

## Cytochrome P450IIE1 Genetic Polymorphisms, Racial Variation, and Lung Cancer Risk

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### Abstract

Cytochrome P450IIE1 is responsible for the activation of carcinogenic *N*-nitrosamines, benzene, urethane, and other low-molecular-weight compounds. Restriction fragment length polymorphisms (*Pst*I and *Rsa*I restriction enzymes) have been identified in the cytochrome P450IIE1 transcription regulatory region that may affect expression. This study describes the *Pst*I and *Rsa*I polymorphisms in different racial populations and in a case-control study of lung cancer. The allelic frequencies were markedly different in Japanese, African-Americans, and Caucasians: the *Pst*I rare allele was present at a frequency of 2% in Caucasians, 5% in African-Americans, and 24% in Japanese ( $P < 0.05$ ). For the *Rsa*I rare allele, frequencies were 2% in Caucasians, 2% in African-Americans, and 27% in Japanese ( $P < 0.05$ ). The assay was also applied to 128 individuals enrolled in a case-control study of lung cancer. Although limited in statistical power, the data indicate no evidence for an association in the aggregate of cytochrome P450IIE1 *Pst*I [for which the odds ratio was 0.7 (95% confidence interval (C.I.) = 0.2-2.8)] or *Rsa*I [for which the odds ratio was 0.9 (95% C.I. = 0.2-5.4)] restriction fragment length polymorphisms with lung cancer in this U.S. population. When analyzed by race, the lung cancer odds ratio for the *Pst*I mutant allele in African-Americans was 0.19 (95% C.I. = 0.03-1.38), and in Caucasians it was 4.13 (95% C.I. = 0.34-48.8). For the *Rsa*I mutant allele, the odds ratios were 0.20 (95% C.I. = 0.02-2.43) and 4.28 (95% C.I. = 0.35-50.6), respectively. The ethnic differences of these restriction fragment length polymorphisms might be related to genetic susceptibilities for lung cancer among Caucasians and for gastric or esophageal cancer among Japanese.

### Introduction

Molecular genetic techniques are useful for studying individual cancer risk because they can evaluate the ability to activate or eliminate carcinogens and repair DNA. Molecular epidemiology can relate such parameters to environmental carcinogen exposure, life style, occupation, and other inherited or acquired host factors (1). Most chemical carcinogens undergo metabolic activation, usually by CYP<sup>2</sup> enzymes (2). More than 100 different human CYP enzymes have been identified or are assumed to exist (3); for many of these there is wide interindividual variation (4). CYP activity can be assessed by urinary phenotyping methods (*e.g.*, CYP2D6; Refs. 5 and 6), adduct (7) or metabolite formation in cultured cells [*e.g.*, aryl hydrocarbon

hydroxylase (8) and glutathione transferase (9, 10)], or genotyping methods [*e.g.*, CYP1A1 (11) and CYP2D6 (12)]. These methods, when applied in well-designed epidemiological studies of cancer, are useful for determining metabolic capacity and cancer risk.

CYP2E1 catalyzes oxidation and DNA adduct formation of many low-molecular-weight potential human carcinogens such as *N*-nitrosamines, aniline, vinyl chloride, and urethane (13, 14). Historically, CYP2E1 was characterized by its ethanol inducibility and metabolism of acetone and alcohols (13). *N*-Nitrosamines are ubiquitous in the environment, present in tobacco smoke, and formed endogenously in the stomach (15). They are potent carcinogens in laboratory animals (15, 16). Epidemiological studies also support a causal relationship of *N*-nitrosamine exposure to human cancers (16-21). Interindividual differences in CYP2E1 activity or induction may result from genetic susceptibility to these chemical carcinogens (13, 22).

Recently, two reports have described RFLPs of CYP2E1. The first, with either *Pst*I or *Rsa*I restriction sites, is located in the transcription regulation region of CYP2E1 (23). This set of polymorphisms, linked with each other, was associated with increased gene expression when a chloramphenicol acetyltransferase-containing construct was transfected into HepG2 cells and analyzed for chloramphenicol acetyltransferase activity (23). Specifically, the wild-type or more common allele had a lower expression rate compared to the mutant or less common allele. The other polymorphism, located in intron 6,<sup>3</sup> is revealed using the *Dra*I restriction enzyme (24). Although a direct relationship of this RFLP to CYP2E1 expression and activity has not been established, the distribution of the *Dra*I genotypes in Japanese was different between lung cancer patients and controls (24). A relationship between the *Dra*I and *Pst*I or *Rsa*I RFLP has not been reported. Moreover, the *Pst*I and *Rsa*I RFLPs have not yet been studied for lung cancer susceptibility.

### Patients and Methods

**Subjects.** Octogenarian Japanese, Americans from a Baltimore autopsy donor program, and Americans enrolled in a Baltimore case-control study of lung cancer were analyzed for CYP2E1 *Pst*I and *Rsa*I genotypes. The case-control study design has been described in detail elsewhere (25). Briefly, cases were patients with histologically confirmed primary lung cancer. Two control groups were accrued. The first group consisted of patients with chronic obstructive pulmonary disease (defined as either abnormal pulmonary function tests or a history of greater than 40 pack-years of tobacco smoking). The second

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<sup>2</sup> The abbreviations used are: CYP, cytochrome P450; RFLP, restriction fragment length polymorphism; C.I., confidence interval; PCR, polymerase chain reaction.

<sup>3</sup> K. Watanabe, personal communication.

group consisted of patients with cancer at anatomical sites other than lung or bladder. The study design allowed for adjustment by age, gender, asbestos exposure, race, and tobacco use in the analysis. All study subjects completed a standardized questionnaire including demographic data, illness, family history, recent or remote diet, occupational history, and information about alcohol and tobacco consumption. A subset of subjects was selected from the original study based upon availability of DNA (128 from a total of 191 subjects).

**RLFP Analysis of CYP2E1.** DNA (peripheral blood buffy coat for case-control study subjects and Japanese; lung for autopsy donors) was isolated from tissues by phenol extraction methods as previously described (26). The PCR was used to amplify the transcription regulation region of CYP2E1 that includes the enzyme recognition sites for both *Pst*I and *Rsa*I (23). Genomic DNA (0.15  $\mu$ g) was amplified with primers (0.8  $\mu$ M) from locus -1370 to -1349 (5'-CCAGTCGAGTCTACAT-TGTCA) and -999 to -978 (5'-TTCATTCTGTCTTCTAACTGG) in buffer (10 mM tris-HCl, 50 mM KCl, 2 mM MgCl<sub>2</sub>, pH 8.3) with 2'-deoxynucleotide-3'-triphosphates (1.875 mM; Pharmacia, Piscataway, NJ) and Taq polymerase (2.5  $\mu$ l; Perkin Elmer, Norwalk, CT) to yield a 412-base pair fragment. The PCR product (15  $\mu$ l) was subjected to *Pst*I restriction enzyme digestion (10 units; New England Biolabs, Inc., Beverly, MA) in buffer (50 mM Tris HCl, 50 mM NaCl, 10 mM MgCl, 1 mM dithiothreitol, pH 8.3, at 37°C for 18 h) or *Rsa*I restriction enzyme digestion (5 units; New England Biolabs, Inc., Beverly, MA) in buffer (90 mM MgCl<sub>2</sub>, 1 mM dithiothreitol at 37°C for 18 h). The samples were then analyzed by electrophoresis in agarose gel (2.2%). The presence of restriction sites yielded two fragments of 120 and 290 base pairs for the *Pst*I restriction digest and 360 and 50 base pairs for the *Rsa*I restriction digest.

**Statistical Methods.** Fisher's exact test and odds ratios were determined by standard methods (27). The Breslow-Day test for homogeneity of the odds ratio was calculated as a test for interaction. For values of zero in 2 x 2 tables, 0.5 was substituted.

## Results and Discussion

Samples subjected to PCR and *Pst*I or *Rsa*I enzymatic digestion revealed predictable base-pair fragment lengths (Fig. 1). The PCR and *Pst*I or *Rsa*I restriction enzyme digests were applied to 194 U.S. and 49 Japanese individuals. The distribution of alleles in Caucasians, African-Americans, and Japanese is shown in Table 1 (23). The allelic frequencies in the Japanese samples were similar to those in a previous report (0.8 and 0.2 wild type and mutant, respectively) (28). However, the allelic frequencies in Japanese were statistically different from Caucasians ( $P < 0.05$ ) and African-Americans ( $P < 0.05$ ), but there was no significant difference between U.S. Caucasians and African-Americans. The allelic frequencies among autopsy samples and case-control study samples were similar. In all groups (by race and diagnosis), the allelic frequencies met Hardy-Weinberg equilibrium. As previously reported (23), the *Pst*I and *Rsa*I genotypes were generally linked, although eight cases were identified where there was no concordance. All were heterozygotes for the *Pst*I allele, 6 were in African-Americans, and 2 were in Japanese. Interestingly, as predicted from the frequencies of the groups, these haplotypes appear to be race-specific among Japanese and African-Americans. In the *Pst*I RFLP heterozygotes, the 6 African-Americans were all *Rsa*I homozygous wild type, while the two Japanese were *Rsa*I RFLP homozygous mutants. This likely represents the temporal relationship for the establishment of the mutation in each population.

Table 2 reports the characteristics of the case-control study subjects. The frequency of genotypes was the same for the cases and controls, whether examined by *Pst*I (Table 3) or *Rsa*I (data

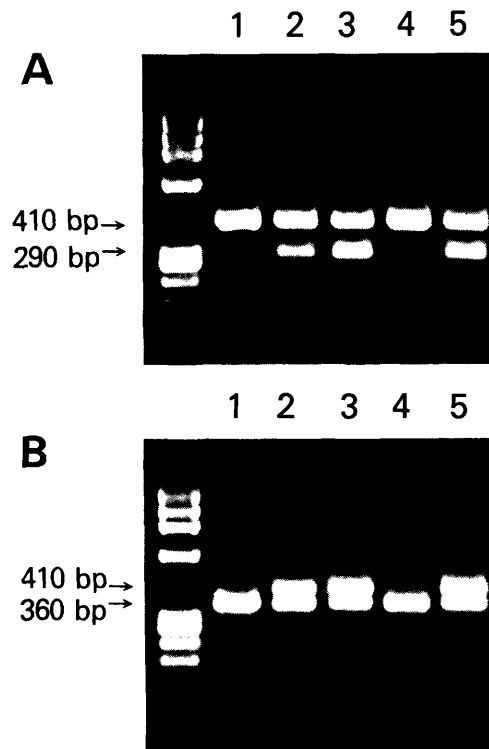


Fig. 1. Amplified PCR products were digested with restriction enzymes *Pst*I (A) or *Rsa*I (B) and analyzed by agarose gel electrophoresis (2.2%). Lanes for A and B correspond to the same individuals. Lanes 1 and 4, *Pst*I and *Rsa*I homozygous wild type; Lanes 2, 3, and 5, heterozygous. *Pst*I and *Rsa*I homozygous mutant types were not observed.

Table 1 Ethnic distributions of CYP2E1 *Pst*I and *Rsa*I restriction fragment length polymorphisms

	No. of subjects	<i>Pst</i> I		<i>Rsa</i> I	
		Wild type	Mutant	Wild type	Mutant
Caucasians <sup>a,b</sup>	107	0.98 (210) <sup>c</sup>	0.02 (4)	0.98 (210)	0.02 (4)
African-Americans <sup>a,b</sup>	87	0.95 (165)	0.05 (9)	0.98 (171)	0.02 (3)
Japanese <sup>a</sup>	49	0.76 (74)	0.24 (24)	0.73 (72)	0.27 (26)

<sup>a</sup> The allelic frequencies for *Pst*I and *Rsa*I RFLPs at the CYP2E1 locus are significantly different between Japanese and Caucasians ( $P < 0.05$ ), and Japanese and African-Americans ( $P < 0.05$ ), but not between Caucasians and African-Americans ( $P > 0.05$ ) (Fisher's exact test).

<sup>b</sup> The allelic frequencies in Caucasians and African-Americans from autopsy samples are similar to those from the case-control study samples.

<sup>c</sup> Parentheses indicate number of alleles.

Table 2 Summary of characteristics of lung cancer case-control study subjects

	Lung cancer cases	COPD <sup>a</sup>	Other cancer <sup>b</sup>
No. of subjects	67	41	20
Mean age (years)	64	61	63
Pack-years <sup>c</sup>	59	67	47
Gender (male/female)	65/2	40/1	14/5
Caucasians (%)	47	56	40

<sup>a</sup> Chronic obstructive pulmonary disease.

<sup>b</sup> Subjects with cancer at anatomical sites other than the lung or urinary bladder.

<sup>c</sup> Average tobacco packs smoked per day multiplied by the number of years consumed.

not shown). There was no unique grouping by lung cancer histological type or smoking status. The results of this analysis would suggest therefore that there is no association of the CYP2E1 genotypes with lung cancer risk. It should be noted that due to the low incidence of heterozygotes and absence of

Table 3 CYP2E1 PstI restriction fragment length polymorphism case status versus genotype<sup>a</sup>

Genotype	Lung cancer cases	Controls			Total
		COPD <sup>b</sup>	Other cancer <sup>c</sup>	Pooled	
W/W <sup>d</sup>	64 (96) <sup>e</sup>	39 (95)	18 (90)	57 (92)	121
W/M	3 (4) <sup>f</sup>	2 (5)	2 (10) <sup>g</sup>	4 (8)	7
M/M	0 (0)	0 (0)	0 (0)	0 (0)	0
Total	67	41	20	61	128 <sup>h</sup>

<sup>a</sup> The allelic frequency of the *Pst*I RFLP at the *CYP2E1* gene locus is not significantly different between lung cancer cases and pooled controls ( $P > 0.05$ ) (Fisher's exact test).

<sup>b</sup> Chronic obstructive pulmonary disease.

<sup>c</sup> Excluding urinary bladder cancer.

<sup>d</sup> W/W, wild-type homozygote; M/M, mutant homozygote; W/M, heterozygote.

<sup>e</sup> Parentheses indicate percentage.

<sup>f</sup> Two cases of squamous cell lung cancer and one small cell lung cancer.

<sup>g</sup> One breast cancer and one esophageal cancer.

<sup>h</sup> Hardy-Weinberg equilibrium conditions fulfilled in total, pooled, and subgroups.

homozygotes, the statistical power of the study is severely limited. In this case, if we assumed an odds ratio of 2 (risk of disease in individuals with one mutant allele compared to those without), the power would be only 0.30; over 600 subjects would be needed to achieve a power of 0.80. In the Japanese population, study size of less than 250 subjects would be adequate.

The crude odds ratio for lung cancer risk in the aggregate data was 0.7 (95% C.I. = 0.2–5.4) for *Pst*I and 0.9 (95% C.I. = 0.2–2.8) for *Rsa*I. The odds ratios for lung cancer risk having at least one *Pst*I mutant allele in African-Americans was 0.19 (95% C.I. = 0.03–1.38;  $\chi^2 = 2.50$ ;  $P = 0.11$ ) and in Caucasians was 4.13 (95% C.I. = 0.34–48.8;  $\chi^2 = 2.0$ ;  $P = 0.16$ ). For *Rsa*I mutant alleles, the odds ratios were 0.20 (95% C.I. = 0.02–2.43;  $\chi^2 = 1.24$ ;  $P = 0.26$ ) and 4.28 (95% C.I. = 0.35–50.6;  $\chi^2 = 2.0$ ;  $P = 0.16$ ), respectively. Thus, future studies need to determine risks separately by race.

Although a larger study size will be required to definitively test this association, these RFLPs are unlikely to be a common lung cancer risk factor in U.S. populations. The lung cancer rates in male Japanese, U.S. Caucasians, and U.S. African-Americans are 28, 79, and 110 per 100,000, respectively (29, 30), which are inversely (Japanese and U.S. in aggregate) related to the presence of the rare allele, suggesting a limited role, if any, in lung cancer risk. However, the marked difference in allelic frequency between Japanese and U.S. individuals might be important for the risk of gastric and esophageal cancer. The rate in Japanese males for esophageal cancer is almost twice that in U.S. Americans and for gastric cancer is almost eight times (29, 30). The association of these tumors with carcinogens such as *N*-nitrosamines that are metabolically activated by CYP2E1 (15) makes further investigations for differences in CYP2E1 genotypes and transcription worthy of study. Differences in CYP2E1 allelic frequencies also are reminiscent of findings for differences in ethanol sensitivity for Orientals and Caucasians (31) as well as for racial differences in alcohol dehydrogenase (32). These relationships need to be further explored.

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