Slower Metabolism and Reduced Intake of Nicotine From Cigarette Smoking in Chinese-Americans

Neal L. Benowitz, Eliseo J. Pérez-Stable, Brenda Herrera, Peyton Jacob III

Background: Lung cancer rates are lower in Asians and Latinos than in whites. Ethnic differences in nicotine metabolism might explain, in part, ethnic differences in cigarette consumption and/or nicotine intake per cigarette and resultant tobacco-related cancer risk. We compared the rate of nicotine metabolism and the intake of nicotine per cigarette smoked among smokers of different ethnicities. Methods: Healthy volunteer smokers, including 37 Chinese-Americans, 40 Latinos, and 54 whites, received simultaneous infusions of deuterium-labeled nicotine and cotinine, a metabolite of nicotine. From blood and urine measurements, the disposition kinetics and daily intake of nicotine from smoking were determined. All statistical tests were two-sided. Results: Total and nonrenal clearance of nicotine and cotinine and metabolic clearance of nicotine via the cotinine pathway were similar in Latinos and whites and statistically significantly lower in Chinese-Americans. Intake of nicotine per cigarette by Chinese-Americans (0.73 mg; 95% confidence interval [CI] = 0.53 to 0.94 mg) was statistically significantly lower than that by Latinos (1.05 mg; 95% CI = 0.85 to 1.25 mg) or whites (1.10 mg; 95% CI = 0.91 to 1.30 mg; P = .039). Among all of the participants, there was a statistically significant positive correlation between nicotine clearance and daily intake of nicotine from cigarette smoking and between nicotine clearance and nicotine intake per cigarette (r = .41 and r = .39, respectively) (P < .001 for both). Conclusions: The lower nicotine (and, therefore, tobacco smoke) intake per cigarette and the fewer cigarettes smoked per day, which may result, in part, from slower clearance of nicotine, may explain lower lung cancer rates in Chinese-Americans. Lower lung cancer rates among Latinos compared with whites, given their similar nicotine intake per cigarette, are probably due to smoking fewer cigarettes. The results with Chinese-Americans may have implications for dosing with nicotine medications to aid smoking cessation in Chinese-American smokers and perhaps in other Asian smokers. [J Natl Cancer Inst 2002;94:108–15]

In the United States, about 90% of lung cancer cases are attributable to cigarette smoking (1). The incidence of lung cancer can, therefore, be taken as a population marker of cigarette smoking-related disease. Considerable ethnic differences are seen in the prevalence of lung cancer. The lowest rates of lung cancer are seen in Asians and in Latinos, with higher rates in whites and the highest rates in African-Americans (2, 3). Differences in exposure to cigarette smoke toxins are likely to account for some or most of the ethnic variation in lung cancer risk. For example, blacks and whites have a similar prevalence of cigarette smoking, but blacks take in more nicotine—and, thus, more tobacco smoke toxins per cigarette—than whites (2, 4, 5). Greater intake of tobacco smoke toxins per cigarette is a potential explanation for the greater lung cancer risk among African-Americans. Latinos and Asians are less likely than whites to smoke cigarettes, and those who do smoke smoke fewer cigarettes per day on average (2, 4). After adjustment for the number of cigarettes smoked per day, the odds ratio (OR) for lung cancer appears to be similar for Latinos and whites (6). Direct comparative data of this sort are not available for Asians and whites. However, epidemiologic data from China suggest that the ORs for lung cancer from smoking, ranging from 2.5 to 4.0, are considerably lower than the ORs for lung cancer in whites who smoke (typical ORs = 10–20) (7, 8). Some of the possible reasons for a lower OR for lung cancer among Asian smokers include the relatively late age of starting to smoke and shorter duration of smoking as well as the relatively high rate of lung cancer that is not related to smoking (7–9). Another possible explanation might be that Asians smoke cigarettes differently from whites—i.e., they may take in a smaller amount of tobacco smoke toxins per cigarette (the opposite of what was observed in African-Americans).

Cigarette smoking is maintained by the pharmacologic actions of nicotine (10). Smokers tend to take in a similar dose of nicotine from smoking each day, presumably to obtain the desired effects of nicotine. Nicotine is metabolized extensively in the body, primarily by the liver cytochrome P450 2A6 (CYP2A6). The major proximate metabolite is cotinine, which is also metabolized extensively via CYP2A6. It has been reported that the presence of a mutant gene for CYP2A6 is protective against the transition from experimental to addictive smoking, suggesting a relationship between the rate of nicotine metabolism and smoking behavior (11). However, a relationship between nicotine metabolic rate and nicotine intake has never been demonstrated explicitly.

Ethnic differences in drug metabolism are well described. For example, Asians, on average, metabolize alcohol more rapidly than whites but metabolize the alcohol metabolite acetaldehyde less rapidly (12). These differences are associated with a greater likelihood of symptoms of intoxication and facial flushing and a lower rate of alcohol abuse in Asians as compared with whites. Asians are also less likely than whites to be poor metabolizers of drugs via the liver enzyme CYP2D6 and more likely than whites to be poor metabolizers via CYP2C19, resulting in different average dose requirements for medications metabolized by these pathways (13–15). Mexicans have been reported to have lower
We hypothesized that ethnic differences in the rate of nicotine metabolism might explain ethnic differences in cigarette consumption and/or nicotine (and tobacco smoke) intake from cigarette smoking among Chinese-Americans, Latinos, and non-Latino whites. Differences in nicotine metabolism could also be important in determining optimal dosing of nicotine medications to aid smoking cessation in different ethnic groups.

One objective of our study was to compare the rate of metabolism of nicotine and its metabolite cotinine in Chinese-Americans, Latinos, and white smokers. On the basis of the metabolite data, we were also able to estimate daily intake of nicotine from cigarette smoking, which presumably reflects the intake of other tobacco smoke toxins, in the same individuals. Using the intake data, we were able to test the hypothesis that the rate of nicotine metabolism is a determinant of nicotine intake from cigarette smoking.

SUBJECTS AND METHODS

Participants

One hundred thirty-one volunteer cigarette smokers were recruited through advertisements in local newspapers and from local community colleges. The participants included whites, whose metabolism data have been reported previously (5,19), as well as Chinese-Americans and Latinos, whose data have not been published previously. Participant selection was intended to include approximately equal numbers of males and females and equal numbers of light (<10 cigarettes/day) and heavy (>10 cigarettes/day) smokers. People were eligible if they were 1) in good health on the basis of history, physical examination, electrocardiogram, and blood chemistry; 2) aged 21–64 years; 3) not pregnant, based on negative pregnancy test or surgical sterilization; and 4) self-identified as Chinese, Latino, or non-Latino white. The Latino participants and/or their families came from Mexico or Central America. Participants were excluded if there was habitual use of any prescription medication, narcotic or sedative drug addiction, or chronic alcoholism. Participants received $250.00 for completing the study successfully. Questionnaires concerning demographics, smoking behavior, nicotine dependence, and brand of cigarettes smoked were administered at the screening visit, during which eligibility to participate in the study was determined. Subjects were studied from the period 1990 through 1993.

The study had the approval of the Committee on Human Research at the University of California, San Francisco, and was in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services. Written informed consent was obtained from each subject.

Experimental Procedure

Participants were asked to come to the General Clinical Study Center at San Francisco General Hospital between 7:00 AM and 8:00 AM, at which time they completed questionnaires on smoking behavior, including questions on alcohol and drug use. They had been asked to abstain from food and cigarette smoking beginning at 10:00 PM the night before their appointment at the Clinical Study Center. Participants received a simultaneous intravenous infusion of deuterium-labeled nicotine (nicotine-d2 = 3’,3’-dideuteronicotine) and cotinine (cotinine-d4 = 2,4,5,6-tetraduterocotinine). Labeled compounds are necessary for metabolic studies because smokers already have considerable levels of nicotine and cotinine in their bodies that would make measurement of clearance of unlabeled nicotine or cotinine impossible. The synthesis of these deuterium-labeled compounds and their preparation for infusion have been described previously (20,21). Participants received 1.5 or 2.0 μg/kg per minute of nicotine-d2 and cotinine-d4 (calculated as the free base) for 30 minutes. During all infusions, participants were monitored continuously by electrocardiogram and frequently by blood pressure measurements. Two hours after the end of the infusion, participants were given a light breakfast. Participants were allowed to smoke cigarettes freely starting 4 hours after the end of the infusion.

Blood samples for measurement of nicotine and cotinine levels were collected at 0, 10, 20, 30, 45, 60, 90, 120, 240, 360, and 480 minutes and then at 24, 48, 72, and 96 hours after the infusion, to include at least three half-lives for cotinine. Because the study was performed before genetic mutations suspected to influence nicotine metabolism had been identified, no blood was collected for genetic studies. Urine was collected during the infusion and up to 480 minutes after the start of the infusion.

Analyses of Nicotine and Cotinine

Analyses of blood samples for concentrations of nicotine and cotinine were performed by gas chromatography with mass selective detection (22,23). Unchanged and glucuronide-conjugated nicotine, cotinine, and trans-3’-hydroxycotinine were measured in the 8-hour urine collection with the use of methods described previously (24).

Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated from blood concentration and urinary excretion data by use of model-independent methods described previously (5,19,25). Total clearances were computed as

\[
\text{CL}_{\text{nic}} = \frac{\text{dose}_{\text{nic-d2}}}{\text{AUC}_{\text{nic-d2}}} \quad \text{and} \quad \text{CL}_{\text{cot}} = \frac{\text{dose}_{\text{cot-d4}}}{\text{AUC}_{\text{cot-d4}}},
\]

where CL is clearance, AUC is area under the plasma concentration-time curve extrapolated to infinity, nic is nicotine, and cot is cotinine. Renal clearances were calculated as

\[
\frac{\text{Urinary excretion}_{\text{nic or cot}}}{\text{AUC}},
\]

based on urine collected and the AUC for the 8 hours during and after the infusion. Nonrenal clearance was estimated as total minus renal clearance.

Fractional conversion of nicotine to cotinine (f) was estimated with the use of blood levels of cotinine generated from infused nicotine and the clearance of cotinine itself, determined by infusion of cotinine, as follows:

\[
f = \frac{\text{AUC}_{\text{cot-d2}}}{\text{dose}_{\text{nic-d2}}} \times \text{CL}_{\text{cot-d4}}.
\]

The metabolic clearance of nicotine via the cotinine pathway (CL_{nic→cot}) was computed as CL_{nic} × f.
Daily intake of nicotine from tobacco was estimated on the basis of knowledge of fractional conversion of nicotine to cotinine and total clearance of cotinine with the use of the equation

$$D_{nic} = \frac{C_{cot} \times CL_{cot-d}}{f},$$

as described and validated previously (25). $D_{nic}$ is the daily intake of nicotine from cigarette smoking, and $C_{cot}$ is the plasma level of cotinine measured during ad libitum smoking. $CL_{cot-d}$ is the clearance of deuterium-labeled cotinine, and $f$ is the fractional conversion of nicotine to cotinine. From this equation, we estimated the daily intake of nicotine and, using each subject’s reported daily cigarette consumption, nicotine intake per cigarette for each subject.

Urinary metabolite concentration data were analyzed as a fraction of total nicotine plus metabolites recovered and as ratios of conjugated over unconjugated parent compound with the use of the 8-hour urine collection.

Statistical Analysis

Ethnic differences were analyzed by the following methods. Chi-square tests were used to examine categoric variables. Continuous variables and various pharmacokinetic parameters were compared by 3 x 2 analysis of variance, examining effects of ethnicity and sex. Where the distributions were not normal, log-term transformation was performed before analysis. Pharmacokinetic data were also examined by use of a general linear model (GLM). The GLM controlled for effects of age, sex, body mass index (kg/m²), number of cigarettes smoked per day, duration of cigarette smoking, and Federal Trade Commission (FTC)-determed nicotine and tar yields of the brand smoked. Group comparisons were made by use of the Bonferroni post hoc test. Pearson correlation analysis was used to examine the relationship between nicotine clearance and cotinine consumption or daily intake of nicotine. All $P$ values are two-sided.

RESULTS

Smoking and Demographic Characteristics

The demographic and smoking characteristics of the participants are given in Table 1. Whites were statistically significantly older than Chinese-Americans, smoked statistically significantly more cigarettes per day than Chinese-Americans or Latinos, had smoked for statistically significantly more years than Chinese-Americans or Latinos, and had statistically significantly higher Fagerström tolerance scores (26), suggesting a higher level of dependence, than Chinese-Americans or Latinos. The cigarettes smoked by whites were statistically significantly less likely to be of menthol brands than those smoked by Chinese-Americans or by Latinos. The FTC method machine-determined nicotine and tar yields of the brands smoked by Latinos and whites were statistically significantly higher than those of the brands smoked by Chinese-Americans.

Disposition Kinetics

Chinese-American smokers, on average, metabolized nicotine 35% more slowly than Latinos or whites, as shown by statistically significantly lower total and nonrenal clearances of nicotine (Table 2). The fractional conversion of nicotine to cotinine and the clearance of nicotine via the cotinine pathway were also statistically significantly lower in Chinese-American smokers than in Latinos and whites. The half-life of nicotine was statistically significantly longer in Chinese-American smokers than in members of the other ethnic groups. Total and nonrenal clearances of cotinine were also slower and the half-life of cotinine was longer in Chinese-Americans than in Latinos or whites (Table 3). Frequency histograms of both total nicotine clearance (Fig. 1) and nonrenal clearance (data not shown) suggest a unimodal distribution of both clearances for all three ethnic groups.

Nicotine Intake From Cigarette Smoking

Chinese-American and Latino smokers had a statistically significantly lower daily intake of nicotine than white smokers (Table 4). For the Latinos, the lower nicotine intake is explained by their smoking fewer cigarettes per day but with the same nicotine intake per cigarette as whites. By contrast, Chinese-American smokers not only smoked fewer cigarettes per day

Table 1. Smoking and demographic characteristics of participants by ethnicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chinese-Americans (n = 37)*</th>
<th>Latinos (n = 40)*</th>
<th>Whites (n = 54)*</th>
<th>$P^†$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25.8‡ (23.7 to 28.0)</td>
<td>30.2 (27.9 to 32.5)</td>
<td>34.5 (31.6 to 37.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>48</td>
<td>48</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>60.4‡ (56.7 to 64.0)</td>
<td>69.1 (65.2 to 73.1)</td>
<td>72.4 (68.5 to 76.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.5§ (20.5 to 22.6)</td>
<td>25.6 (24.3 to 26.9)</td>
<td>24.2 (23.2 to 25.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cigarettes smoked/day</td>
<td>11.2§ (8.5 to 13.8)</td>
<td>12.0§ (9.5 to 14.5)</td>
<td>20.2 (16.8 to 23.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Menthol brand, %</td>
<td>27¶</td>
<td>27§</td>
<td>7</td>
<td>.017</td>
</tr>
<tr>
<td>Smoking history, y</td>
<td>7.9† (5.7 to 10.1)</td>
<td>12.2 (10.0 to 14.3)</td>
<td>18.1 (14.7 to 21.6)</td>
<td>.001</td>
</tr>
<tr>
<td>FTC nicotine yield, mg, per cigarette</td>
<td>0.96§ (0.88 to 1.04)</td>
<td>1.09 (1.01 to 1.16)</td>
<td>1.09 (1.02 to 1.16)</td>
<td>.031</td>
</tr>
<tr>
<td>FTC tar yield, mg, per cigarette</td>
<td>13.3§ (12.0 to 14.6)</td>
<td>15.1 (13.9 to 16.3)</td>
<td>15.7 (14.6 to 16.9)</td>
<td>.016</td>
</tr>
<tr>
<td>Blood cotinine, ng/mL</td>
<td>104§ (75 to 135)</td>
<td>126§ (97 to 156)</td>
<td>234 (192 to 275)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fagerström tolerance score</td>
<td>2.8§ (2.2 to 3.4)</td>
<td>3.0§ (2.4 to 3.7)</td>
<td>5.3 (4.4 to 6.2)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Values are means (95% confidence interval).
†Sex and menthol brand were analyzed by chi-square test; the other characteristics were analyzed by analysis of variance. Bonferroni post hoc tests were performed. Log transformation was needed for age, cigarettes smoked per day, smoking history (years), and Fagerström tolerance score.
‡Values for Chinese-Americans are statistically significantly different from those for whites and Latinos.
§Values for Chinese-Americans and/or Latinos are statistically significantly different from those for whites.
¶The Fagerström tolerance score is a measure of the level of nicotine dependence (26).
Our study makes the novel observations that Chinese-Americans metabolize nicotine more slowly than Latinos and whites and that they take in less nicotine from each cigarette smoked than Latinos or whites. We also demonstrate for the first time a statistically significant correlation between the rate of nicotine metabolism and the intake of nicotine from cigarette smoke. The latter observation is consistent with the hypothesis that slow nicotine metabolism is partially responsible for the lower intake of nicotine among Chinese-American smokers.

Another potential bias could result if the number of cigarettes smoked influences nicotine metabolism. Our previous research has shown that smoking is associated with a slower rate of metabolism.

than whites but also took in statistically significantly less nicotine per cigarette than Latinos or whites.

If we consider all of the participants, the daily dose of nicotine from smoking and the nicotine intake per cigarette were statistically significantly and positively correlated with total nicotine clearance ($r = .41$ and $r = .39$, respectively; both $P < .001$) (Fig. 2). Thus, the variance in daily or per cigarette dose of nicotine accounted for by nicotine clearance ($r^2$) is about 16%.

### Urine Metabolite Excretion

The values for percentage recovery of nicotine and its metabolites derived from the nicotine-d$_2$ that was infused are shown in Table 5. The 8-hour urine recovery of nicotine was statistically significantly higher in Chinese-Americans than in Latinos, and the recovery of 3'-hydroxycotinine was statistically significantly lower in Chinese-Americans than in Latinos or whites. The ratios of nicotine glucuronide/nicotine, cotinine glucuronide/cotinine, and 3'-hydroxycotinine/cotinine were not statistically significantly different among the ethnic groups.

### DISCUSSION

Our study makes the novel observations that Chinese-Americans metabolize nicotine more slowly than Latinos and whites and that they take in less nicotine from each cigarette smoked than Latinos or whites. We also demonstrate for the first time a statistically significant correlation between the rate of nicotine metabolism and the intake of nicotine from cigarette smoke. The latter observation is consistent with the hypothesis that slow nicotine metabolism is partially responsible for the lower intake of nicotine among Chinese-American smokers.

It is important to consider several potential biases that could have influenced these results. The participants, all from the San Francisco Bay Area, were not selected at random but were rather recruited by advertisements in local newspapers and colleges. The three ethnic groups differed in age, in average daily cigarette consumption, in type of cigarette smoked (e.g., mentholated versus nonmentholated cigarettes), and in duration of smoking. However, the average number of cigarettes smoked per day in the three ethnic groups was similar to national averages on cigarette consumption among these ethnic groups (2,27). Moreover, the fact that the participants volunteered for this study should not affect biologic differences observed by ethnicity. In addition, although all of our subjects came from the same area, we are unaware of regional factors that would be expected to affect drug metabolism in Chinese-Americans differentially from that of other ethnic groups.

### Table 2. Disposition kinetics of nicotine in Chinese-American, Latino, and White smokers

<table>
<thead>
<tr>
<th>Kinetic</th>
<th>Chinese-Americans (n = 37)*</th>
<th>Latinos (n = 40)*</th>
<th>Whites (n = 54)*</th>
<th>$P^†$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance, mL/min per kg</td>
<td>17.2 ± 7.6† (14.7 to 19.8)</td>
<td>21.5 ± 6.7 (19.3 to 23.6)</td>
<td>20.6 ± 9.5 (8.1 to 23.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$V_{n,d}$, L/kg</td>
<td>3.0 ± 1.09 (2.7 to 3.3)</td>
<td>3.0 ± 0.8 (2.8 to 3.3)</td>
<td>3.3 ± 1.2 (3.0 to 3.6)</td>
<td>.23</td>
</tr>
<tr>
<td>Half-life, min</td>
<td>152 ± 67† (129 to 174)</td>
<td>122 ± 25 (113 to 129)</td>
<td>134 ± 43 (123 to 146)</td>
<td>.023</td>
</tr>
<tr>
<td>Renal clearance, mL/min per kg</td>
<td>0.71 ± 0.59 (0.52 to 0.91)</td>
<td>0.53 ± 0.64 (0.33 to 0.74)</td>
<td>0.55 ± 0.57 (0.40 to 0.71)</td>
<td>.72</td>
</tr>
<tr>
<td>Nonrenal clearance, mL/min per kg</td>
<td>16.5 ± 7.9 (14.0 to 19.0)</td>
<td>21.0 ± 6.8 (18.8 to 23.2)</td>
<td>20.1 ± 9.4 (17.5 to 22.2)</td>
<td>.003</td>
</tr>
<tr>
<td>$f$</td>
<td>0.75 ± 0.12 (0.70 to 0.79)</td>
<td>0.82 ± 0.09 (0.79 to 0.85)</td>
<td>0.86 ± 0.10 (0.82 to 0.88)</td>
<td>.003</td>
</tr>
<tr>
<td>$\text{CL}<em>{\text{nic}}$/ $V</em>{\text{ss}}$, L/kg</td>
<td>13.8 ± 6.3† (11.5 to 16.1)</td>
<td>17.8 ± 6.6 (15.7 to 19.9)</td>
<td>17.8 ± 8.5 (15.5 to 20.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation (95% confidence interval).
†Analysis by general linear model, controlling for age, sex, body mass index (kg/m$^2$), number of cigarettes smoked per day, duration of smoking, and Federal Trade Commission machine-determined nicotine and tar yields of the brand smoked.
‡Values for Chinese-Americans are statistically significantly different from those for whites and Latinos.
§Steady-state volume of distribution.
¶Fractional conversion of nicotine to cotinine.
#Clearance of nicotine via the cotinine pathway.

### Table 3. Disposition kinetics of cotinine in Chinese-American, Latino, and white smokers

<table>
<thead>
<tr>
<th>Kinetic</th>
<th>Chinese-Americans (n = 37)*</th>
<th>Latinos (n = 40)*</th>
<th>Whites (n = 54)*</th>
<th>$P^†$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance, mL/min per kg</td>
<td>0.60 ± 0.23‡ (0.53 to 0.68)</td>
<td>0.76 ± 0.32 (0.66 to 0.87)</td>
<td>0.76 ± 0.35 (0.67 to 0.86)</td>
<td>.001</td>
</tr>
<tr>
<td>$V_{c,d}$, L/kg</td>
<td>0.83 ± 0.19 (0.77 to 0.89)</td>
<td>0.79 ± 0.21 (0.73 to 0.86)</td>
<td>0.93 ± 0.24 (0.86 to 1.00)</td>
<td>.12</td>
</tr>
<tr>
<td>Half-life, min</td>
<td>1099 ± 326‡ (990 to 1208)</td>
<td>874 ± 310 (774 to 973)</td>
<td>965 ± 311 (880 to 1050)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal clearance, mL/min per kg</td>
<td>0.14 ± 0.06† (0.12 to 0.16)</td>
<td>0.10 ± 0.04 (0.09 to 0.12)</td>
<td>0.09 ± 0.05 (0.08 to 0.11)</td>
<td>.006</td>
</tr>
<tr>
<td>Nonrenal clearance, mL/min per kg</td>
<td>0.46 ± 0.22 (0.39 to 0.53)</td>
<td>0.66 ± 0.33 (0.55 to 0.76)</td>
<td>0.67 ± 0.34 (0.58 to 0.76)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation (95% confidence interval).
†Analysis by general linear model, controlling for age, sex, body mass index (kg/m$^2$), number of cigarettes smoked per day, duration of smoking, and Federal Trade Commission machine-determined yield.
‡Values for Chinese-Americans are statistically significantly different from those for whites and Latinos.
§Steady-state volume of distribution.
||Value for Chinese-Americans is statistically significantly different from that for whites.

### Table 5. The 8-hour urine recovery of nicotine and its metabolites after intravenous infusion of nicotine-d$_2$

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Chinese-Americans</th>
<th>Latinos</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>16%</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Nicotine glucuronide</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Nicotine glucuronide/ cotinine</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Cotinine</td>
<td>16%</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Cotinine glucuronide</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Cotinine glucuronide/ cotinine</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

It is important to consider several potential biases that could have influenced these results. The participants, all from the San Francisco Bay Area, were not selected at random but were rather recruited by advertisements in local newspapers and colleges. The three ethnic groups differed in age, in average daily cigarette consumption, in type of cigarette smoked (e.g., mentholated versus nonmentholated cigarettes), and in duration of smoking. However, the average number of cigarettes smoked per day in the three ethnic groups was similar to national averages on cigarette consumption among these ethnic groups (2,27). Moreover, the fact that the participants volunteered for this study should not affect biologic differences observed by ethnicity. In addition, although all of our subjects came from the same area, we are unaware of regional factors that would be expected to affect drug metabolism in Chinese-Americans differentially from that of other ethnic groups.
nicotine metabolism (28,29), presumably because some component of tobacco smoke inhibits nicotine metabolism. Thus, if anything, an effect of smoking fewer cigarettes would bias the data in favor of faster metabolism of nicotine in individuals who smoke fewer cigarettes per day, which was opposite to what we observed among the Chinese-American smokers. Additional evidence that neither cigarette consumption nor type of cigarette can explain ethnic differences in metabolism comes from the observation that Latino and Chinese-American smokers were more similar in their smoking behavior and in the types of cigarettes smoked than either group was to whites, but Latinos and Chinese-Americans differed with respect to nicotine metabolism and intake of nicotine from cigarette smoking. Finally, our data analysis was performed by use of a general linear model that controlled for the effects of age, sex, body mass index, number of cigarettes smoked per day, duration of smoking, and machine-determined yield. The same results were seen with and without controlling for these factors (data not shown).

Ethnic differences in drug metabolism by cytochrome P450 enzymes have been well described, particularly in comparing Asians and whites (12–15). Differences between Mexicans and non-Latino whites in drug metabolism via CYP3A4 have also been reported (16–18). Nicotine and cotinine, the primary proximate metabolite of nicotine, are both metabolized primarily by CYP2A6 in the liver (30,31). Our study indicates that nicotine metabolism via the cotinine pathway (CL \text{nic} \rightarrow \text{cot}) is expected to be a good marker for CYP2A6 activity, which is substantially lower in Chinese-Americans than in whites or Latinos, indicating the existence of ethnic differences in CYP2A6 enzymatic activity. The findings of higher urinary excretion of nicotine and lower urinary excretion of 3'-hydroxycotinine are also consistent with slower metabolism of nicotine and cotinine in Chinese-Americans. Nicotine and cotinine are also metabolized by glucuronidation (24), but ratios of the conjugate to parent compounds were not different among these ethnic groups, which suggests that ethnic differences in glucuronide formation do not explain lower nicotine and cotinine metabolism in Chinese-Americans.

It has been reported that the prevalence of genes for mutant alleles of CYP2A6 is greater in Asians than in whites (32,33). It is unclear whether these mutations, which occur at a relatively low frequency even in Asians, can explain the considerable population differences that we observed in nicotine metabolism between Chinese-Americans and whites. Unfortunately, blood was not available for CYP2A6 genotyping when methods for genotyping became available subsequent to our study. However, it should be noted that the frequency distribution for nicotine clearance in Chinese-Americans appears unimodal rather than

### Table 4. Nicotine intake from cigarette smoking in Chinese-American, Latino, and white smokers

<table>
<thead>
<tr>
<th>Intake</th>
<th>Chinese-Americans (n = 37)*</th>
<th>Latinos (n = 40)*</th>
<th>Whites (n = 54)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes smoked/day</td>
<td>11.2 ± 8.0‡ (8.5 to 13.8)</td>
<td>12.0 ± 7.8‡ (9.5 to 14.5)</td>
<td>20.2 ± 12.2 (16.8 to 23.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Daily intake of nicotine, mg</td>
<td>7.7 ± 6.2§ (5.4 to 10.0)</td>
<td>12.3 ± 10.4 (9.0 to 15.6)</td>
<td>20.5 ± 14.8 (16.5 to 24.6)</td>
<td>.011</td>
</tr>
<tr>
<td>Nicotine intake/cigarette, mg</td>
<td>0.73 ± 0.55§ (0.53 to 0.94)</td>
<td>1.05 ± 0.63 (0.85 to 1.25)</td>
<td>1.10 ± 0.72 (0.91 to 1.30)</td>
<td>.039</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation (95% confidence interval).
†Analysis by general linear model, controlling for age, sex, body mass index (kg/m²), duration of smoking, and Federal Trade Commission machine-determined nicotine and tar yields of the brand smoked. Log transformation was needed for daily intake of nicotine.
‡Value for Chinese-Americans is statistically significantly different from that for whites.
§Values for Chinese-Americans are statistically significantly different from those for whites and Latinos.
bimodal. A bimodal distribution would have been expected if a specific polymorphism is responsible for the lower average nicotine clearance in Chinese-Americans. The unimodal distributions in all three ethnic groups, with differences in the mode, suggest instead that multiple genes and/or environmental factors underlie the ethnic differences that we observed.

The results of our study may be helpful in understanding ethnic differences in cigarette smoking behavior and individual differences in disease risk from cigarette smoking. Because the clearance and half-life of nicotine were slower in Chinese-Americans than in Latinos and whites, it is expected that Chinese-Americans would need to smoke less frequently and to take in less nicotine per day to achieve the same levels of nicotine and nicotine-related effects as are achieved by whites, who metabolize nicotine more rapidly. Our data showing a correlation between nicotine clearance and nicotine intake from cigarette smoking support this hypothesis. It should be noted, however, that the variance in nicotine intake accounted for by nicotine clearance was only 16%. Thus, factors other than nicotine clearance account for most of the individual, as well as ethnic, variability in smoking behavior and nicotine intake from smoking.

Asians have been reported to have a lower risk of lung cancer from cigarette smoking than white Americans (7–9). This lower cancer risk may be related, in part, to smoking fewer cigarettes per day and also to taking in less cigarette smoke per cigarette, as shown in our study. Our data suggest that smoking fewer cigarettes per day and/or taking in less smoke per cigarette is associated, at least in part, with slower metabolism of nicotine.

Like Asian smokers, Latino smokers are reported to have lower lung cancer rates than non-Latino white smokers (2). However, for Latinos, the lower rates of lung cancer appear to be due entirely to smoking fewer cigarettes per day (6). Our study is consistent with this epidemiologic finding, showing that exposure to tobacco smoke per cigarette is similar in Latinos and whites. Why Latinos smoke fewer cigarettes per day than whites is unclear, given that they metabolize nicotine at a rate similar to whites. The difference may be related to cultural factors (2).

Our finding that CYP2A6 activity is lower in Chinese-Americans than in whites may have implications for cancer risk, in addition to its implications for the intake of cigarette smoke. CYP2A6 is involved in the metabolic activation of 4-(methyl-nitrosamine)-1-(3-pyridyl)-1-butanone, a tobacco-specific nitrosamine that is believed to contribute to smoking-related lung cancer, as well as in the metabolic activation of other potential carcinogens, including aflatoxin B, N-nitrosodiethylamine, and 1,3-butadiene (34,35). Two recent small case–control studies (36,37) have reported that the presence of a CYP2A6 gene polymorphism, which presumably reflects decreased CYP2A6 activity, is associated with a lower risk of lung cancer. Thus, the lower CYP2A6 activity in Chinese smokers may contribute to a lower lung cancer risk in two ways: 1) because it is associated with reduced smoking levels and 2) because it leads to less activation of nicotine-derived nitrosamines. Of course, ethnic variability in enzymes other than CYP2A6 that activate or detoxify tobacco smoke carcinogens may also contribute to ethnic differences in smoking-related lung cancer risk.

The findings of this study that Chinese-Americans take in less nicotine per cigarette smoked are in contrast with findings from our previous report (5), which showed that blacks take in more nicotine and presumably more cigarette smoke per cigarette than whites. The greater intake of smoke per cigarette may explain, at least in part, the higher lung cancer rates in blacks than in other ethnic groups.

The ethnic differences that we observed in the rate of cotinine metabolism are important in that cotinine is often used as a biomarker for nicotine and tobacco smoke exposure (38). Cotinine has a much longer half-life than nicotine. Since cotinine clearance is slower in Chinese-Americans than in whites or Latinos, then, for a given level of nicotine intake, cotinine levels will be higher in Chinese-Americans than in whites or Latinos.

Fig. 2. Relationship between total nicotine clearance and daily intake of nicotine from cigarette smoking (A) and between total nicotine clearance and nicotine intake per cigarette (B). Subjects from all ethnic groups are included.
Table 5. Urine nicotine and metabolite excretion in Chinese-American, Latino, and white smokers

<table>
<thead>
<tr>
<th>Excretion</th>
<th>Chinese-Americans (n = 37)*</th>
<th>Latinos (n = 40)</th>
<th>Whites (n = 54)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>28.6 ± 16.4‡ (23.1 to 34.1)</td>
<td>19.2 ± 16.3 (14.0 to 24.4)</td>
<td>23.1 ± 16.4 (18.7 to 27.6)</td>
<td>.009</td>
</tr>
<tr>
<td>Nicotine glucuronide</td>
<td>14.6 ± 9.5 (11.4 to 17.7)</td>
<td>10.3 ± 7.3 (7.9 to 12.6)</td>
<td>11.6 ± 5.8 (10.0 to 13.2)</td>
<td>.042</td>
</tr>
<tr>
<td>Cotinine</td>
<td>24.9 ± 10.3 (21.5 to 28.4)</td>
<td>26.0 ± 10.3 (22.7 to 29.3)</td>
<td>23.6 ± 7.5 (21.5 to 25.6)</td>
<td>.93</td>
</tr>
<tr>
<td>Cotinine glucuronide</td>
<td>10.9 ± 8.5 (8.1 to 13.7)</td>
<td>12.1 ± 9.1 (9.2 to 15.0)</td>
<td>13.4 ± 8.8 (11.0 to 15.8)</td>
<td>.03</td>
</tr>
<tr>
<td>3'-Hydroxycotinine</td>
<td>14.5 ± 10.9§ (10.9 to 18.2)</td>
<td>23.5 ± 16.3 (14.0 to 24.4)</td>
<td>20.6 ± 11.4 (17.5 to 23.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3'-Hydroxycotinine glucuronide</td>
<td>6.5 ± 6.2 (4.4 to 8.6)</td>
<td>8.9 ± 8.6 (6.1 to 11.6)</td>
<td>7.7 ± 5.3 (6.3 to 9.2)</td>
<td>.07</td>
</tr>
</tbody>
</table>

*Based on excretion of nicotine-d₄ and metabolites as a percentage of total recovery in 8-hour urine. Values are means ± standard deviation (95% confidence interval).
†Analysis by general linear model, controlling for age, sex, body mass index (kg/m²), number of cigarettes smoked per day, duration of smoking, and Federal Trade Commission machine-determined yield.
‡Values for Chinese-Americans are statistically significantly different from those for Latinos.
§Values for Chinese-Americans are statistically significantly different from those for whites and Latinos.

Thus, when using cotinine as a biomarker of nicotine exposure, one must consider ethnic differences in the relationship between cotinine levels and nicotine intake.

Information on the rate of metabolism of nicotine in different ethnic groups may be important in selecting optimal doses of the nicotine medications that are used to aid smoking cessation. Clinical trials of nicotine medications have been conducted primarily in the United States and in Europe, with mostly white participants. However, there are more smokers in China than in any other country of the world, with more than 300 million male and 200 million female smokers (38). Nicotine medications to aid cessation are not widely used in China at the present time but are likely to be used much more in the near future. If our finding that the clearance of nicotine in Chinese-Americans is 35% lower than in whites applies to Chinese people in general, then a standard dose of nicotine based on studies in whites would result in substantially higher levels of nicotine in Chinese. The observation that Chinese metabolize nicotine more slowly, in conjunction with our finding that Chinese take in less nicotine from cigarette smoking per day, suggests that there may be a different dose–response for nicotine medication in aiding smoking cessation in Chinese than in whites. Our findings reinforce the idea that research in drug development needs to consider ethnic differences in drug metabolism.

REFERENCES

(22) Jacob P 3rd, Yu L, Wilson M, Benowitz NL. Selected ion monitoring method for determination of nicotine, cotinine, and deuterium-labeled ana...


NOTES

Supported by grant IRT-0521 from the State of California Tobacco Related Disease Research Program; by Public Health Service (PHS) grants DA02277 and DA12393 (National Institute on Drug Abuse) and CA39260 and CA32389 (National Cancer Institute), National Institutes of Health (NIH), Department of Health and Human Services (DHHS); and by the General Clinical Research Center at San Francisco General Hospital Medical Center with support by PHS grant RR00083 from the Division of Research Resources, NIH, DHHS. J. Pérez-Stable was a Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine during the period of the study.

We thank Gunnard Modin for statistical analysis, Patricia Buley and Sandra Tinetti for assistance in conducting the study, Sylvia Wu, Lisa Yu, and Irving Fong for performing the analytic chemistry, and Kaye Welch for editorial assistance.

Manuscript received April 16, 2001; revised October 25, 2001; accepted November 7, 2001.