens, notably aromatic and heterocyclic amines, and also metabolizes nicotine. Human *CYP1A2* has 72% sequence identity with *CYP1A1* and, in contrast to extrahepatic CYP1A1, CYP1A2 appears to be expressed mainly in the liver and only weakly in the peripheral lung (44). Like CYP1A1, CYP1A2 is regulated in part by the Ah-receptor system and is induced in humans by a variety of chemicals. The activity of this enzyme can be determined in a noninvasive assay involving measurement of caffeine 3-demethylation.

Recently, a genetic polymorphism in the 5′ flanking region of the human *CYP1A2* was identified that affects inducibility (45). Another single nucleotide polymorphism was found in intron 1, which is associated with high catalytic activity when subjects are exposed to tobacco smoke (46, 47). Individuals who are homozygous for the high inducibility genotype were shown to account for ~45% of healthy Caucasians. A subgroup of smokers had a 1.6-fold increase in the caffeine demethylation ratio (ratio of paraxanthine:caffeine in serum) over that in nonsmokers.

Gene-gene interactions between *GSTM1* 0/0 and CYP1A2 and CYP1A1 enzyme induction have been observed in smokers; *GSTM1* deficiency not only led to increased hepatic CYP1A2 activity in current smokers but also to significantly increased levels of bulky PAH-DNA adducts in lung parenchyma of smokers and ex-smokers, over that in individuals with wild-type *GSTM1* (4, 38, 39, 48). CYP1A2 activity was higher in *GSTM1* 0/0 subjects after exposure to cigarette smoke and heterocyclic amines from cooked meat. Exposed individuals with *CYP1A1 Ile-Val* alleles had greater CYP1A2 activity than those with wild-type *CYP1A1* (49). *GSTM1* 0/0 led to higher levels of 4-aminobiphenyl-hemoglobin adducts in smokers (50). Such gene-gene interactions are probably attributable to a greater bioavailability of aromatic inducer compounds in *GSTM1* 0/0 subjects, leading to a higher rate of induction of CYP1A1 and CYP1A2 in smokers, which in turn increases macromolecular carcinogen binding.

Urinary Tract Cancer. In one preliminary case-control study (Table 5, study 3), patients with the intron 1 variant had an OR of 1.7 for bladder cancer if they were smokers; if they also had the slow NAT2 phenotype, the OR was 2.2.

CYP1B1 CYP1B1, 1A2, and 3A4 all catalyze 2- and 4-hydroxylation of 17β-estradiol, but 4-hydroxylation is selectively catalyzed by CYP1B1. This enzyme activates many PAH-dihydrodiols, aromatic amines, and other groups of procarcinogens. CYP1B1 is also induced by Ah-receptor ligands. This enzyme is expressed in human kidney, prostate, ovary, and breast, and three CYP1B1 polymorphisms have been identified in exon 3, two of which are associated with amino acid substitutions, *i.e.,* Val^{432}Leu and Asn^{453}Ser in the heme-binding domain of the enzyme (51).

Breast Cancer. In the only study conducted thus far, no association was found with the *CYP1B1* genotype. Caucasian patients with the codon 432 *Val-Val* genotype were more likely to

Table 7 CYPs and lung cancer

Study no.	Gene	Mutation/ allele	Major cancer subtypes[a] (*n*)	Country/ ethnicity	Cases/controls (*n*)	Genotype frequencies[b] (% cases/controls)	Significance[c] OR (95% CI)	Comments	References
1	*CYP2A6*	*2, *3	Not specified	United States population	182/460	mut/mut: 1.1/2.4 wt/wt: 78.0/77.2	**NS** RR, 1 variant allele: 1.0 (0.6–1.6) 2 variant alleles: 0.5 (0.1–2.1)		London *et al.* (55), 1999
2	*CYP2D6*	*4	SCC (145) AC (74) SCLC (52)	English Caucasians	361/720	PM: 3.6/4.3 EM: 64.8/66.1	NS $P = 0.9$	Effect on LC[d] risk not modified by histological type.	Smith *et al.* (116), 1992; study population overlapping with Wolf *et al.* (117), 1992
3	*CYP2D6*	*3, *4, *5	SCC (58) AC (36)	Finnish Caucasians	106/122	PM: 0.9/5.7 HEM + EM: 99.1/94.3	**S** EM: 6.4 (1.0–143)	Effect on LC risk not modified by amount of smoking or histological type.	Hirvonen *et al.* (93), 1993; study population overlapping with Hirvonen *et al.* (118), 1993
4	*CYP2D6*	*3, *4, *9	Epidermoid (48) AC (20) Microcytic (15)	Spanish Caucasians	89/98	PM: 3/8 (*9 allele incl) PM: 0/7 (*9 not incl) HEM: 36/24 EM: 61/68	**S** $P < 0.02$ if *9 allele not included as PM	*9 allele does not abolish CYP2D6 activity completely.	Agundez *et al.* (119), 1994
5	*CYP2D6*	*3, *4, *5, *7	SCC (74) SCLC (72) AC (38) LCLC (22)	Norwegian Caucasians	218/289	PM: 9.8/5.1 EM: 60.8/59.0 (*7 not included in genotype frequencies)	**NS** $P = 0.22$	Effect on LC risk not modified by amount of smoking or histological type.	Tefre *et al.* (120), 1994
6	*CYP2D6*	*3, *4	SCC (84) SCLC (50) LCLC (33) AC (33)	Slovenian Caucasians	200/107	PM: 2.5/6.5 HEM: 27/31 EM: 70.5/62.5	S $P = 0.056$	Effect on LC risk not modified by histological type.	Dolzan *et al.* (121), 1995
7	*CYP2D6*	*3, *4, *5	AC (27) SCC (23)	United States population	54/50	PM: 7.4/16 EM: 37/50	**NS** EM + HEM: 2.4 (0.6–10.2)	*CYP2E1, GSTM1, GSTT1* combination NS	El Zein *et al.* (122), 1997; study population overlapping with El Zein *et al.* (123), 1997
8	*CYP2D6*	*3, *4, *5, *16, *2xn	AC (121) SCC (82) SCLC (46)	United States Caucasians and A-A	341/710	PM: all: 4.4/4.9 (Cauc.: 5.9/5.8; A-A: 2.5/3.3) EM: 71.4/65.2 UM: 5.2/4.5 (Cauc.: 4.9/4.3; A-A: 5.7/4.9)	**NS** Cauc.: PM: 1.0 (0.4–2.3)[e] A-A: PM: 0.7 (0.2–2.2)[e] but AC: for UMs in A-A: **S:** 3.6 (1.1–11.7)[e]	Effect on LC risk not modified by smoking, asbestos, or PAH exposure or histological type.	London *et al.* (124), 1997
9	*CYP2D6*	SSCP >40 mutations detected	SCC (115) AC (58) SCLC (49)	French Caucasians	249/265	PM: 8.0/8.4 HEM + EM: 89/90 UM: 3.0/1.6	**NS** but *1A/*2 genotype significantly associated with LC, especially SCLC: **S:** 3.6 (1.1–11.9)[e]		Legrand Andreoletti *et al.* (63), 1998; study population overlapping with Legrand *et al.* (125), 1996 and Stücker *et al.* (126), 1995
10	*CYP2D6*	*3, *4, *5, *6A, *9, *10 A	AC (35) SCLC (30) SCC (16)	Canadian Caucasians	98/110	PM: 7.1/2.7 EM: 54.1/57.3	**NS** HEM: 0.3 (0.05–1.6)[e] EM: 0.3 (0.05–1.5)[e]		Shaw *et al.* (127), 1998; study population overlapping with Shaw *et al.* (128), 1997
11	*CYP2E1*	*Dra*I	SCC (14) AC (14) SCLC (13)	Not defined	47/56	*CC:* 0/10.7 *CD:* 46.8/30.4 *DD:* 53.2/59.9	S $P < 0.05$		Uematsu *et al.* (129), 1991; study population may overlap with Uematsu *et al.* (130), 1992 and (131), 1994

Table 7 Continued

Study no.	Gene	Mutation/ allele	Major cancer subtypes[a](*n*)	Country/ethnicity	Cases/controls (*n*)	Genotype frequencies[b] (% cases/controls)	Significance[c] OR (95% CI)	Comments	References
12	CYP2E1	*Pst*I *Rsa*I	SCC (31) AC (19)	United States Caucasians and A-A	67/61	*Pst*I *c2c2:* 0/0 *c1c1:* 96/92	**NS** *Pst*I *c1c2:* 0.7 (0.2–5.4) *Rsa*I *c1c2:* 0.9 (0.2–2.8)	20 controls had other cancers; effect on LC risk not modified by race or histological type.	Kato *et al.* (132), 1992
13	CYP2E1	*Dra*I	SCC (23) AC (25) SCLC (10) LCLC (10)	Not defined	74/73	*CC:* 2.7/13.7 *CD:* 45.9/28.8 *DD:* 51.4/57.5	S $P < 0.05$		Uematsu *et al.* (130), 1992; study population may overlap with Uematsu *et al.* (129), 1991 and (131), 1994
14	CYP2E1	*Dra*I, *Rsa*I	SCC (54) AC (35)	Finnish Caucasians	101/121	*Dra*I: *CC:* 2.0/0.8 *DD:* 84.2/79.3 *Rsa*I: allele frequency: *c2* = 0.02/0.012	**NS** $P = 0.44$	Effect on LC risk not modified by smoking or histological type.	Hirvonen *et al.* (133), 1993
15	CYP2E1	*Dra*I, *Taq*I, *Rsa*I	SCC AC (27) SCLC LCLC	Swedish Caucasians	195/206	*Dra*I: *CC:* 0/1 *DD:* 83/81 *Taq*I: *A1A1:* 0/0.5 *A2A2:* 81/81 *Rsa*I: *c2c2:* 0/0.5 *c1c1:* 96/90	**NS** but allele frequency of *c2* (*c2* = 0.02/0.05) significantly lower among cases than controls		Persson *et al*. (134), 1993
16	CYP2E1	*Dra*I	SCC (24) AC (36) SCLC (21) LCLC (10)	Not defined	91/76	*CC:* 2.2/14.5 *CD:* 46.2/28.9 *DD:* 51.6/56.6	**S** *CC:* 0.13 (0.04–0.51) but: *CD:* 2.1 (1.1–4.0)	Effect on LC risk not modified by histological type.	Uematsu *et al.* (131), 1994; study population may overlap with Uematsu *et al.* (129), 1991 and (130), 1992
17	CYP2E1	*Dra*I	SCC (31) AC (19)	United States Caucasians and A-A	58/56	*CC:* 0/0 *DD:* 79/86	**NS** *CD:* 1.6 (0.6–4.2)[e]	Same population as Kato *et al.* (132), 1992. 18 controls had other cancers. Effect on LC risk not modified by histological type; A-A and Cauc. had similar allele frequencies.	Kato *et al.* (135), 1994
18	CYP2E1	*Rsa*I	AC (143) SCC (104) SCLC (51)	Japanese	316/503	*c2c2:* 4.1/3.2 *c1c1:* 65.5/63.0	**NS**	Effect on LC risk not modified by smoking, alcohol consumption or histological type.	Watanabe *et al.* (136), 1995
19	CYP2E1	*Rsa*I	Not specified	Brazilians	99/108	*c2c2:* 0/0 *c1c1:* 90/89	**NS** *c1c2:* 0.9 (0.4–2.1)[e]	Effect on LC risk not modified by histological type.	Hamada *et al.* (100), 1995; study population overlapping with Sugimura *et al.* (99), 1995
20	CYP2E1	*Rsa*I	AC (121) SCC (82) SCLC (44)	United States Caucasians and A-A	341/706 A-A: 157/247 Cauc.: 184/459	*c2c2:* 0% for all *A-A:* c1c1: 98.1/98.0 *Cauc.:* c1c1: 94.6/92.2	**NS** *c1c2:* 0.7 (0.4–1.5)[e]	Effect on LC risk not modified by histological type, asbestos exposure, vitamins, or dietary intake. No racial difference.	London *et al*. (137), 1996

Table 7 Continued

Study no.	Gene	Mutation/ allele	Major cancer subtypes[a](*n*)	Country/ ethnicity	Cases/controls (*n*)	Genotype frequencies[b] (% cases/controls)	Significance[c] OR (95% CI)	Comments	References
21	CYP2E1	*Pst*I	AC (73) SCC (53)	Japanese	126/612	*c2c2:* 5.6/4.1 *c1c1:* 69.0/63.9	**NS** *c2c2:* 1.4 (0.6–3.3) borderline for SCC: *c2c2:* 2.5 (0.9–6.5)	*c2c2* genotype correlated positively with *p53* mutations.	Oyama *et al.* (138), 1997
22	CYP2E1	*Pst*I	SCC (23) AC (27)	United States population	54/50 all smokers	*c2c2:* 1.9/0.0 *c1c1:* 87/94	**NS but c1c2 + c2c2 vs c1c1** **AC: S:** 18.9 (1.0–351)	Small number of subjects	El Zein *et al.* (122), 1997; study population overlapping with El Zein *et al.* (139), 1997
23	CYP2E1	*Pst*I	Not specified	M-A and A-A	137/206 A-A: 92/144 M-A: 45/92	All: *c2c2:* 0.7/1.0 *c1c2:* 11/19.4 *c1c1:* 88.3/79.6 M-A: *c2c2:* 2.2/1.1 *c1c2:* 11.1/28.2 *c1c1:* 86.7/70.7 A-A: *c2c2:* 0/0.9 *c1c1:* 89.1/86.8	**S only for M-A:** *c1c1 vs. c1c2 + c2c2;* M-A 14.0 (1.9–102)[e] M-A males: 15.0 (1.9–121)[e] *c1c1* + smoking: 16.3 (2.1–127)[e]	Cancer at earlier age in *c1c1* patients. *c1c1* not associated with LC among A-A, nonsmokers, or women.	Wu *et al.* (140), 1997
24	CYP2E1	*Dra*I	Not specified	M-A and A-A	126/193 A-A: 85/104 M-A: 41/89	All: *CC:* 0.8/2.1 *CD:* 12.7/23.3 *DD:* 86.5/74.6 M-A: *CC:* 2.4/3.4 *DD:* 78.1/69.6 A-A: *CC:* 0.0/1.0 *DD:* 90.6/78.8	**S** **All (***DD vs. CD + CC*): 2.4 (1.1–5.3)[e] Men (*DD vs. CD + CC):* 3.4 (1.3–8.7)[e] DD + smokers: 22.7 (3.0–174.6)[e]	Same population as Wu *et al.* (140), 1997. Combined smoking and *DD* genotoxic effect greater than multiplicative (OR, 22.7). *DD* not associated with LC among nonsmokers or women.	Wu *et al.* (141), 1998
25	CYP2E1	*Dra*I, *Rsa*I	SCC (74) AC (162) SCLC (51)	Caucasians, Hawaians, and Japanese	341/456	*Dra*I: *CC:* 1.5/5.5 *CD:* 27.5/26.8 *DD:* 71/67.7 *Rsa*I: *c2c2:* 0.6/3.1 *c1/c2:* 19.6/22.5 *c1c1:* 79.8/74.4	**S** *Dra*I all LC: *CC:* 0.2 (0.1–0.7)[e] *AC:* *CC:* 0.1 (0.0–0.5)[e] RsaI: c2c2: 0.1 (0.0–0.5)[e]	Ethnic groups not studied separately.	Le Marchand *et al.* (109), 1998
26	CYP2E1	*Dra*I, *Rsa*I	AC (38) SCLC (18) SCC (14)	Chinese	76/122	*Dra*I: *CC:* 6.6/4.9 *DD:* 61.8/48.4 *Rsa*I: *c2c2:* 2.6/4.9 *c1c1:* 63.2/51.6	**NS** *5/*5: 0.5 (0.1–2.1) *6/*6: 1.1 (0.3–3.4)		Persson *et al.* (114), 1999
27	CYP2C9	*2	AC (115) SCC (80) SCLC (43)	A-A and Caucasians	A-A: 152/239 Cauc.: 177/461	A-A: *2/*2 + *1/*2: 5.9/7.1 *Cauc.:* *2/*2 + *1/*2: 28.3/19.3	**NS** *Cauc.:* *c2:* 1.6 (0.96–2.5)[e] A-A: c2: 1.2 (0.5–3.1)[e] but AC in Cauc. **S** *c2:* 2.0 (1.1–3.8)[e]	Effect on LC risk not modified by histological type.	London *et al.* (142), 1996
28	CYP2C9	*2, *3	Not specified	Caucasians	173/457	*2/*2: 1.7/0.7 *3/*3: 0.6/0.0 *1/*1: 63/66.1	**NS** 1 variant allele: 1.1 (0.7–1.6)[e] 2 variant alleles: 2.4 (0.8–6.8)[e]	Effect on LC risk not modified by histological type.	London *et al.* (143), 1997
29	CYP2C19	*2, *3	SCC (14)	Japanese	14/64	PM: 42.9/14.1 HEM: 35.7/39 EM: 21.4/46.9	**S** "risk factor": PM: 4.6 (1.3–16.4)	Very few subjects.	Tsuneoka *et al.* (144), 1996

[a] SCC, squamous cell carcinoma; AC, adenocarcinoma; SCLC, small cell lung cancer; LCLC, large cell lung cancer.
[b] mut, mutation; wt, wild type; Cauc., Caucasian; A-A, African-American; M-A, Mexican-American.
[c] NS, not significant; S, significant; RR, relative risk.
[d] LC, lung cancer.
[e] Data adjusted for confounding factors such as smoking, age, gender, and others (for details, refer to original publication).

have breast tumors containing estrogen and progesterone receptors (Table 6, study 7).

CYP2A6. In humans, CYP2A6 mediates 7-hydroxylation of coumarin, a component of cigarette smoke, and activates several nitrosamines in tobacco smoke, including NNK (15, 52). The catalytic selectivity of CYP2A6 appears to overlap with that of CYP2E1. The location of CYP2A6 and 2E1 in extrahepatic tissues such as lung, nasal and pharyngeal areas is of interest. Two *CYP2A6* variant alleles have been identified (*2 and *3). The prevalence of the $Leu^{160}His$ variant allele in Caucasians is ~2%, and it is associated with lower coumarin 7-hydroxylation activity. A new allele has been described in which exons 5–9 are deleted (53). Individuals lacking functional *CYP2A6* have impaired nicotine metabolism and may thus be protected against tobacco dependence. In one study using a disputed genotyping method, carriers of the variant allele were reported to smoke fewer cigarettes (54). These findings were not confirmed in another study (55). The discrepancy could be resolved by newly available genotyping methods (56, 57).

Lung Cancer. The only case-control study published thus far (Table 7, study 1) showed no associations with CYP2A6*2.

CYP2D6. Individuals with the PM phenotype (*i.e.*, deficient in debrisoquine 4-hydroxylation) were first reported in 1984 to have a lowered risk for lung cancer (58). The PM phenotype, inherited as an autosomal recessive trait, is attributable to several defective allelic *CYP2D6* variants, three of which account for >90% of all PM individuals. The mutations that cause loss of gene function are attributable mainly to two point mutations that result in *CYP2D6**3 (formerly *A*) and *CYP2D6**4 (*B*) alleles and deletion of the entire *CYP2D6**5 allele (*D*). A *CYP2D6**2xn (*L2*) allele associated with 2–12-fold amplification of the *CYP2D6* gene is found in carriers known as UMs (59). Conflicting data exist on whether *CYP2D6* is expressed in human lung (60). Most searches for procarcinogens that are activated by *CYP2D6* have been unsuccessful. It can activate the tobacco-specific nitrosamine NNK and also nicotine, but other P-450s are more active in this respect.

Associations have been found between nicotine dependence and PM (61) and between UM and smoking addiction (62). These findings may make establishing causality between this polymorphism and cancer risk more complex.

Lung Cancer. Nine genotyping studies have been conducted, including several with large samples and with control for confounding factors. In three studies (Table 7, study nos. 3, 4, and 6), a significant association was found between lung cancer and EM genotype, and in one study an association with UM genotype and lung cancer risk was found for African-Americans (Table 7, study 8). Legrand Andreoletti *et al.* (Ref. 63; Table 7, study 9) screened over 40 alleles in cases and controls. They found no significant association for lung cancer overall, but the *1A/*2-EM genotype combination was significantly associated with lung cancer. Two meta-analysis showed no association or one of borderline significance between the EM genotype and increased risk (64, 65).

Head and Neck Cancer. One of three studies of Caucasians showed a significantly higher frequency of the PM genotype among cases (Table 3, study 9).

Urinary Tract Cancer. One of four studies showed an association only with the HEM (Table 7, study 4). The HEM genotype in smokers was associated with more aggressive bladder tumors (66).

Breast Cancer. One American study (Table 6, study 8) of alleles *3, *4 and *5 showed no association with the *CYP2D6* genotype, whereas a slightly larger study in Spain (Table 6, study 9) of alleles *3, *4 and *9 showed a significant association with HEM.

Analyses of all results on *CYP2D6* genotype and lung cancer risk found no or a borderline protective effect of the PM genotype. For other cancer sites, the association with disease susceptibility was inconclusive.

CYP2E1. The ethanol-inducible *CYP2E1* metabolizes many known procarcinogens, including NNN, NNK, and other volatile nitrosamines found in tobacco smoke. Chlorzoxazone 6-hydroxylation is catalyzed by CYP2E1. Wide interindividual variation in the expression of the *CYP2E1* gene has been reported in humans, which is possibly attributable to gene-environment interaction. *CYP2E1* is induced in mice exposed to cigarette smoke by inhalation (67). Its regulation involves complex transcriptional and posttranscriptional mechanisms. Although in Caucasians no relationship was found between *in vivo* activity of this enzyme and genotype, in Japanese the presence of the variant *c2* alleles resulted in a significant reduction in the oral clearance of chlorzoxazone, after adjustment for age and sex. The mean activity in individuals with the *c2/c2* genotype was significantly lower than that in individuals with either the homozygous wild-type or the heterozygote genotype. Body weight and dietary factors were the major modulators of interindividual variation (68).

The human *CYP2E1* gene is functionally well conserved, but several polymorphic alleles occurring at low frequency have now been identified. The RFLPs, revealed by either *Rsa*I $G_{-1259}C$ or *Pst*I $C_{-1091}T$, are located in the 5′ flanking transcription region of this gene and appear to be in complete linkage disequilibrium with each other (*c1*, common allele; *c2*, rare allele). Although the primary sequence of the enzyme is not altered, increased gene transcription has been suggested (69). A $T_{-7668}A$ substitution in intron 6 of the *CYP2E1* gene is revealed by a *Dra*I RFLP (*C*, minor allele; *D*, common allele). The *Rsa*I and the *Dra*I polymorphisms appear to be linked, *i.e.*, individuals with the *Rsa*I polymorphism also had a mutant *Dra*I allele, although the reverse is not true. A *Taq*I RFLP at position 9930 (intron 7) of the *CYP2E1* gene has been reported, but no phenotype has been associated with this mutation.

Lung Cancer. The wild-type *Dra*I genotype was associated with an increased risk for lung cancer in 3–5 of 16 studies in Japanese, Mexican-Americans, and mixed populations (Table 7, study nos. 11, 13, 16, 24, and 25). More conflicting results have been published concerning the *Rsa*I/*Pst*I mutation. The rare *Pst*I/*Rsa*I *c2* allele has been associated with decreased risk for cancer in two studies of 11 (Table 7, study nos. 23 and 25), and in one study the *c2* allele frequency was significantly lower among cases than controls (Table 7, study 15); however, in an additional study, the *c2/c2* genotype correlated positively with *p53* mutations and with squamous cell carcinoma (Table 7, study 21). Additionally, in one small study the *c2/c2* genotype was associated with adenocarcinoma (Table 7, study 22).

Head and Neck Cancer. Five studies showed no association between head and neck cancer and *CYP2E1* variants; however, Chinese patients who were not betel quid chewers had a higher prevalence of the *c2* allele (*Pst*I/*Rsa*I; Table 3, study 11).

Esophageal Cancer. The *c2* allele was overrepresented among Chinese esophageal cancer patients (Table 4, study 9).

Urinary Tract Cancer. Three studies found no association with bladder cancer. One study in Caucasian women revealed

a higher risk for renal carcinomas among those with *Dra*I variants (OR, 8.0; Table 5, study 10).

Breast Cancer. The only study of the *Dra*I polymorphism in Caucasians (Table 6, study 10) found a significant association among premenopausal smokers only (OR, 11.1).

Because the frequencies of variant alleles are very low in Caucasians and African-Americans, the statistical power of the studies is low. Altogether, conflicting results have been reported on the importance of *CYP2E1* genotypes in well-documented tobacco-related cancers.

CYP2C9. The levels of all smoking-related DNA adducts in the larynx were correlated with the presence of P4502C protein, suggesting a role of CYP2C9 in DNA adduction of PAH-type tobacco carcinogens (70). Two mutant alleles, *CYP2C9**2 ($Arg^{144}Cys$) and *3 ($Ile^{359}Leu$), have been described, and CYP2C9 has a specific substrate, tolbutamide. The level of bulky DNA adducts in normal bronchial tissue of smokers was found to be higher in individuals with the homozygous *CYP2C9**3/*3 genotype (71).

Lung Cancer. One of two large (Table 7, study 27), well-designed studies in African-Americans and Caucasians (Table 7, study nos. 27 and 28) revealed an association of the *2 allele with borderline-increased risk (OR, 1.6).

CYP2C19. Members of the human *CYP2C* gene subfamily are constitutively expressed, and at least seven human *CYP2C* genes may exist. Several defective *CYP2C19* alleles are the basis for the (*S*)-mephenytoin 4′-hydroxylase polymorphism. In addition to (*S*)-mephenytoin, CYP2C19 also metabolizes a variety of clinically used drugs. The most common variant allele, *2, has an aberrant splice site in exon 5 (72). The premature stop codon mutant *3 allele has thus far been found only in Asians (73).

Lung and Bladder Cancer. A very small study on Japanese patients (Table 7, study 29) revealed a significant association of the PM genotype with squamous cell carcinoma of the lung, but the association with bladder cancer seen in Caucasians was not found (Table 5, study 11).

CYP3A4. This isoform is the major P450 expressed in human liver and small intestine. It can activate numerous procarcinogenic PAH dihydrodiols, such as BPDE, and also metabolizes NNN (74). Whether genetic or solely environmental factors are responsible for the wide variation in human 3A4 activity is unknown. Although the three *CYP3A* genes, *3A4*, *3A5*, and *3A7*, are expressed at widely different levels, polymorphism has been found only for *CYP3A4* and *CYP3A5* to date. Several allelic variants of the *CYP3A4* gene were reported (75), but none was apparently related to catalytic activity in the liver samples from which the DNA was derived. No extensive studies on *CYP3A4* polymorphism have been reported.

CYP17. This gene codes for the cytochrome P450C17α-enzyme, which mediates both steroid 17α-hydroxylase and 17,20-lyase activities and functions at key branch points in human steroidogenesis. The 5′-U terminal repeat of *CYP17* contains a 1-bp polymorphism that creates a recognition site for the *Msp*AI restriction enzyme and has been used to designate two alleles, *A1* and *A2*. Premenopausal women with *CYP17A2* variants have higher serum concentrations of estradiol and progesterone (76).

Breast Cancer. Four studies in mainly Caucasian populations (Table 6, study nos. 12–15) and one in a mixed Hawaiian population (Table 6, study 11) showed no association with the *CYP17* genotype.

CYP19. This gene encodes aromatase, which is responsible for the rate-limiting step in the metabolism of C19 steroids to estrogens. Aromatase activity has been found in a number of tissues, including normal and transformed breast tissue. A common, high-heterozygosity tetranucleotide simple tandem repeat polymorphism in intron 4 has been described (77), but it is not known whether this polymorphism is associated with a specific phenotype.

Breast Cancer. Two studies of the tandem repeat polymorphism in Caucasian women showed that an increased proportion of breast cancer patients had the short alleles; however, the allele frequencies varied greatly between the two study populations (Table 6, study nos. 16 and 17).

CYP1A1-GSTM1 Genotype Dependence of Bulky (PAH)-DNA Adduct Levels and of Other Effect Markers in Smokers

The genotype dependence of various effect markers, such as DNA adducts, cytogenetic damage and *p53* mutations, have been studied, most effort having been focused on PAH-(BPDE)-DNA adducts related to tobacco smoking. Overall, the data indicate that smokers have higher PAH-DNA adduct levels in target tissues and leukocytes than ex- and nonsmokers (Table 8). The increased formation and the wide variation in levels of PAH-DNA adducts in some smokers occupationally exposed to PAH suggest that polymorphisms in genes related to PAH metabolism lead to increased DNA binding and cancer risk (reviewed in Ref. 14).

The relationship between *CYP1A1* variants, alone or in combination with *GSTM1*, and the formation of bulky (PAH)-DNA adducts in human tissues (autopsy tissues excluded) and leukocytes remained controversial for some time (Table 8). Several studies showed a weak or no effect of *m1* and *m2* on adduct levels (Table 8, study nos. 3, 4, 6, 8 and 9). More recent studies, in which specific, sensitive detection methods were used (such as for (+)-*anti*-BPDE-DNA adducts), have shown clearly the dependence of adduct levels on *CYP1A1* genotype, which is most pronounced in *GSTM1*-deficient smokers. Lung and leukocytes of Caucasian smokers with the *CYP1A1 m1/m1-GSTM1* 0/0 combination clearly contained more BPDE-DNA adducts (Table 8, study nos. 1, 2, and 5). One study in which an ELISA was used (Table 8, study 7) showed a similar effect of *m2-GSTM1* combinations.

In bronchial tissues of smokers with highly induced CYP1A1 enzyme and *GSTM1* 0/0, the BPDE-DNA levels were 100-fold higher than in subjects with active *GSTM1* (Table 8, study 2). Another study found no effect of the *CYP1A1* [*Msp*I (*m1*) or Ile-Val (*m2*) mutations] or *GSTM1* 0/0 genotypes on bulky DNA adduct levels, when the ^{32}P-postlabeling method was used (Table 8, study 3); however, carriers of homozygous *CYP1A1 m1* had higher BPDE-DNA adduct levels than individuals with the wild type (Table 8, study 1).

Studies of leukocytes from mostly Caucasians exposed to PAH, including smokers and nonsmokers, gave contradictory results (Table 8). No effect of *m1* and *m2* was observed in leukocyte DNA from lung cancer patients (Table 8, study 11), but a significant, 2-fold increase in PAH-DNA adduct level was found when *m2* variants were combined with *GSTM1* 0/0 or wild type (Table 8, study 7). Heterozygous *m1* or *m2* variants were associated with an increase in the median BPDE adduct level when compared with the wild type (180). One Caucasian subject with the very rare *m1/m1* genotype in combination with *GSTM1* 0/0 had an extremely high level of BPDE adducts: $44/10^8$ nucleotides (Table 8, study 5).

Table 8 Modulation of bulky DNA adducts by *CYP1A1/GSTM1* genotypes in smokers' tissue and leukocytes

Study no.	Ethnicity	PY or cig/day[a]	Detection method	*CYP1A1/GSTM1* combination	Subjects (*n*)	Adduct levels (per 10^8 nucleotides)		Effect and significance	References
						Present (*n*)	Mean ± SD or range		
I. Lung parenchyma and bronchus									
1	Russian Caucasian	10–40 cig/day	*HPLC*/fd[b]	*wt/wt-GSTM1* active (*A*)	11	0	<0.2[c]	*A vs. C* $P < 0.001$	Rojas *et al.* (39), 1998
				wt/m1 (m2)-GSTM1 active (*B*)	3	0	<0.2	*B vs. D* $P < 0.001$	
				wt/wt-GSTM1 0/0 (*C*)	4	4	0.68 ± 0.13		
				m1/m1-GSTM1 0/0 (*D*)	2	2	4.15 ± 3.18	*D vs. C* $P < 0.01$	
2	Finnish Caucasian	10–20 cig/day 20–40 cig/day	*HPLC*/fd	Inducible *CYP1A1-GSTM1* 0/0 (*A*)	3	3	122	*A vs. B* $P < 0.001$	Bartsch (38), 1996
				Inducible *CYP1A1-GSTM1* active (*B*)	2	2	<1		
3	Hungarian Caucasian	NA	^{32}P	*wt/wt-GSTM1* active	40	na	8.4 ± 3.8		Schoket *et al.* (178), 1998
				wt/m1 (m1/m1)-GSTM1 active	10	na	9.0 ± 5.3	NS[d]	
				wt/wt-GSTM1 0/0	36	na	8.7 ± 4.4		
				wt/m1 (m1/m1)-GSTM1 0/0	12	na	9.5 ± 4.1		
II. Leukocytes									
a) Smokers also occupationally exposed to PAH									
4	Swedish Caucasian	NA	^{32}P	*wt/wt*	23	23	0.95 (0.60–1.42)		Ichiba *et al.* (179), 1994
				wt/m1	5	5	0.55 (0.45–0.96)	NS	
				GSTM1 active	16	16	0.83 (0.59–1.21)		
				GSTM1 0/0	12	12	0.88 (0.57–1.35)		
5	French Caucasian	23 ± 12 cig/day	HPLC/fd	*wt/wt-GSTM1* active (*A*)	8	0	<0.2	*A vs. C* $P < 0.001$	Rojas *et al.* (180), 2000
				wt/m1 (m2)-GSTM1 active (*B*)	6	0	<0.2	*B vs. D* $P < 0.001$	
				wt/wt-GSTM1 0/0 (*C*)	11	11	2.3 (0.8–3.6)		
				wt/m1 (m2)-GSTM1 0/0 (*D*)	9	9	2.8 (1.8–6.1)	*D vs. C* NS	
				m1/m1-GSTM1 0/0	1	1	44		
b) Smokers not occupationally exposed to PAH									
6	Swedish Caucasian	NA	^{32}P	*wt/wt*	9	9	0.69 (0.57–1.30)		Ichiba *et al.* (179), 1994
				wt/m1	3	3	0.7 (–)	NS	
				GSTM1 active	5	5	0.7 (0.68–1.55)		
				GSTM1 0/0	7	7	0.66 (0.39–1.10)		
7	American Caucasian	39 ± 23	ELISA	*wt/wt* (*A*)	148	NA	4.7 ± 5.3		Mooney *et al.* (35), 1997
				wt/m2 (*B*)	10	NA	9.8 ± 8.5	*B vs. A* $P < 0.01$	
				wt/wt-GSTM1 active (*C*)	78	NA	4.5 ± 5.8		
				wt/m2-GSTM1 active (*D*)	6	NA	10.5 ± 7.2	*D vs. C* $P < 0.004$	
				wt/wt-GSTM1 0/0 (*E*)	70	NA	4.4 ± 4.7		
				wt/m2-GSTM1 0/0 (*F*)	4	NA	8.7 ± 11.5		
8	Polish Caucasian	41 ± 33	^{32}P	*wt/wt*	NA	NA	3.96 ± 4.6		Butkiewicz *et al.* (181), 1998
				wt/m2	NA	NA	5.11 ± 4.15		
				wt/wt-GSTM1 active	NA	NA	3.25 ± 3.56	NS	
				wt/m2-active	NA	NA	0.4 (0.4–0.4)		
				wt/wt-GSTM1 0/0	NA	NA	4.80 ± 5.60		
				wt/m2-GSTM1 0/0	NA	NA	6.30 ± 3.69		
9	Japanese	<20 cig/day	^{32}P	*wt/wt*	29	29	1.01 ± 0.85		Ichiba *et al.* (182), 1998

Table 8 Continued

Study no.	Ethnicity	PY or cig/day[a]	Detection method	*CYP1A1/GSTM1* combination	Subjects (*n*)	Adduct levels (per 10^8 nucleotides)		Effect and significance	References
						Present (*n*)	Mean ± SD or range		
				wt/m2	9	9	0.85 ± 0.54		
				m2/m2	3	3	2.01 ± 1.04	NS	
				wt/wt-GSTM1 0/0	17	17	1.09 ± 0.97		
				wt/m2-GSTM1 0/0	4	4	1.64 ± 1.13		
10 sameas #5	French Caucasian	22 ± 12	HPLC/fd	*wt/wt-GSTM1* active (A)	15	0	<0.2	*A vs. C* $P < 0.001$	Rojas *et al.* (180), 2000
				wt/m1 (m2)-GSTM1 active (B)	5	0	<0.2	*B vs. D* $P < 0.001$	
				wt/wt-GSTM1 0/0 (C)	16	16	0.7 (0.2–4.1)		
				wt/m1 (m2)-GSTM1 0/0 (D)	8	8	0.9 (0.4–6.1)	*D vs. C* NS	
11	Italian Caucasian	63 ± 5	GC/MS[e]	*wt/wt*	38	NA	2.46 ± 0.44		Pastorelli *et al.* (183), 1998
				wt/m1	6	NA	3.99 ± 1.96	NS	
				GSTM1 active	21	NA	2.53 ± 0.78		
				GSTM1 0/0	23	NA	2.79 ± 0.56		

[a] PY, pack-years; cig/day, cigarettes per day; NA, not applicable.
[b] HPLC/fd, HPLC/fluorescence detection.
[c] Limit of detection 0.2 BPDE-DNA adducts per 10^8 nucleotides.
[d] NS, not significant.
[e] GC/MS, gas chromatography/mass spectroscopy.

Overall, the data are compatible with the assumption that *GSTM1* 0/0 is a moderately strong susceptibility factor but may become a dominant risk factor in the presence of certain gene-gene combinations. This results in increased DNA damage and mutational events in target and surrogate tissues (leukocytes). These findings provide a mechanistic background why such "at risk" genotypes correlate with increased risks for tobacco-related lung cancer, even at a low level of cigarette smoking (Ref. 78, Table 2). This was seen more clearly in Japanese populations where the "at risk" alleles occur much more frequently than in Caucasians.

A suggested gender difference in lung cancer susceptibility was supported by a study showing that female smokers had a significantly higher level of aromatic DNA adducts in lung tissue than males at an equal cigarette smoking dose (pack-year; Ref. 79).

Lung tumors in Japanese smokers were found to harbor significantly more *p53* mutations in people who had the susceptible *CYP1A1* genotype. Individuals with the combination of *CYP1A1 m2/m2* and *GSTM1* 0/0 genotypes had an 8-fold greater frequency of *p53* mutations than persons with neither genotype (80). Also, lung cancer patients with this "at risk" genotype combination who had undergone an operation had a remarkably shortened survival (81). Shorter survival of operated lung cancer patients with high pulmonary *CYP1A1* enzyme inducibility was reported previously (82).

Taken together, because an elevated DNA and mutational damage associated with the "at risk" alleles has been found in both Asian and Caucasian smokers, large-scale studies should prove the prediction that carriers of (homozygous) *CYP1A1* variants/*GSTM1* 0/0 combinations of any ethnicity could be at an increased risk for tobacco-related (lung, head, and neck) cancers.

Perspective and Future Strategies for Molecular Epidemiology

Molecular epidemiology has contributed to a growing awareness of the importance of relatively common genetic and acquired susceptibility factors in modulating risks associated with exposure to environmental carcinogens. Because cancer is largely a preventable disease, the future challenge of molecular epidemiology is to analyze individuals who are exposed to carcinogens for a combination of genotypes associated with susceptibility to cancer. It is evident that use of more precisely measurable intermediary risk markers, like DNA adducts, cytogenetic damage, and mutations, rather than cancer as an end point, will allow the identification of combinations of cancer-relevant genes that positively or negatively affect cancer outcome in humans. Such associations could then be verified in epidemiological studies designed to address the association or hypothesis to be confirmed. Thus, further progress is expected from studies in which biomarkers for carcinogen exposure, early biological effects, and susceptibility are integrated, which should allow establishment of the risk profiles of individuals and subgroups in given exposure situations.

Many of the published studies listed in Tables 2–8 have shortcomings that should be avoided in future, if possible. Furthermore, there is a bias against publishing (and citing) the absence of correlations. IARC (83, 84) provided state-of-the-art reviews of the application of biomarkers and the design and analysis of molecular epidemiological studies. The prerequisites for proper study design and conduct include: (*a*) clear definition of representative study populations and controls; (*b*) a sample size adequate to provide enough statistical power; (*c*) proper documentation (or measurement) of exposure; (*d*) avoidance of confounding because of use of study subjects of mixed ethnic background; and (*e*) study only of gene polymorphisms that have been shown to lead to altered phenotypic expression.

Rapid advances in high-throughput gene analysis by DNA chip technology will speed up the identification of new mutations in predisposing cancer genes. The main task, however, will be to characterize the functional significance of these gene variants in humans. Such efforts are under way, *e.g.*, the Environmental Genome Project pursued by the National Institute

for Environmental Health Sciences in the United States (85). The aims are to define genetic variation in a selected number of (~200) genes in the American population and to relate them to disease risk and individual susceptibility, particularly in combination with specific chemical and physical exposures.

Knowledge of the prevalence and distribution of common genetic susceptibility factors and the ability to identify susceptible individuals or subgroups will have substantial preventive implications, in particular if more data are collected to show that people with certain "at risk" genotypes are more susceptible to low levels of exposure (see "Environmental Tobacco Smoke and Exposure to Low Doses of Carcinogens"). It is conceivable that such subjects could be: (*a*) more easily persuaded to avoid hazardous exposure like tobacco use; (*b*) targeted for intensive smoking cessation programs; (*c*) be enrolled in chemoprevention trials; and (*c*) be involved in cancer screening programs that are not appropriate for the general population. However, before results of individual screening for genetic traits can be used efficiently to implement preventive measures, more cancer-predisposing genes need to be studied and gene-environment and gene-gene interactions elucidated. To this purpose, the need of well-designed, large-scale studies is emphasized.

Acknowledgments

We are indebted to Ulrike Wagner for skilled secretarial help and to Elisabeth Heseltine and Gernhild Bielefeldt for editing.

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