Research Article

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Time to First Cigarette and 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol (NNAL) Levels in Adult Smokers; National Health and Nutrition Examination Survey (NHANES), 2007–2010

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Abstract

Background: The time to first cigarette (TTFC) is a good indicator of several dimensions of nicotine dependence. An early TTFC is also associated with increased lung and oral cancer risk. Our objective was to determine the relationship between TTFC and exposure to tobacco smoke carcinogens.

Methods: We conducted a cross-sectional analysis of a nationally representative subsample of smoking adults that had urinary samples analyzed for tobacco biomarkers. The study included 1,945 participants from the 2007–2008 and 2009–2010 National Health and Nutrition and Examination Survey. The main outcome measure was creatinine-adjusted urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels.

Results: The cigarette-per-day adjusted levels of NNAL were twice as high in participants who smoked within 5 minutes after waking than in participants who refrained from smoking for at least 1 hour (0.58 vs. 0.28 ng/mL, $P < 0.001$). In multivariate linear models, a shorter TTFC was significantly associated with increasing NNAL levels, after adjusting for cigarettes smoked per day (or cotinine), secondhand smoke exposure, age, sex, race/ethnicity, and other potential confounders.

Conclusions: These data show that in a nationally representative sample, there is a dose-dependent relationship between earlier smoking in the day and higher biologic exposure to a tobacco smoke carcinogen.

Impact: Our study provides further evidence that highlights the relationship between TTFC, nicotine dependence, and cancer risk. *Cancer Epidemiol Biomarkers Prev; 22(4); 615–22. ©2013 AACR.*

Introduction

The time to first cigarette (TTFC) is an indicator of several dimensions of nicotine dependence including ability to quit smoking (1). Smokers who consume cigarettes immediately after waking have higher blood cotinine levels than smokers who refrain from smoking a half hour or more after waking (2–6). The levels of cotinine are about twice as high in smokers who smoke within 5 minutes after waking than in smokers who waited for an hour or more after adjusting for the number of cigarettes smoked per day (CPD). An early TTFC is also associated with an increased risk of lung and other tobacco-related cancers (7–10). It is uncertain why early morning smokers are at increased risk as nicotine and its metabolites are not carcinogens. We hypothesize that the TTFC is an indicator of exposure to tobacco smoke carcinogens as well as nicotine. This is supported by data that show a correlation between urinary cotinine and the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in active smokers (11). Furthermore, while NNAL levels increase with cigarettes per day (CPD), there is up to a 100-fold difference within smoking strata (e.g., 1–5 CPD, 5–10 CPD, etc.; ref. 12). This unexplained variation in NNAL concentrations is likely due, in part, to interindividual variation in the metabolic pathways of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), the precursor from which NNAL is derived (13). It seems likely though that variation in NNAL levels may also be attributed to other cigarette smoking behaviors besides CPD that affect cigarette smoke uptake, such as the intensity of smoking or TTFC. The current study examines the relationship between TTFC in the National Health and Examination Nutrition Survey (NHANES).

Materials and Methods

Participants

The analysis was conducted by pooling the 2007–2008 and 2009–2010 National Health and Nutrition and Examination Survey data. NHANES uses a multistage probability sampling design to obtain a representative sample of the noninstitutionalized U.S. population, with oversampling in minority and older age groups (14). For the

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current study, we selected all adult participants who reported currently smoking and who had provided urine samples for NNAL analyses.

Measures

NHANES collects demographic measures from all participants including age, race, sex, and education. Information on smoking was collected from the "Smoking – Cigarette Use," "Smoking – Household Smokers," and "Smoking – Recent Tobacco Use" questionnaires. Items on this questionnaire included the number of days smoked in the last 5, average number of cigarettes smoked per day in the last 5 days, TTFC, and whether there are other smokers in their home to assess exposure to secondhand smoke. Current smokers were defined as those who had smoked more than 100 cigarettes in their lifetime and had smoked at least once in the previous 30 days. The item "*how soon after you wake do you smoke*" was classified into 4 categories: 1 = within 5 minutes; 2 = 6–30 minutes; 3 = from more than 30 minutes to 1 hour; and 4 = more than 1 hour.

Urine samples were collected and processed according to the defined NHANES protocol. For a full description of collection and procession of biologic specimens, see the NHANES Laboratory/Medical Technologists Procedures Manual (LPM; ref. 15). We analyzed data on total urinary NNAL measurements (e.g., NNAL and its glucuronides) and urinary creatinine. Cotinine measurements were conducted from serum samples. All procedures were approved by the National Center for Health Statistics Research Ethics Review Board.

Statistical analyses

Statistical analysis was conducted using SPSS, version 20. Descriptive statistics included frequency, measure of central tendency, and exploration of normality of distributions. Differences in TTFC between different racial/ethnic groups and NNAL was initially explored using bivariate statistics such as independent samples *t* tests and ANOVA comparing NNAL levels by TTFC between different racial/ethnic groups. Analysis of covariance was conducted controlling for CPD, as CPD was considered the major predictor of NNAL levels.

The multivariate strategy used a backward-elimination linear regression approach. NNAL levels were log-transformed to normalize the skewness in NNAL values. All analyses controlled for creatinine levels to account for differences in urinary dilution (16). Per the recommendations of the Centers for Disease Control, NHANES sampling weights were used to produce an unbiased national estimate. The analysis began with a saturated model with all relevant predictors and interaction terms entered simultaneously. In the models, each predictor is evaluated for the reduction of the overall model R^2 that would result from that variable's deletion from the model (17). Those variables whose removal from the model that result in an insignificant reduction in R^2 are then deleted. The final model resulted when no further predictor variables could be deleted from the model. The backward-elimination model was selected as it allows for an evaluation of the joint predictive capability of all variables before the potential removal of individual variables that do not predict the outcome individually. Regression models predicting log-transformed NNAL added 8 control variables: (i) current age, (ii) the age at which participant started smoking regularly, (iii) gender, (iv) urinary creatinine, (v–vii) dummy-coded variables for ethnicity (non-Hispanic white, non-Hispanic Black, and Mexican-American), and (viii) presence of other smokers in the home (to control for secondhand smoke exposure). Next, a variable for nicotine uptake was added [linear and nonlinear (e.g., squared) terms for CPD in the last 30 days or cotinine, based on previous studies which showed a nonlinear relationship between NNAL and CPD; ref. 18]. Finally, TTFC was then added as the final predictor variable in all models. In the first set of models, TTFC was added as a continuous variable. TTFC is recorded as a categorical variable (1 = less than 5 minutes; 2 = 6–30 minutes; 3 = 31–60 minutes; 4 = >60 minutes), although it has been modeled as a continuous measure in the literature with each value indicating a longer TTFC (a value of "4" is a greater TTFC than a value of "3"). Alternatively, our second set of models entered TTFC as dummy-coded variables representing each time category (5; 6–30; 31–60; >60 minutes). Given that there is a nonlinear association between CPD and cotinine, we used alternative ways to control for dose of cigarette smoke exposure. We conducted one set of models using CPD and a second set of models using blood cotinine levels. Overall, we conducted 4 sets of models using (i) linear and nonlinear terms for CPD and TTFC as a continuous variable, (ii) linear and nonlinear terms for CPD and TTFC as a dummy-coded variable, (iii) cotinine instead of CPD and TTFC and a continuous variable, and (iv) cotinine instead of CPD and TTFC as a categorical variable.

Results

A total of 1,945 adult participants (55% male) were included. Table 1 describes the sample characteristics and Table 2 describes sample characteristics by the TTFC.

The average age of the study sample was 44.82 (SD, 14.89), ranging from 20 to 80 years. The mean age of smoking onset and duration was 17.54 years (SD, 5.75) and 27.28 years (SD, 9.14), respectively. The study sample smoked an average of 15.33 (SD, 11.80) CPD over the previous 30 days and had smoked on an average of 29.38 (SD, 2.99) days in the last 30 days. The racial/ethnic makeup was 10.5% Mexican-American, 7.6% other Hispanic background, 55.1% non-Hispanic White, 22.7% non-Hispanic Black, and 4.1% other racial background. Among all smokers, 32.4% smoked within 5 minutes of waking, 31.3% smoked between 6 and 30 minutes of waking; 17.7% smoked between 31 and 60 minutes of waking; and 18.5% smoked more than 1 hour after waking. ANOVA analyses showed that non-Hispanic Whites were significantly more likely to smoke sooner after

Table 1. Sample demographics and smoking characteristics, NHANES participants

	Male (n = 1,072) Mean (SD)	Female (n = 873) Mean (SD)
Age	45.36 (15.31)	44.16 (14.35)
Age first smoked whole cigarette	17.12 (5.24)	18.06 (6.28)
Creatinine, mg/dL	142.68 (85.56)	111.14 (76.36)
TTFC of the day	2.20 (1.08)	2.25 (1.09)
NNAL, ng/mL	0.47 (.21)[a] (0.45)	0.45 (0.22)[a] (0.46)
Cotinine, ng/mL	226.30 (148.30)	224.12 (146.51)
NNAL (ng/mg creatinine)	0.006 (0.003)	0.004 (0.004)
CPD during past 30 d	16.36 (12.51)	14.08 (10.73)
	Frequency (%)	Frequency (%)
Race ethnicity		
Mexican-American	125 (11.7)	79 (9)
Other Hispanic	88 (8.2)	60 (6.9)
Non-Hispanic White	550 (51.3)	521 (59.7)
Non-Hispanic Black	254 (24)	185 (21.2)
Other race/multi-racial	52 (4.9)	28 (3.2)
Smokers in the home	669 (62.4)	596 (68.3)

[a]Geometric mean.

waking than all other racial/ethnic groups, and Mexican-Americans were significantly more likely to smoke later after waking than all other groups, $F(4, 1940) = 36.73$, $P < 0.001$. ANCOVA models controlling for the number of CPD show that both non-Hispanic Whites and Blacks smoked earlier after waking than Mexican-American smokers, $F(4, 1937) = 31.46$, $P < 0.001$. However, there were no significant differences in the TTFC between non-Hispanic Whites and Blacks.

NNAL levels ranged from 0.004 to 4.57 ng/mL, with a mean of 0.46 (SD, = 0.46). The levels of NNAL per milligram of creatinine are illustrated in Tables 1 and 2. NNAL was significantly correlated with age, age started smoking regularly, TTFC, number of days smoked in the previous 30 days, number of CPD, creatinine, and having other smokers in the home (Table 3). The initial analyses explored the effects of demographics on NNAL levels. No differences were found in mean NNAL levels between men and women. Mexican-Americans had significantly lower levels of NNAL ($M = 0.35$, SD = 0.40) than both non-Hispanic whites ($M = 0.53$, SD = 0.51) and non-Hispanic Blacks ($M = 0.40$, SD = 0.34). Non-Hispanic whites had significantly higher levels of NNAL than the other racial/ethnic groups.

Table 2. Characteristics of sample by TTFC

	<5 min. Freq. (%)	6–30 min. Freq. (%)	31–60 min. Freq. (%)	>60 min. Freq. (%)
Male	351 (55.6)	347 (57)	179 (51.9)	195 (54.2)
Female	280 (44.4)	262 (43)	166 (48.1)	165 (45.8)
Mexican-American	32 (5.1)	47 (7.7)	35 (10.1)	90 (25.0)
Non-Hispanic White	398 (59.1)	360 (59.1)	181 (52.5)	132 (36.7)
Non-Hispanic Black	154 (24.4)	133 (21.8)	82 (23.8)	73 (20.3)
Smokers in home	516 (81.8)	409 (67.2)	190 (55.1)	150 (41.7)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	45.61 (14.46)	46.65 (14.67)	43.89 (15.77)	42.26 (15.76)
Age started smoking	16.40 (5.29)	17.39 (4.87)	18.30 (5.85)	19.07 (7.01)
No. of d smoked in last 30 d	29.69 (2.38)	29.69 (2.30)	29.22 (3.48)	28.17 (4.98)
CPD	20.65 (13.93)	15.37 (9.82)	12.55 (9.42)	7.74 (5.84)
NNAL, ng/mL	0.58 (0.53)	0.48 (0.46)	0.40 (0.36)	0.28 (0.30)
Cotinine, ng/mL	310.41 (131.76)	273.45 (125.29)	221.89 (113.44)	156.15 (121.19)
NNAL (ng/mg creatinine)	0.006 (0.005)	0.004 (0.004)	0.003 (0.003)	0.002 (0.002)

Table 3. Correlation matrix of smoking and demographic measures

Measure	NNAL	Age	Age 1st	TTFC	Day smoked	CPD	Creatinine	Gender	Household
NNAL	—								
Age	0.07[a]	—							
Age 1st	0.12[b]	0.15[b]	—						
TTFC	−0.29[b]	−0.08[b]	0.17[b]	—					
Days smoked	0.10[b]	−0.004	−0.01	−0.17[b]	—				
CPD	0.29[b]	−0.08[b]	−0.14[b]	−0.40[b]	0.14[b]	—			
Creatinine	0.38[b]	−0.18[b]	−0.02	0.08[b]	−0.02	−0.06[c]	—		
Gender	−0.02	−0.04	0.08[b]	0.02	0.04	−0.10[b]	−0.19[b c]	—	
Household	−0.23[b]	−0.13[b]	0.06**	0.30[b]	−0.09[b]	−0.23[b]	0.003	−0.06[c]	—

NOTE: Household = other smokers in the household.
[a]$P < 0.05$.
[b]$P < 0.001$.
[c]$P < 0.01$.

There was a linear relationship between earlier TTFC and higher NNAL levels (Fig. 1). An initial ANOVA model showed that those who smoke within 5 minutes of waking were significantly more likely to have higher NNAL levels, $F(3,1941) = 60.13$, $P < 0.001$, see Fig. 1 for the relationship between TTFC and NNAL. An earlier TTFC was associated with higher NNAL levels in each of the race/ethnic groups. A follow-up ANCOVA model controlling for CPD, cotinine, and creatinine also shows that those who smoke within 5 minutes of waking were significantly more likely to have higher levels of NNAL, $F(3,1842) = 26.97$, $P < 0.001$.

Model 1

Results show that the final overall model is statistically significant, $F(10,1913) = 96.68$, $P < 0.001$, adjusted $R^2 = 0.33$. In this model, current age, age started smoking, creatinine, non-Hispanic White, having another smoker in the home, linear and nonlinear CPD, and TTFC all predicted NNAL levels (Table 3). TTFC modeled as a continuous variable was negatively associated with NNAL indicating a shorter TTFC is associated with significantly higher NNAL levels (Table 4). An examination of standardized regression coefficients showed that creatinine had the greatest effect on NNAL levels. The next biggest predictors were TTFC and the terms for CPD.

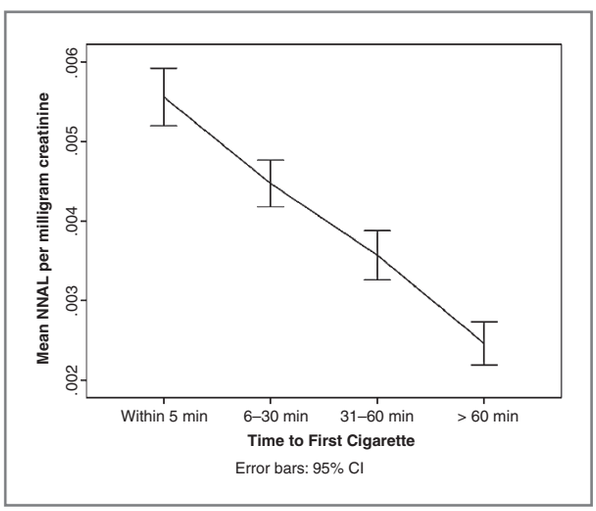

Figure 1. Relationship between TTFC and urinary NNAL (ng/mg creatinine) controlling for CPD.

Model 2

The final overall model was statistically significant, $F(11,1911) = 88.99$, $P < 0.001$, adjusted $R^2 = 0.34$. Again, age, age started smoking, gender, creatinine, non-Hispanic White, having another smoker in the home, and linear and nonlinear CPD predicted NNAL. The indicator terms for smoking greater than 60 minutes after waking and smoking between 31 and 60 minutes of smoking were negatively associated with NNAL, which was interpreted as those who smoke earlier (coded as "0") had significantly higher NNAL levels (Table 5).

Model 3

The final overall model was statistically significant, $F(9,1821) = 145.47$, $P < 0.001$, adjusted $R^2 = 0.42$. In this model, age, age started smoking, gender, creatinine, non-Hispanic Black and non-Hispanic White race/ethnicity, having another smoker in the home, cotinine, and TTFC as a continuous variable were all significant predictors of NNAL. Non-Hispanic Black race/ethnicity was negatively associated with NNAL, which was interpreted as those participants who were not Black (coded as "0") had significantly higher levels of NNAL. Non-Hispanic White was positively associated with NNAL, see Table 6 for results.

Model 4

The final overall model was statistically significant, $F(10,1819) = 131.36$, $P < 0.001$, adjusted $R^2 = 0.42$. Similar to

Table 4. Model 1–final backward-elimination regression analysis of TTFC (continuous), CPD and other covariates on NNAL levels

	Unstandardized coefficient		Standardized coefficient	
	B	SE B	β	*P*
Current age	0.010	0.002	0.128	0.000
Age started smoking	−0.017	0.004	−0.080	0.000
Gender	0.203	0.042	0.093	0.000
Creatinine, mg/dL	0.006	0.000	0.457	0.000
Non-Hispanic White	0.179	0.062	0.074	0.004
Non-Hispanic Black	−0.134	0.080	−0.042	0.093
Smoker in the home	−0.223	0.046	−0.099	0.000
CPD last 30 d (linear)	0.030	0.004	0.322	0.000
CPD last 30 d (nonlinear)	0.000	0.000	−0.152	0.000
TTFC	−0.181	0.022	−0.182	0.000

model 3, age, age started smoking, gender, creatinine, non-Hispanic Black ethnicity, non-Hispanic White race/ethnicity, having another smoker in the home, and cotinine were significant predictors of NNAL. The indicator terms for smoking greater than 60 minutes after waking was negatively associated with NNAL and smoking less than 5 minutes after waking was positively associated with NNAL. The results suggest that those who smoke earlier than 60 minutes after waking (coded as "0") and those who smoke within 5 minutes of waking had significantly higher NNAL levels, see Table 7 for results.

Discussion

The current study examined the relationship between the TTFC and the tobacco-specific carcinogen in a nationally representative sample of adult smokers. We found that an increasingly shorter interval between waking up and smoking the first cigarette was associated with higher total urinary NNAL levels. The findings were adjusted for the frequency of smoking and other factors that predict urinary NNAL concentrations in a series of alternative models. These findings indicate that the relationship between an early TTFC and increased risk of tobacco-related cancers found in case–control data is likely due to a greater exposure to NNAL and possibly other tobacco carcinogens. The case–control studies were conducted with predominantly white subjects. In the NHANES dataset, TTFC was associated with total NNAL levels for all racial and ethnic groups, suggesting that an early TTFC may be a possible lung cancer risk factor for non-Whites as well.

The specific reasons why TTFC is associated with cancer risk are unclear. Smoking topography studies have found that the intensity of puffing is associated with NNAL levels (19). The TTFC may be an indicator of the intensity of smoke exposure such as puff frequency and

Table 5. Model 2—final backward-elimination regression analysis of TTFC (categorical), CPD and other covariates on NNAL levels

	Unstandardized coefficient		Standardized coefficient	
	B	SE B	β	*P*
Current age	0.009	0.002	0.121	0.000
Age started smoking	−0.017	0.004	−0.082	0.000
Gender	0.208	0.042	0.096	0.000
Creatinine, mg/dL	0.006	0.000	0.457	0.000
Non-Hispanic White	0.156	0.062	0.064	0.012
Non-Hispanic Black	−0.147	0.080	−0.046	0.066
Smoker in the home	−0.237	0.046	−0.105	0.000
CPD last 30 d (linear)	0.030	0.004	0.319	0.000
CPD last 30 d (nonlinear)	0.000	0.000	−0.142	0.000
TTFC (31–60 min)	−0.216	0.057	−0.076	0.000
TTFC (>60 min)	−0.544	0.062	−0.191	0.000

Table 6. Model 3—final backward-elimination regression analysis of TTFC (continuous), cotinine, and other covariates on NNAL levels

	Unstandardized coefficients		Standardized coefficient	
	B	SE B	β	*P*
Current age	0.008	0.001	0.108	0.000
Age started smoking	−0.013	0.004	−0.059	0.001
Gender	0.174	0.040	0.080	0.000
Creatinine, mg/dL	0.006	0.000	0.453	0.000
Non-Hispanic White	0.145	0.059	0.059	0.013
Non-Hispanic Black	−0.425	0.078	−0.132	0.000
Smoker in the home	−0.181	0.044	−0.080	0.000
Cotinine, ng/mL	0.003	0.000	0.392	0.000
TTFC	−0.124	0.020	−0.124	0.000

puff volume. More intense or frequent puffing might also explain other observations showing that TTFC predicts nicotine uptake. Ultimately, it is most likely that TTFC reflects greater dependence, greater dependence means smoking cigarettes for intensively, thus resulting in greater exposure to tobacco carcinogens. Further studies are needed to determine these relationships. The TTFC could also be an indicator of rapid nicotine metabolism, which effects mean and total puff volume (20) and potentially greater NNAL levels. An alternative explanation may be that the current results were due to residual confounding from inaccurate measurement of CPD. Klesges and colleagues examined measurement error in the self-report of cigarette use in the NHANES dataset and suggested there may be a bias toward round numbers, (e.g., 20 CPD; ref. 21). However, there was no evidence of systematic under- or over-reporting across the range of reported CPD.

The current study has several limitations. The data are cross-sectional, which limits our ability to infer causality about TTFC and cancer risk. Measurements within case–control or cohort studies would be needed to directly attribute the TTFC–cancer risk association to increased NNAL exposure. The accuracy of information on self-reported TTFC is unknown, although other smoking-related behaviors such as CPD are generally reported with a high degree of accuracy. Also, our main outcome variable, NNAL, was measured with a high degree of analytic accuracy (18). It is possible that the results might have been confounded by exposure to secondhand smoke, as urinary NNAL levels have been detected in nonsmokers (22, 23). We used an assessment of home exposure to control for exposure to secondhand smoke, although there are other sources of SHS outside the home. Urinary NNAL levels from exposure to secondhand smoke is about 30 times lower than from exposure to active smoking (24), and there is little information that suggests that TTFC might be related to exposure to secondhand smoke in active smokers.

Table 7. Model 4—final backward-elimination regression analysis of TTFC (categorical), cotinine, and other covariates on NNAL levels

	Unstandardized coefficients		Standardized coefficient	
	B	SE B	β	*P*
Current age	0.008	0.001	0.108	0.000
Age started smoking	−0.013	0.004	−0.060	0.001
Gender	0.176	0.040	0.081	0.000
Creatinine, mg/dL	0.006	0.000	0.453	0.000
Non-Hispanic White	0.132	0.059	0.054	0.025
Non-Hispanic Black	−0.437	0.078	−0.135	0.000
Smoker in the home	−0.191	0.044	−0.085	0.000
Cotinine, ng/mL	0.003	0.000	0.392	0.000
TTFC (31–60 min)	0.118	0.046	0.051	0.010
TTFC (>60 min)	−0.295	0.057	−0.104	0.000

The major metabolic activation pathways of NNK and its proximate metabolite NNAL occur by α-hydroxylation, whereas the detoxification of NNAL to NNAL-Gluc occurs by glucuronidation (25). While there may be interindividual differences in the metabolism of NNK and NNAL, NNAL is an excellent indicator of tobacco carcinogen exposure and particularly useful in epidemiologic studies because unlike many other known tobacco carcinogens, it is not found in other environmental sources. NNK induces lung tumors in several rodent species, and NNAL levels in human smokers are prospectively associated with increased lung cancer risk (26, 27). NNAL levels are stable in smokers over time, and a single measurement can accurately reflect an individual's exposure over time (28). Consequently, the association between TTFC and NNAL in NHANES is unlikely to be substantially biased. In addition, relatively small differences in NNAL levels are associated with increased cancer risk. In the Shanghai cohort study, mean NNAL levels of smokers were an average of 40% higher in baseline lung cancer cases versus controls (28). This difference is consistent with the magnitude of the difference in NNAL levels between early and late morning smokers in the present study.

Our study provides further evidence that highlights the role of the TTFC in characterizing nicotine dependence and its role in cancer risk. TTFC is an interesting measure of nicotine dependence, yet little is known about the epidemiology of TTFC. In our study, TTFC was associated with several factors including the number of cigarettes smoked per day, number of days smoked in the last 30 days, current age and age first started smoking regularly, and having other smokers in the home. The TTFC might be an important factor in the identification of high-risk smokers and in the development of interventions targeted toward early morning smokers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.A. Branstetter, J.E. Muscat
Development of methodology: J.E. Muscat
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.A. Branstetter, J.E. Muscat
Writing, review, and/or revision of the manuscript: S.A. Branstetter, J.E. Muscat

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