

# Similar Uptake of Lung Carcinogens by Smokers of Regular, Light, and Ultralight Cigarettes

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## Abstract

Cigarette design has changed markedly over the past 60 years and sales-weighted levels of tar and nicotine have decreased. Currently, cigarettes are classified as regular (>14.5 mg tar), light (>6.5–14.5 mg tar), and ultralight (≤6.5 mg tar), based on a Federal Trade Commission–specified machine-smoking protocol. Epidemiologic studies suggest that there is no difference in lung cancer risk among people who smoke light or ultralight cigarettes compared with regular cigarettes, but the uptake of lung carcinogens in smokers of these types of cigarettes has never been reported. We recruited 175 smokers, who filled out a tobacco use questionnaire in which their current brand was identified as regular, light, or ultralight. Urine samples were collected and analyzed for 1-hydroxypyrene (1-HOP), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL plus its glucuronides) and total cotinine (cotinine plus its glucuronides). 1-HOP and total NNAL are biomarkers of uptake of polycyclic aromatic hydrocarbons

and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, lung carcinogens in cigarette smoke. Total cotinine is a biomarker of nicotine uptake. There were no statistically significant differences in urinary levels of 1-HOP, total NNAL, and total cotinine in smokers of regular, light, and ultralight cigarettes, whether the results were expressed per mg urinary creatinine, per mL of urine, or per mg creatinine divided by cigarettes per day. Levels of machine measured tar were available for the cigarettes smoked by 149 of the subjects. There was no correlation between levels of tar and any of the biomarkers. These results indicate that lung carcinogen and nicotine uptake, as measured by urinary 1-HOP, total NNAL, and total cotinine is the same in smokers of regular, light, and ultralight cigarettes. The results are consistent with epidemiologic studies that show no difference in lung cancer risk in smokers of these cigarettes. (Cancer Epidemiol Biomarkers Prev 2005;14(3):693–8)

## Introduction

In response to reports linking smoking and cancer in the 1950s, cigarette manufacturers began to change the design of their products (1). Filters and numerous other changes were introduced resulting in decreases in delivery of nicotine and tar as measured using the Federal Trade Commission (FTC)–specified machine-smoking protocol (35-mL puff volume drawn for 2 seconds once per minute; ref. 2). Tar is defined as that portion of cigarette smoke retained on a glass fiber filter, minus water minus nicotine (3). Sales-weighted levels of tar and nicotine fell by over 60% from the 1950s to the present (4). Cigarettes are currently classified into three categories based on tar measurements using the FTC method. Cigarettes with tar levels of >14.5 mg are called “regular,” those with >6.5 to 14.5 mg tar are termed “light,” and those with ≤6.5 mg tar are called “ultralight” (5). Inherent in this terminology is the implied message that light and ultralight cigarettes are less harmful.

Some epidemiologic studies indicate that smokers of cigarettes with lower tar yields have a lower risk for lung cancer (6). The results of these studies, together with the decreased tar yields that have occurred in the past 50 years, would predict decreases in lung cancer death rates greater than those which have been observed (6). A recent study examined cigarette tar yields in relation to lung cancer mortality in a prospective cohort and found no difference in lung cancer risk among people who smoked light or

ultralight cigarettes compared with those who smoked regular filter brands (7). The reasons for the lower than expected decreases in lung cancer incidence and death rates in people who smoked light and ultralight cigarettes are unclear. A number of studies, beginning in the 1980s, estimated nicotine uptake by measuring cotinine and other biomarkers in smokers of these different types of cigarettes (reviewed in ref. 8). Most of these studies found either weak or no significant correlations between nicotine uptake and FTC nicotine yields. This suggests that uptake of lung carcinogens would not be different in smokers of regular versus light or ultralight cigarettes. A direct approach to evaluating lung carcinogen exposure would be to compare levels of appropriate carcinogen biomarkers in smokers of regular, light, and ultralight cigarettes. Remarkably, there are no reports in the literature using this straightforward approach.

Therefore, in this study, we compared levels of two urinary biomarkers of lung carcinogen uptake in smokers of regular, light, and ultralight cigarettes. We quantified 1-hydroxypyrene (1-HOP), a widely accepted biomarker of polycyclic aromatic hydrocarbon (PAH) uptake, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides, metabolites and biomarkers of uptake of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; ref. 9). PAH and NNK are widely considered major causative agents for lung cancer in smokers (10–13).

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## Materials and Methods

**Subjects.** The study was approved by the University of Minnesota Research Subjects' Protection Programs Institutional Review Board Human Subjects Committee. Subjects were participants in two studies aimed at determining the effects of reduced cigarette smoking on levels of carcinogen

biomarkers. The data reported in the present investigation were obtained at baseline in those studies. In study 1, cigarette smokers ages 18 to 70 years and interested in reducing cigarette use but not quitting within the next 30 days were recruited with advertisements. They were screened to determine whether they met specific inclusion criteria. These included (a) smoking 15 to 45 cigarettes/d (CPD) for the past year; (b) in apparently good physical health with no unstable medical condition; (c) no contraindications for nicotine replacement use; (d) in good mental health; (e) not using other tobacco or nicotine products; and (f) for females, not pregnant or nursing. Baseline levels of carcinogen biomarkers and total cotinine in urine were determined at two intervals 1 week apart and averaged. Details of the study design have been described (14). In study 2, cigarette smokers ages 18 to 80 years who also had heart disease and were interested in reducing cigarette use but not quitting within the next 30 days were recruited with invitation letters and advertisements. Eligibility criteria included (a) smoking  $\geq 15$  CPD; (b) having at least one of the following diagnoses: coronary artery disease, arrhythmia, congestive heart failure, peripheral vascular disease, or history of a cerebrovascular event; (c) no unstable angina within the past 2 weeks; (d) no unstable psychiatric or substance use diagnoses; or (e) no contraindications to nicotine replacement therapy (including pregnancy or intention to become pregnant). Participants were randomized to a smoking reduction intervention that used a combination of behavioral and pharmacologic treatment to encourage at least 50% reduction in cigarette consumption or usual care and followed for 18 months. Carcinogen biomarkers and total cotinine were measured once at baseline. Subjects in both studies completed a tobacco use questionnaire in which they identified their current brand as regular, light, or ultralight and estimated number of CPD. The questionnaire was filled out 1 to 2 weeks before the baseline urine sample was collected. We also determined tar yields for each brand reported using the FTC report for 2000. Tar yields were available for 149 of the 175 subjects; the others smoked brands of cigarettes not listed in the FTC report (3).

### Methods

**Biomarker Analyses.** Total cotinine (cotinine plus cotinine-glucuronide; ref. 15), NNAL and NNAL-Gluc (15, 16), 1-HOP (17), and creatinine (15) in urine were determined as described previously. Coefficients of variation for all assays are  $<10\%$ , and all are highly sensitive and specific for the compounds measured. Total NNAL reported here is the sum of NNAL and NNAL-Gluc, determined separately.

**Statistical Analyses.** SAS for Windows, release 8.02, was primarily used for conducting the statistical analyses. Multiple linear regression analysis was used to determine whether levels of the biomarkers in smokers were related to the type of cigarette smoked—regular, light, or ultralight. Pairwise comparisons were done among cigarette types. The Bonferroni method was used to adjust *P*s for multiple comparisons (18). Because the data were collected from two separate studies, the interactions of cigarette types and studies were tested to determine whether the data from the two studies could be combined. After the data were combined, mean levels of urinary biomarkers for different types of cigarettes were calculated and their 95% confidence intervals (95% CI) determined. All statistical tests were two sided.

### Results

Demographic data are summarized in Table 1. There were 115 subjects in study 1 and 60 in study 2. Subjects in study 2, which was carried out at the Veterans Administration Medical Center, were predominantly male, significantly older ( $P < 0.0001$ ), and smoked significantly more regular cigarettes ( $P = 0.03$ ) and more CPD ( $P < 0.0001$ ) than the subjects in study 1. In the combined data set, the distribution of smokers of different types of cigarettes was regular (26.9%), light (45.7%), and ultralight (27.4%). More of our subjects smoked regular and ultralight cigarettes than would be expected based on domestic market share in the United States in 2001. Market shares were 88.7% for cigarettes with  $\leq 15$  mg tar (approximately equal to light plus ultralight) and 13.2% for cigarettes with  $\leq 6$  mg tar (approximately equal to ultralight; ref. 19).

Levels of total NNAL, 1-HOP, and total cotinine, expressed per mg creatinine, in the urine of smokers of regular, light, and ultralight cigarettes are summarized in Table 2. There were no significant differences in levels of total NNAL, 1-HOP, and total cotinine among smokers of regular, light, and ultralight cigarettes in study 1 or study 2, although there was a suggestion of decreasing total NNAL levels in study 2 among smokers of regular versus light versus ultralight cigarettes, respectively. Results in study 1 and study 2 were very similar and, based on multiple regression analysis of the biomarkers, interactions between cigarette type and studies were insignificant. Therefore, we also combined data from study 1 and study 2. The pooled data for the urinary biomarkers in 175 subjects are shown in Table 2 and Fig. 1. There were no significant differences in biomarker levels among the three groups. There were no significant differences in biomarker levels among the three groups when men and women were considered separately. There were also no effects of age. When the data were

**Table 1. Demographic information for study subjects**

	No. subjects, <i>n</i> (%)	Gender (% male)	Mean age* (95% CI)	Mean CPD (95% CI)
Study 1				
Regular	23 (20.0)	61	45.6 (40.8-50.3)	23.6 (21.0-26.2)
Light	58 (50.4)	50	45.4 (42.7-48.2)	23.4 (22.1-24.7)
Ultralight	34 (29.6)	38	46.7 (43.4-50.1)	23.8 (21.7-26.0)
Study 2				
Regular	24 (40.0)	91	55.6 (51.3-59.9)	32.0 (27.3-36.7)
Light	22 (36.7)	90	59.8 (55.3-62.0)	26.0 (22.0-29.9)
Ultralight	14 (23.3)	93	62.6 (58.3-67.0)	31.6 (20.5-42.6)
Pooled				
Regular	47 (26.9)	72	50.5 (47.0-54.0)	27.9 (25.0-30.8)
Light	80 (45.7)	59	49.1 (46.4-51.7)	24.1 (22.6-25.6)
Ultralight	48 (27.4)	54	51.4 (48.0-53.1)	26.1 (22.5-30.0)

\*Data were missing for four subjects in study 2.

**Table 2. Total NNAL, 1-HOP, and total cotinine in the urine of smokers of regular, light, and ultralight cigarettes, per mg creatinine**

	<i>n</i>	Mean (95% CI)		
		Total NNAL (pmol/mg creatinine)	1-HOP (pmol/mg creatinine)	Total cotinine (pmol/mg creatinine)
Study 1				
Regular	23	2.11 (1.76-2.46)	1.94 (1.45-2.44)	28.2 (21.8-34.6)
Light	58	2.21 (1.93-2.48)	1.41 (1.15-1.66)	25.2 (22.2-28.0)
Ultralight	34	2.42 (1.97-2.88)	1.58 (1.24-1.92)	27.0 (22.0-32.1)
Study 2				
Regular	24	3.23 (2.45-4.13)	1.53 (1.13-1.93)	25.8 (22.5-29.0)
Light	22	2.65 (2.10-3.20)	1.62 (1.03-2.22)	28.2 (23.0-33.5)
Ultralight	14	2.33 (1.36-3.31)	1.40 (0.84-1.96)	21.9 (14.2-29.6)
Pooled*				
Regular	47	2.68 (2.22-3.14)	1.73 (1.42-2.05)	27.0 (23.4-30.5)
Light	80	2.33 (2.08-2.58)	1.47 (1.22-1.71)	26.0 (23.4-28.6)
Ultralight	48	2.40 (1.97-2.82)	1.53 (1.24-1.81)	25.5 (21.3-29.8)

\**P*s: regular versus light, NNAL 0.50, 1-HOP 0.56, cotinine 1.0; regular versus ultralight, NNAL 0.94, 1-HOP 1.0, cotinine 1.0; light versus ultralight, 1.0 for all measures.

expressed per mL urine instead of per mg creatinine, there were also no differences in levels of the biomarkers among smokers of regular, light, and ultralight cigarettes. Levels of total NNAL, 1-HOP, and total cotinine, expressed per mg creatinine per CPD are summarized in Table 3. There were no significant differences in levels of these biomarkers among smokers of the three types of cigarettes.

Levels of tar, measured by the FTC method in the three types of cigarettes, and available for 149 subjects, were 16.9 mg (15.8, 19.1 mg) in regular cigarettes, 10.4 mg (10.1, 10.7 mg) in light cigarettes, and 5.26 mg (4.52, 5.99 mg) in ultralight cigarettes. These values were significantly different ( $P < 0.0001$ ). There were no statistically significant differences in the levels of the urinary biomarkers among smokers of the three types of cigarettes in this set of subjects, either in the studies individually or in the pooled data.

Plots of FTC tar in the cigarettes versus levels of total NNAL, 1-HOP, and total cotinine, expressed per mg creatinine per CPD for 149 subjects are illustrated in Fig. 2. There was no correlation between levels of FTC tar and any of the biomarkers.

## Discussion

Levels of total NNAL and 1-HOP in smokers' urine are significantly greater than those in nonsmokers (9). When people

stop smoking, total urinary NNAL gradually diminishes and ultimately is undetectable in urine (15). Levels of 1-HOP decrease in urine upon smoking cessation but do not disappear because people are exposed to pyrene from sources other than cigarette smoke (20). When people decrease their CPD, total urinary NNAL and 1-HOP also decrease, although to a lesser extent than CPD (14, 21). These results indicate that total urinary NNAL and 1-HOP are responsive to dose of the corresponding carcinogens from cigarettes, although the relationship is stronger for NNAL, which is tobacco specific, than for 1-HOP. Therefore, if the uptake of the lung carcinogens NNK and PAH were significantly decreased in smokers of light and ultralight cigarettes compared with smokers of regular cigarettes, we should have seen a decrease in total NNAL and 1-HOP in urine. Because this was not observed, we conclude that there was little or no difference in uptake of these lung carcinogens.

Our data suggest that there would be no decreased risk for lung cancer in smokers of ultralight and light cigarettes compared with regular cigarettes, because uptake of these established carcinogens is apparently the same in smokers of these cigarettes. Our results are consistent with those of a recent report in which tar yields were examined in relation to mortality from lung cancer in a large prospective study (7). The results of that study found no difference in lung cancer risk among smokers of filter cigarettes with 15 to 21 mg tar compared with those with 8 to 14 or <7 mg tar. Our

**Table 3. Total NNAL, 1-HOP, and total cotinine in the urine of smokers of regular, light, and ultralight cigarettes, per mg creatinine per CPD**

	<i>n</i>	Mean (95% CI)		
		Total NNAL (pmol/mg creatinine/CPD)	1-HOP (pmol/mg creatinine/CPD)	Total cotinine (pmol/mg creatinine/CPD)
Study 1				
Regular	23	0.093 (0.077-0.109)	0.085 (0.064-0.105)	1.28 (0.975-1.58)
Light	58	0.106 (0.096-0.117)	0.061 (0.050-0.072)	1.11 (0.974-1.24)
Ultralight	34	0.106 (0.083-0.130)	0.069 (0.054-0.085)	1.18 (0.942-1.42)
Study 2				
Regular	24	0.100 (0.082-0.118)	0.053 (0.037-0.069)	0.877 (0.736-1.02)
Light	22	0.109 (0.086-0.133)	0.068 (0.044-0.092)	1.20 (0.934-1.47)
Ultralight	14	0.093 (0.046-0.139)	0.050 (0.029-0.071)	0.858 (0.484-1.23)
Pooled				
Regular	47	0.097 (0.085-0.109)	0.068 (0.055-0.082)	1.07 (0.900-1.24)
Light	80	0.099 (0.089-0.110)	0.063 (0.053-0.073)	1.13 (1.01-1.25)
Ultralight	48	0.102 (0.081-0.123)	0.064 (0.051-0.077)	1.09 (0.883-1.29)

results are also consistent with the observation of lower than expected decreases in lung cancer mortality in the United States based on the market share of low yield cigarettes (6).

Previous studies examined nicotine uptake and other biomarkers such as exhaled CO and urinary mutagenicity in smokers of different types of cigarettes (8). These studies,

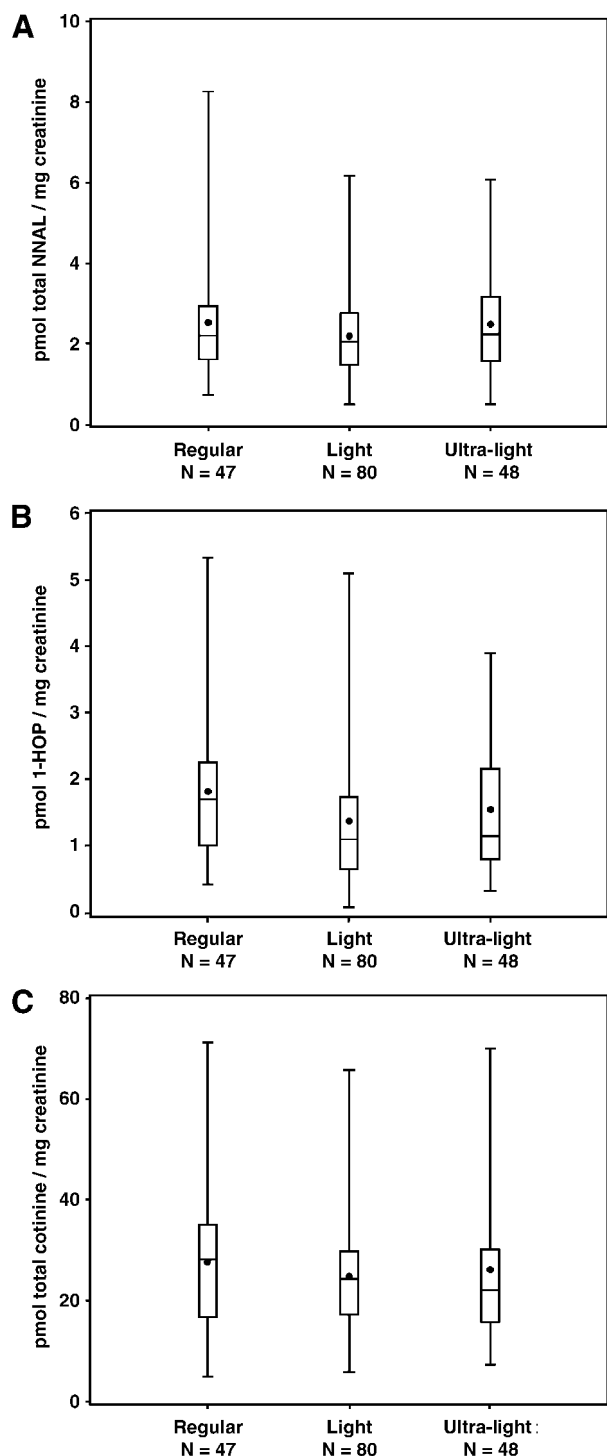
carried out in populations smoking self-selected brands of cigarettes, as in the present study, generally showed small differences in nicotine exposure and CO uptake between smokers of high and low yield cigarettes. The differences observed were not nearly as great as the differences in nominal yields of nicotine and CO, measured by the FTC method (8). Urinary mutagenicity did not correlate with tar yield (22). Our data, showing no differences in total cotinine, total NNAL, and 1-HOP among smokers of regular, light, and ultralight cigarettes, and no correlation of the biomarkers with FTC tar levels, are consistent with these reports. Compensation, a change in smoking behavior to adjust for different smoke yields and to regulate nicotine intake, is one likely explanation for these results (8, 23).

Our data are generally consistent with previous studies that measured levels of NNK and PAH in cigarette smoke using machine methods. Fischer et al. showed that there was no correlation between levels of NNK in mainstream smoke and tar yield of German cigarettes, using the FTC method, although Chepiga et al. did observe a correlation in U.S. cigarettes (5, 24). Fischer et al. proposed that the total volume drawn through a cigarette was the main factor influencing NNK delivery (25). As total volume increased, so did levels of NNK in mainstream smoke. Djordjevic et al. showed that smokers of low- and medium-yield cigarettes took larger puffs at shorter intervals and drew larger total smoke volumes than specified in the FTC protocol (26). This resulted in ~2-fold higher levels of NNK and benzo(a)pyrene, a prototypic PAH carcinogen, in mainstream smoke than measured by the FTC method.

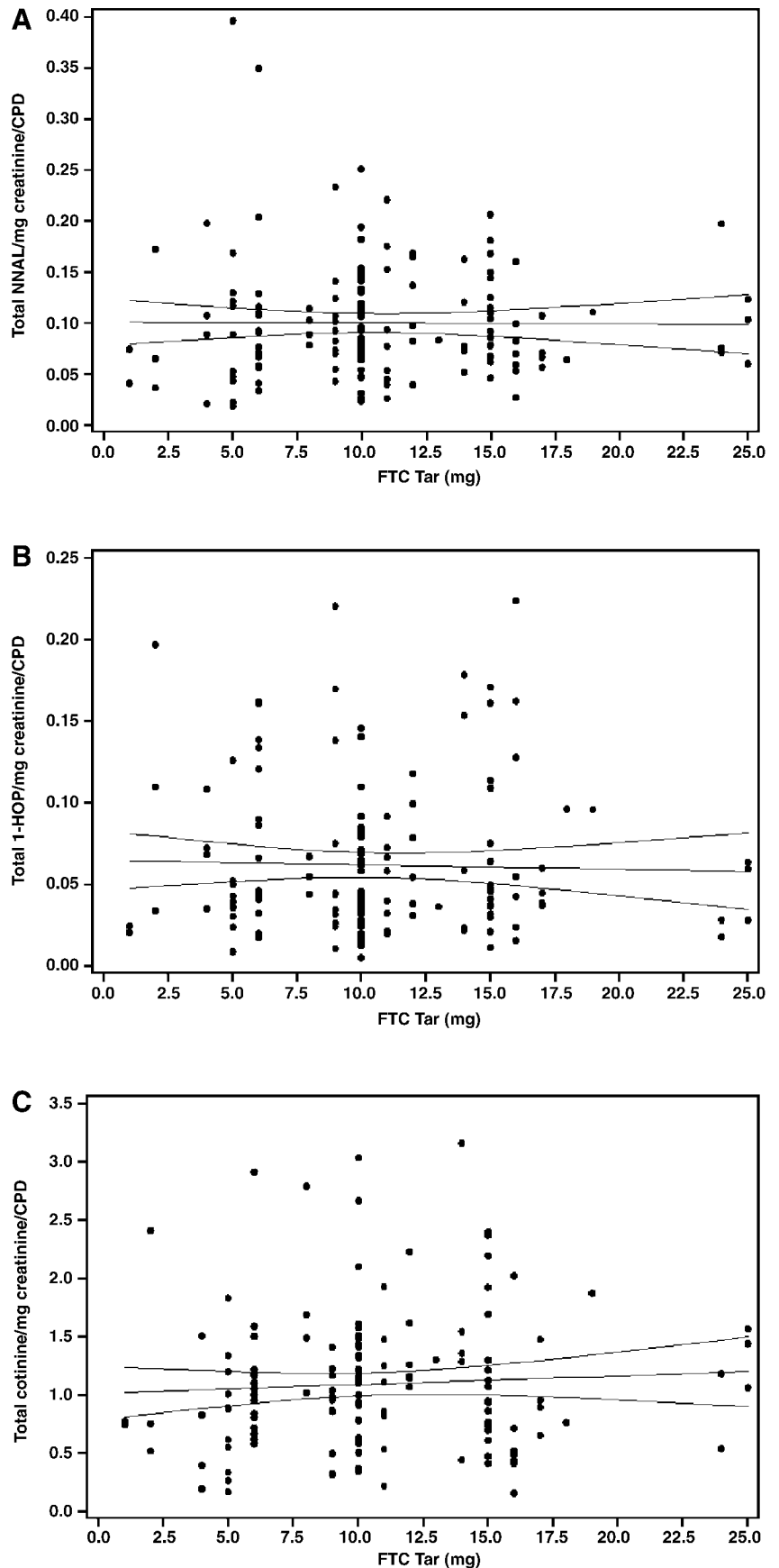
The plots of FTC tar levels versus urinary biomarkers shown in Fig. 2 are reminiscent of the data presented by Jarvis et al., in which FTC nicotine yields were plotted against salivary cotinine levels (27). In their study, there was a wide variation in cotinine concentrations among subjects at any given FTC nicotine yield. In our study, there was a wide variation in urinary biomarkers at any given FTC tar yield. The results are also consistent with previous observations of correlations between urinary cotinine and total NNAL (9).

A possible limitation of our study is that the group of smokers investigated here is not representative of a general population of smokers. It is possible that these smokers may be more heavily dependent and prone to compensatory smoking behavior. Nevertheless, our results are consistent with other studies that have included a more general population of smokers (7, 8). A second limitation is that we do not know how long our subjects have been smoking their brand of cigarette and thus cannot fully evaluate the potential role of compensation in our results. A third limitation involves the biomarkers themselves. Both total NNAL and 1-HOP are metabolites of cigarette smoke carcinogens and their levels in urine will be affected by interindividual differences in metabolism. Furthermore, urinary levels of 1-HOP are confounded by dietary factors and do not correlate with CPD; these problems do not exist for total NNAL, which is a metabolite of the tobacco-specific carcinogen NNK.

The results of this study show the importance of measuring carcinogen uptake in people who smoke new brands of cigarettes purported to be less harmful. Many such products, referred to as "potential reduced exposure products" by the Institute for Medicine, are now appearing on the market (28). Evaluation of these products by the traditional FTC machine smoking method is essentially useless with respect to carcinogen uptake. If the biomarkers used here had been available when light and ultralight cigarettes had been introduced, the ensuing confusion, in which smokers were misled by FTC machine values for tar and nicotine into thinking that these products were less harmful, perhaps could have been avoided.



**Figure 1.** Levels of (A) total NNAL, (B) 1-HOP, and (C) total cotinine, all per mg creatinine, in the urine of smokers of regular, light, and ultralight cigarettes ( $n = 175$ ). •, mean; line in box, median; top and bottom bars, 25th to 75th percentile, respectively; top bar, maximum observation; bottom bar, minimum observation.



**Figure 2.** Relationship between tar, measured by the FTC method, and levels of (A) total NNAL, (B) 1-HOP, and (C) total cotinine, all expressed per mg creatinine per CPD, in smokers' urine ( $n = 149$ ). Center line, predicted value of the biomarker obtained by modeling the biomarker against the tar value. Area between the top and bottom lines is the 95% CI.

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