Time to First Cigarette after Waking Predicts Cotinine Levels

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Abstract

There is wide variability in cotinine levels per cigarette smoked. We hypothesized that in addition to smoking frequency, other behavioral measures of nicotine dependence, such as the time to first cigarette after waking, are associated with cotinine levels. To test this hypothesis, we measured plasma and urinary cotinine in a community-based study of 252 black and white daily cigarette smokers. Among one pack per day smokers, plasma cotinine levels varied from 16 to 1,180 ng/mL, a 74-fold difference. Two nicotine dependence phenotypes were discerned by time after waking. Subjects in the "low" dependent phenotype smoked >30 minutes after waking and nearly all smoked ≤20 cigarettes per day. Cotinine levels increased linearly with cigarette consumption in this group. Subjects in the "high" dependent phenotype smoked ≤30 minutes after waking but had a wide range in the frequency of daily cigarettes (6-70). Compared with the low dependent phenotype, there were relatively small differences in cotinine by cigarette frequency with evidence of a plateau effect in heavy smokers (~30). After adjusting for cigarette frequency, the levels of cotinine by time to first cigarette were as follows: ≤5 minutes, 437 [95% confidence limits (CL), 380-494]; 6 to 30 minutes, 352 (95% CL, 291-413), 31 to 60 minutes, 229 (95% CL, 140-317), and >60 minutes, 215 (95% CL, 110-321). Similar findings were observed for urinary cotinine. These findings suggest that the time to first cigarette is a strong predictor of nicotine uptake and should be considered in the design of smoking interventions. (Cancer Epidemiol Biomarkers Prev 2009;18(12):3415–20)

Introduction

Nicotine uptake, as measured by the major nicotine metabolite cotinine, increases with the numbers of cigarettes smoked per day in a dose-dependent relationship (1-9). In most studies, cotinine levels tend to level off or even slightly decrease at about one pack per day. In the National Health and Nutrition Examination Surveys, the ratio of cotinine per cigarette smoked tended to decline linearly and leveled off at 20 cigarettes per day (10). This plateau effect as well as differences in demographics, cigarette nicotine yields, and nicotine metabolism partly explain why the frequency of daily smoking is only moderately correlated with cotinine levels (r = 0.36-0.82; refs. 1, 2, 4, 10). Because the risk of lung cancer risk associated with cigarette smoking also plateaus with high smoking consumption (11-14), cotinine levels might be a marker of risk and not just exposure.

In pharmacodynamic studies, nicotine intake stimulates neural systems at low doses and suppresses at high doses (15). Many smokers develop nicotine tolerance, and smoking cessation causes withdrawal symptoms, including cravings, depression, and increased appetite. Smokers consume nicotine to both experience its stimulative effects and avoid withdrawal symptoms. In particular, the cravings of the smokers after overnight abstinence and the ability to tolerate cigarettes immediately after waking are strong indicators of nicotine dependence (16-18). The time to first cigarette after waking up has become increasingly recognized as one of the best measures of nicotine dependence because it is also associated with many other aspects of dependence, including smoking cessation (18, 19), smoking relapse (20), and tolerance (21). Time to first cigarette is one of the items that comprise the six-item Fagerström Test for Nicotine Dependence (FTND), and much of the predictive value of the FTND has been attributed to the time to first cigarette (22-24).

The time to first cigarette was originally conceptualized as a categorical variable (≤5 minutes, 6-30 minutes, 31-60 minutes, and >60 minutes) based on its relationship with "heavy smoking." A quicker time to first cigarette was associated with higher expired carbon monoxide and cotinine levels (24). The current analysis was therefore conducted to determine whether this simple behavioral measure of dependence affects the physiologic uptake of nicotine (e.g., cotinine) independently of cigarettes per day and whether it affects the shape of the relationship between smoking frequency and cotinine.

Materials and Methods

We designed and conducted a participatory-based study of adult cigarette smokers ages 18 to 55 y in lower and central Westchester County, New York, to investigate racial differences in smoke exposure and metabolism. The details were described previously (1). The study included subjects who smoked at least five cigarettes per day for 1 or more years. Subjects were recruited by community civic and church leaders, word-of mouth recommendations

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Table 1. Correlation matrix of cigarettes smoked per day and cotinine in a community-based study, New York

Measure	Time to first cigarette	Plasma cotinine (ng/mL)	Urinary cotinine
Cigarettes per day	0.34*	0.14*	0.28†
Time to first cigarette	—	0.33*	0.27*
Plasma cotinine (ng/mL)		—	0.54*

*$P < 0.01$.
†$P < 0.05$.

from participants, as well as newspaper advertisements and other media. All subjects signed a consent form approved by the Institutional Review Board of the American Health Foundation/Institute for Cancer Prevention. Trained interviewers administered a structured questionnaire that contained detailed items on cigarette smoking history and, for a subset of subjects, the six-item FTND. One of the FTND items is the question "How soon after waking up do you smoke your first cigarette?" Nicotine uptake was determined by measuring plasma cotinine (ng/mL) and urinary cotinine (μg/mg creatinine). There were 242 subjects who had plasma cotinine determinations and 252 had urinary cotinine determinations.

Statistical Analysis. All analyses were done using Statistical Analysis System statistical software (version 9; SAS). Univariate analysis of untransformed statistics is presented, including means and SDs. The Pearson correlation coefficient was used to assess the association between time to first cigarette, based on a four-point scale, and smoking measures, such as cigarette frequency and cotinine. All statistical tests were two-sided. Graphs of the relationship between cigarettes per day and cotinine levels were produced using Microsoft Excel.

Linear regression methods were used to model cotinine levels against cigarettes per day. A departure from linearity was tested using a squared term for cigarettes per day. Cotinine levels were not further regressed against the FTND because of its high collinearity with cigarettes per day. Multivariate modeling was conducted using the natural logarithm of cotinine. In addition to daily cigarette consumption, the following covariates were included in each model: age (continuous), years of education (continuous), race (categorical), sex (categorical), and time to first cigarette (>30 min versus ≤30 min). For each covariate, we tested for effect modification by including interaction terms with cigarettes per day. Differences in mean cotinine levels were also compared between the four categories of time to first cigarette. Significance level was set at 0.05.

Results

There was substantial variability in the levels of cotinine per cigarette smoked. The levels of plasma cotinine in subjects who smoked 20 cigarettes per day varied from 16 to 1,180 ng/mL, a 74-fold difference. Two nicotine dependence phenotypes could be discerned from these data. A "low" dependent phenotype included subjects who smoked >30 minutes after waking up. Almost all of these subjects smoked ≤20 cigarettes per day and had relatively low mean levels of plasma cotinine (204 ± 202 ng/mL) and urinary cotinine (2,690 ± 3,100 μg/mg creatinine). The levels of cotinine increased linearly with no evidence of a plateau effect, as there were few heavy smokers ($n = 4$). The "high" dependent phenotype included subjects who smoked ≤30 minutes after waking. In contrast to the low dependent phenotype, there was a wide range of cigarette consumption in this group. The mean level of plasma cotinine (397 ± 294 ng/mL) and urinary cotinine (4,490 ± 3,540 μg/mg creatinine) was almost twice as high as that for smokers in the low dependent group. Highly dependent subjects who smoked 10 cigarettes per day had higher cotinine levels than low dependent subjects who smoked 20 cigarettes daily (plasma: 326 ± 291 versus 268 ± 270 ng/mL; urinary: 3,050 ± 2,230 versus 2,970 ± 2,320 μg/mg creatinine). The levels of biomarkers in the highly dependent group did not increase with cigarette frequency as much as that in the less dependent group, and there was a clear plateau effect at ~30 cigarettes.

Table 1 shows that the time to first cigarette was significantly correlated with cigarettes per day ($r = 0.34$) and both plasma ($r = 0.33$) and urinary cotinine ($r = 0.27$). Figure 1A shows the relationship between cigarettes per day and log-transformed plasma and urinary cotinine concentrations. The slope for both measures levels off at about 25 to 30 cigarettes per day. In a linear regression model of log-transformed plasma cotinine that included the covariates and their interaction terms, age was a significant predictor ($P < 0.01$). The test for the slope of cigarettes per day by time after waking categories (≤30 minutes versus >30 minutes) was statistically significant ($P < 0.05$). We subsequently modeled cotinine separately by these two categories. Cigarette frequency was not a significant predictor in subjects who smoked within 30 minutes (e.g., the high dependent group) but was significant in the low dependent group. Figure 1B shows the time to first cigarette-specific relationship between plasma cotinine and cigarette frequency.

In the model of log-transformed urinary cotinine, the effect of age did not reach statistical significance ($P = 0.08$). Interaction terms for cigarette frequency * time to first cigarette and cigarette frequency * sex were both statistically significant ($P < 0.01$). The relationships are shown in Fig. 1C and D for men and women, respectively. As with plasma cotinine, the slopes were flatter for highly dependent smokers and showed evidence of a plateau effect. [In women who smoked ≥30 minutes after waking, there was only one subject who smoked >20 cigarettes (i.e., 60 cigarettes per day).]

The mean levels of plasma cotinine were compared between the four categories of the time to first cigarette variable. After adjusting for cigarettes per day and race, there was a clear trend in decreasing cotinine levels with a longer time to first cigarette. The differences in mean levels between each group were significant, except for the 31- to 60-minute group versus the >60-minute group (Table 2). Similar findings were observed for urinary cotinine (Table 3).

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Discussion

The higher cotinine levels associated with a shorter time to cigarette smoking after waking might be due to more intense smoking in response to overnight abstinence. More highly dependent smokers, as defined by the Fagerström Tolerance Questionnaire (an earlier version of the FTND), have increased compensatory smoking behaviors such as puff number and puff duration than less dependent smokers when switching to a low nicotine cigarette (25). There are little data on the time to first cigarette and smoking intensity. One recent study in adult smokers in the United Kingdom measured puffing behaviors in relation to the time of the day that cigarettes were smoked (26). Cigarettes that were smoked within 5 minutes after waking were associated with a significantly lower mean total smoke volume than cigarettes smoked afterwards. These data would seem to indirectly contradict our hypothesis, although cotinine measurements were not reported in the United Kingdom study. Our studies would need additional data on puffing profiles to make more definitive conclusions on whether the association between time to first cigarette and cotinine could be attributed to more intense puffing behaviors and whether symptoms of nicotine cravings are greater after waking.

In our study, highly dependent subjects who smoked 10 cigarettes per day had higher cotinine levels than less dependent subjects who smoked 20 cigarettes per day. The lack of a significant linear relationship between cigarette frequency and cotinine in the highly dependent group indicates important physiologic or metabolic factors such as the saturation of nicotine uptake and nicotine metabolism may be occurring and/or reduction in stress that affects inhalation. In smoking reduction trials, there was no linear relationship between cigarettes per day and baseline urinary cotinine in highly dependent subjects (e.g., high FTND, time to first cigarette ≤30 minutes, those who had difficulty giving up the first cigarette, and subjects who smoked when ill).

The two suggested phenotypes in these data are not entirely distinct nor would they be expected to be because time to first cigarette and daily cigarette frequency are just two behavioral measures of nicotine dependence, which is characterized by a physiologic desire and craving for nicotine, the perceived good feelings it generates, and unpleasant withdrawal symptoms. There are several behavioral/symptom scales of nicotine dependence in use (26), and their lack of a high concordance highlights the complexity in defining nicotine dependence. We did not measure the many physiologic and psychological attributes of

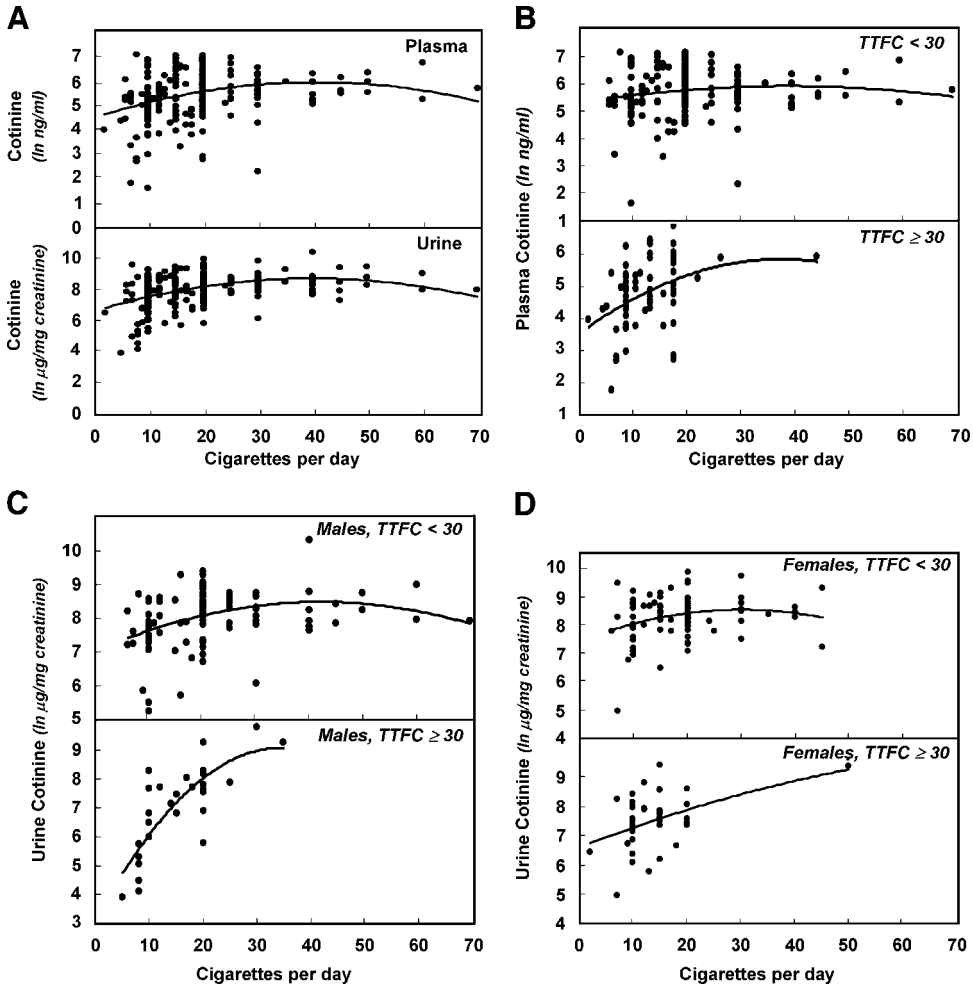

Figure 1. **A.** Relationship between cigarettes per day and log-transformed plasma and urinary cotinine concentrations. **B.** Relationship between cigarettes per day and log-transformed plasma cotinine by time to first cigarette. **C.** Relationship between cigarettes per day and log-transformed urinary cotinine/creatinine in men by time to first cigarette. **D.** Relationship between cigarettes per day and log-transformed urinary cotinine/creatinine in women by time to first cigarette.

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Table 2. Mean plasma cotinine values by time to first cigarette after waking in a community-based study, New York

	n	Plasma cotinine (ng/mL)	*P* value for pairwise comparison of mean plasma cotinine levels			
			95% CL	6-30 min	31-60 min	>60 min
Time to first cigarette (min)						
<5	96	437	380-494	0.05	<0.001	<0.001
6-30	79	352	291-413	—	0.02	0.03
31-60	40	229	140-317		—	0.85
>60	27	215	110-321			

NOTE: Mean values are adjusted for cigarettes per day, sex, and race.
Abbreviation: CL, confidence limits.

nicotine dependence, which may also independently or collectively help explain much of the remaining variation in cotinine levels. Unmeasured genetic variability in addiction and environmental factors that affect dependence may also account for cotinine variability. In addition, smoking intensity may be due to factors besides nicotine dependence, including the tar yield and taste (27).

The regression slope for plasma cotinine did not differ by sex, but significant differences by sex were found for urinary cotinine. In pooled baseline data from four smoking reduction trials, urinary cotinine levels peaked in men (~34 cigarettes daily) but continued to rise with cigarettes per day in women (9). Sex differences in nicotine pharmacology have been reported but it is uncertain whether these differences are due to physiologic, hormonal, or environmental factors (28-30). One possible explanation for the effect of sex on urinary cotinine only is that there are sex differences in the excretion of creatinine, which was used as an adjustment factor for urinary volume. Age was a significant independent predictor of plasma cotinine levels in our data, but the regression of cotinine against cigarette frequency did not differ significantly by age as was reported in the smoking reduction trials (9).

These observations underscore the methodologic issue of the relative merits of blood, urine, and saliva as biological sources for cotinine measurements. All three measures are consistent in determining smoking status. When measuring exposure dose, the levels of biomarkers will depend on assay sensitivity and specificity, exposure conditions, and variation in metabolism and excretion. Plasma and urinary cotinine are considered comparable measurements of nicotine exposure based on similar rates of elimination (31). However, creatinine production and excretion is lower in the elderly, in women than in men, in whites than in blacks, and in old age (32-34). The extent to which creatinine adjustment affects the correlation between urine and blood cotinine levels may vary (35). In our data, the differences in correlation coefficients between plasma cotinine and unadjusted or adjusted urinary cotinine were minor.

Another methodologic issue is that nicotine is converted into over one dozen metabolites. Cotinine accounts for ~10% of nicotine metabolites, but a complete metabolic profile would provide greater accuracy for comparing nicotine uptake between individuals. We are planning such an analysis in the near future.

Nicotine dependence may be a factor in the success of harm reduction programs, where success is measured by decreased cigarette frequency and levels of smoking and disease risk biomarkers (36, 37). In a meta-analyses of 13 nicotine replacement trials, there was an overall reduction in the average daily numbers of cigarettes smoked but wide variability in the reduction of cotinine, carbon monoxide, and thiocyanate levels (38). The reduced consumption of cigarettes might have been offset by nicotine-dependent driven compensatory smoking behaviors (39). Even if interventions successfully reduce cigarette consumption, concurrent reductions in biological exposure to tobacco smoke might depend on nicotine dependence. In intervention programs, high dependence may require a proportionally greater reduction in smoking frequency to receive similar health benefits as subjects who are less dependent. A limited number of tobacco pharmacotherapy treatment trials in black smokers measured time to first cigarette. Participants who smoked >30 minutes after waking were more successful quitters (40). In case-control data, the excess odds ratio for lung cancer increases with smoking frequency up to 20 cigarettes per day but plateaus with higher cigarette frequency (14). This

Table 3. Mean urinary cotinine values by time to first cigarette after waking in a community-based study, New York

	n	Urinary cotinine (μg/mg creatinine)	*P* value for pairwise comparisons of mean urinary cotinine levels			
			95% CL	6-30 min	31-60 min	>60 min
Time to first cigarette (min)						
<5	102	4,600	3,900-5,260	0.54	0.11	0.01
6-30	82	4,270	3,530-5,010	—	0.25	<0.05
31-60	41	3,530	2,450-4,610		—	0.28
>60	27	2,650	1,370-3,930			

NOTE: Mean values are adjusted for cigarettes per day, sex, and race.

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parallels the cigarette per day–cotinine relationship, supporting the notion that biomarker levels reflect risk and not just exposure.

A strength of the current study is that subjects were not recruited as part of a smoking reduction trial where a high motivation to quit could possibly bias the findings. Limitations include possible misclassification of nonsmokers as smokers, although none of the participants had blood cotinine levels <5 ng/mL, an optimal cutpoint for distinguishing passive from active smoking (41). We also assessed misclassification of reported smoking amount in 133 subjects by comparison with the number of cigarette butts saved and stored in a plastic container the week before the study day (0.95 in Blacks and 0.83 in Whites; ref. 1).

Differences in the time to first cigarette may represent a constellation of factors that includes genetic variation in nicotine dependence, variation in nongenetic behavioral and social factors, and possibly variation in characteristics of the cigarettes including taste. The fact that a simple question is such a strong predictor of a biomarker of nicotine dependence seems quite noteworthy particularly because considerable efforts have been made to discover relatively small effects of variants on nicotine dependence in genome-wide scans. Because nicotine dependence (cigarettes per day, time after waking) is the major explanatory variable for the variation in cotinine levels, and because cotinine levels seem to reflect the risk of lung cancer, time to first cigarette may be an important risk factor for lung cancer and should be considered in the design of smoking cessation programs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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