The Association of a Tobacco-Specific Biomarker and Cigarette Consumption and Its Dependence on Host Characteristics

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Abstract

The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a potent carcinogen, which can be characterized by urinary concentrations of the metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-butanol (NNAL) and its glucuronide. Using baseline data in current smokers from four clinical trials, we examine the associations of urinary cotinine with CPD and of total NNAL with cotinine and the modification of these associations by several host factors. There was a linear relationship between ln(cotinine) and ln(CPD) within categories of the Fagerstrom Test of Nicotine Dependence and of age. The increasing trend was significantly smaller for subjects with high and very high nicotine addiction and for older subjects and larger in females than males. The regression of ln(total NNAL/cotinine) on ln(cotinine) declined linearly, suggesting reduced NNK uptake per unit cotinine with increasing cotinine. The decline in trend was greater in subjects with increased CPD, with greater nicotine addiction, and at older ages and was smaller in females, although gender differences were small. Variations in the ratio with host characteristics were generally similar to a recent epidemiologic analysis of effect modification of the association between lung cancer and cigarette smoking. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1852–7)

Introduction

The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a potent carcinogen in rodents and, together with the related compound *N*′-nitrosonornicotine, is considered to be a potent human carcinogen (1-3). Uptake of NNK can be characterized by measuring urinary concentrations of the metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-butanol (NNAL) and its glucuronide (termed ''total NNAL'').

An analysis in current smokers found an increasing, but curvilinear, relationship for total NNAL and cigarettes per day (CPD), with the rate of increase in total NNAL declining with increasing CPD (4). This relationship is suggestive of the attenuation of odds ratios (OR) with increasing CPD observed in epidemiologic studies of lung and bladder cancers (5, 6) and later quantified for several smoking-related cancers (7-9). If attenuation of ORs by CPD derives from biological effects, then we would expect comparable patterns for biomarkers of exposure and effect. It is well known that age, frequency, and depth of inhalation and sex can modify ORs by cigarette exposure (10). Thus, we would anticipate that patterns for biomarkers may also vary by host factors, which may provide insights into mechanisms of action.

In this article, we use data from Joseph et al. (4) to evaluate the relationships between urinary cotinine and CPD and between total NNAL and cotinine and modification of the relationships by various host factors. This represents the first detailed examination of the regression of total NNAL on cotinine and factors influencing the relationship. Joseph et al. also analyzed 1-hydroxypyrene, which is a metabolite of pyrene, a noncarcinogenic polycyclic aromatic hydrocarbon. However, 1-hydroxypyrene is not tobacco specific, and we do not consider it further.

Materials and Methods

Data. We combine baseline data for current smokers from four clinical trials (4). (*a*) Tobacco Reduction Intervention Program: the study was a clinical trial of cigarette smokers ages 18 to 70 years, who wanted to reduce, but not quit, smoking. All subjects smoked 15 to 45 CPD for at least 1 year prior, were apparently in good health, had no contraindications to nicotine replacement treatments, had no history of schizophrenia or unstable depressive disorder, did not use other tobacco products, and were not pregnant or nursing. CPD was calculated from a daily diary. Biomarker data were determined at two points, 1 week apart, and averaged. The study included 69 males and 82 females. (*b*) Reduction of

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Smoking in Cardiac Patients Study: the study was a clinical trial of cigarette smokers ages 18 to 80 years with at least one diagnosis of heart disease who wanted to reduce, but not quit, smoking. All subjects smoked ≥15 CPD, did not use other tobacco products, were diagnosed with at least one cardiac disease (coronary artery disease, arrhythmia, congestive heart failure, or peripheral vascular disease) or had a history of cerebrovascular disease, had no unstable angina in the prior 2 weeks, had no unstable mental health or substance use diagnoses, and had no contraindications to nicotine replacement therapy. CPD was based on recall for the prior week. Biomarkers were measured once at baseline. The study included 135 males and 17 females. (*c*) Adult Cross-Sectional Study: the study recruited subjects from the Minneapolis-Saint Paul metropolitan area under the Tobacco Reduction Intervention Program eligibility criteria. The study included 86 subjects (34 males, 46 females, and 6 with unknown gender). (*d*) Low Level Smoking Study: the study recruited subjects from the Minneapolis Veterans Affairs Medical Center under the Reduction of Smoking in Cardiac Patients eligibility criteria, with the additional restriction that smokers consumed <15 CPD for 1 or more years. The study included 11 subjects (8 males and 3 with unknown gender).

The pooled data set includes 400 subjects. Nine subjects have unknown gender, 48 are missing total NNAL or cotinine measurements, and 3 are missing CPD, leaving 340 subjects. We omit two smokers with extreme cotinine values (0.17 nmol/mg creatinine, one third the next higher value; and 159.4 nmol/mg creatinine, over two times the next lower value) and one smoker who consumed 100 CPD (40 CPD more than the next lower value). The final data set includes 337 subjects and currently represents the largest data set of smokers with total NNAL measurements. Means (SDs) for CPD for males and females are the following: Tobacco Reduction Intervention Program, 24.3 (6.2) and 22.8 (5.2); Reduction of Smoking in Cardiac Patients, 27.0 (10.0) and 28.6 (11.0); Adult Cross-sectional Study, 11.3 (10.0) and 8.2 (6.2); and Low Level Smoking Study, 7.1 (3.6).

Statistical Analysis. We apply standard linear regression methods with either cotinine or total NNAL as dependent variable. Within categories of sex and CPD, cotinine and total NNAL are consistent with log-normal distributions, and we therefore apply logarithmic transformations. For response Y and continuous variable X, we fit the linear regression

$$\ln(Y) = \beta_0 + \beta_1 \ln(X) + \beta_2 Z \qquad (A)$$

where β_1 is the slope parameter (i.e., the exponent in a power relationship between Y and X) and Z is a vector of adjustment variables. We evaluate departures from linearity by including $[\ln(X)]^2$ and testing the null hypothesis that its coefficient equals zero.

Depending on the analysis, adjustment factors (Z) include age (four levels: <40, 40-49, 50-59, ≥60 years), the Fagerstrom Test of Nicotine Dependence (FTND) score (11, 12) grouped into five levels of addiction (0-2, very low; 3-4, low; 5, medium; 6-7, high; 8-10, very high), and sex. We calculate a likelihood ratio test of homogeneity of the effect of ln(X) over an adjustment variable by adding to the model the product of ln(X) and the indicator variables for the adjustment variable.

We first regress ln(cotinine) on ln(CPD) and evaluate the shape of the regression and its modification by age, FTND, and sex. We then regress ln(total NNAL/cotinine) on ln(cotinine). We use the ratio because it approximates a measure of smoking potency (i.e., the uptake of NNK per unit cotinine). In addition, a horizontal line represents a proportional relationship between total NNAL and cotinine so that deviations from proportionality are easily identified. Because the half-life of total NNAL is 3 to 4 days (13) and of cotinine is 15 to 19 h (14, 15), the ratio is temporally appropriate for current smokers.

There is homogeneity across studies for the associations between cotinine and CPD ($P = 0.75$ for males and $P = 0.40$ for females) and between total NNAL and cotinine ($P = 0.58$ for males and $P = 0.33$ for females after adjusting for CPD). Therefore, we do not further consider study effects.

Results

Females smoke fewer CPD than males, with means (SDs) of 18.1 (10.2) and 23.3 (10.9) CPD, respectively. Means for cotinine and total NNAL increase with CPD, with variability generally higher at lower CPD (Table 1). Adjusting for CPD, concentrations do not differ by sex for cotinine ($P = 0.24$) or total NNAL ($P = 0.82$).

Cotinine and CPD Association. Cotinine increases with CPD but at a diminishing rate at higher CPD (Fig. 1, *top left*). Compared with males, cotinine levels in females are similar at lower CPD but higher at higher CPD. In females, cotinine increases across CPD, whereas in males cotinine increases to 34.0 CPD [maximum for fitted line at $\exp(\beta_1/-2\beta_2)$] and then declines.

Figure 1 also shows the regression of ln(cotinine) on ln(CPD) within FTND categories. Cotinine increases

Table 1. Statistics on urinary cotinine (nmol/mg creatinine) and total NNAL (pmol/mg creatinine) for categories of CPD, including number of subjects, arithmetic mean, geometric mean, and geometric SD

	CPD	*n**	Cotinine			Total NNAL		
			AM	GM	GSD	AM	GM	GSD
Males	Overall	216	21.4	17.0	2.23	2.13	1.75	1.96
	10	28	9.6	6.8	2.66	0.99	0.74	2.30
	11-20	80	21.5	17.7	2.13	2.07	1.79	1.73
	21-30	71	25.5	22.5	1.70	2.34	2.04	1.71
	31+	37	22.0	18.2	2.02	2.72	2.35	1.73
Females	Overall	121	23.2	15.8	2.85	2.09	1.48	2.62
	10	32	7.8	5.0	2.82	0.77	0.52	2.55
	11-20	40	25.0	19.9	2.18	2.15	1.76	2.02
	21-30	39	30.6	26.7	1.77	2.60	2.36	1.62
	31+	10	36.6	32.7	1.78	4.11	3.50	1.94

NOTE: Data from four clinical trials of smokers (see text).
Abbreviations: AM, arithmetic mean; GM, geometric mean; GSD, geometric SD.
*Omits two males with extreme cotinine measurement of 0.17 and 159.4 nmol/mg creatinine, one subject who smoked 100 CPD, and subjects with missing data.

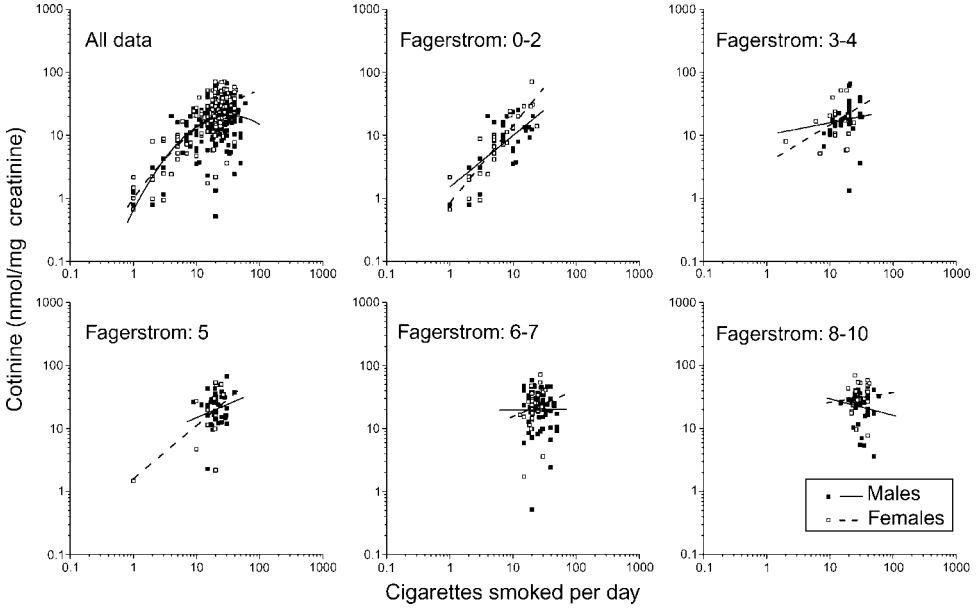

Figure 1. Scatter plot of urinary cotinine concentrations in nmol/mg creatinine by CPD and fitted model A for females and males, overall and within scores of the FTND, grouped into levels of addiction (0-2, very low; 3-4, low; 5, medium; 6-7, high; 8-10, very high).

with CPD in subjects with very low, low, and medium addiction scores but is unrelated to CPD in subjects with high and very high addiction scores. Homogeneity of slopes by FTND category is rejected ($P < 0.001$). The female differential is significant ($P = 0.01$) but similar across FTND category ($P = 0.35$). The FTND index measures nicotine dependency and is the sum of categorical scores for CPD and five other variables. Thus, the inclusion of CPD in the FTND score may have influenced these results. Adjusting for sex and each component, regression patterns of ln(cotinine) on ln(CPD) within each component are consistent with overall FTND results (i.e., increased trends in lower addictive categories and diminished trends in higher addictive categories). Homogeneity of slopes across categories, however, is not always rejected. Tests of homogeneity for FTND components include time to first cigarette on awaking ($P < 0.01$), difficulty in refraining from smoking ($P = 0.14$), difficulty giving up first morning cigarette ($P = 0.02$), increased smoking during the morning ($P = 0.31$), and smoke when ill ($P < 0.01$).

The regression of ln(cotinine) on ln(CPD) varies by age group ($P = 0.01$) and sex ($P = 0.03$), with a greater slope at ages under 50 and for females (Fig. 2). In the oldest age group, three subjects who consumed one CPD are highly influential. Omitting these subjects, slopes decline monotonically by age group [$P < 0.001$, estimates of β_1 for males are 0.93, 0.64, 0.44, and 0.28 (dot line), respectively]. The female differential is homogeneous across age groups ($P = 0.90$).

The regressions remain significantly modified by sex ($P = 0.02$), age ($P = 0.05$), and FTND ($P < 0.01$) when these factors are jointly analyzed.

Total NNAL and Cotinine Association. The ratio of total NNAL to cotinine decreases with increasing cotinine, indicating a decrease in NNK uptake per unit cotinine (Fig. 3, *top left*). Linearity on log-log scales is not rejected ($P = 0.12$), although curvilinearity is suggested in males ($P = 0.05$; dot line).

Trends decline within each CPD category (Fig. 3) and are consistent with linearity ($P = 0.72$). Homogeneity of slopes is rejected ($P = 0.01$), with β_1 estimates for males of -0.39, -0.63, -0.75, and -0.69, respectively. The female differential effect is significant ($P = 0.01$). The power parameter is increased for females by 0.20 with 95% confidence interval of 0.03 to 0.44.

The regression of ln(total NNAL/cotinine) on ln(cotinine) across FTND scores varies significantly ($P < 0.01$), due primarily to the very low addiction group, and

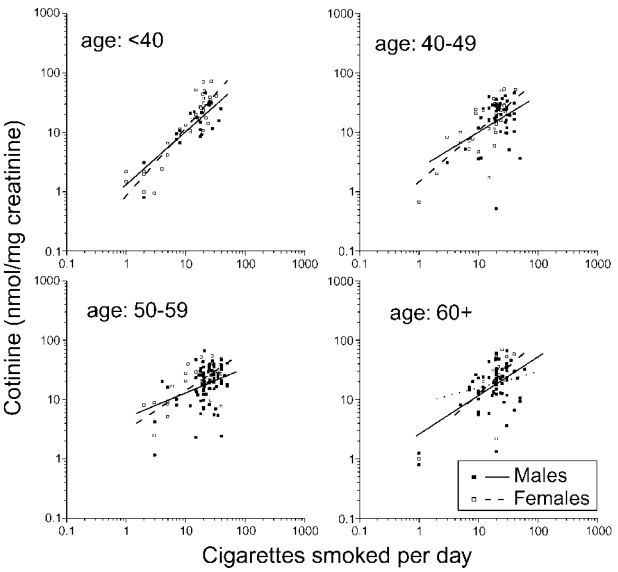

Figure 2. Scatter plot of urinary cotinine concentrations in nmol/mg creatinine by CPD and fitted model A for females and males within categories of age. Dot line is fitted model A for males with one cigarette per day smokers omitted.

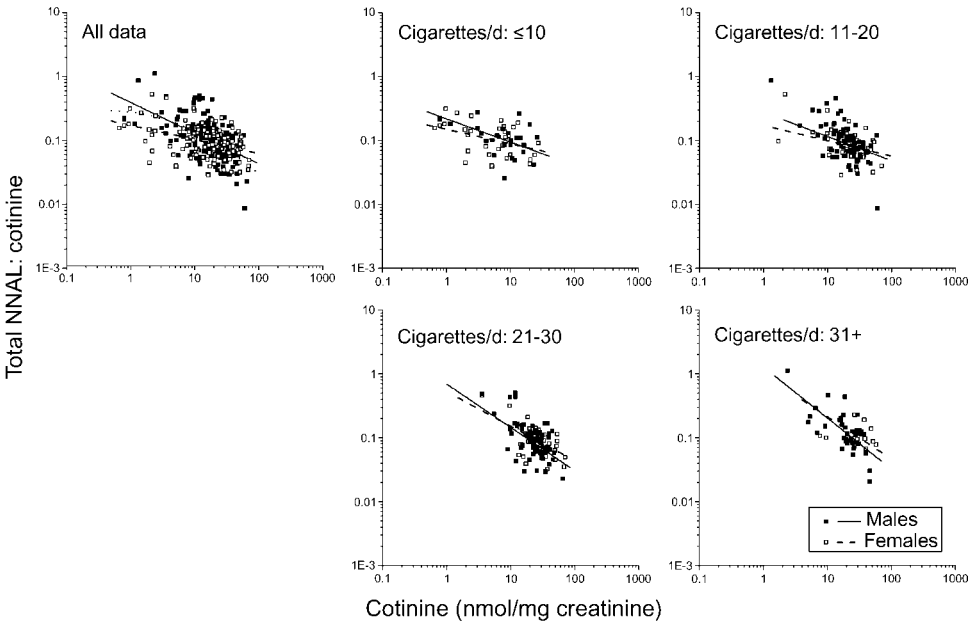

Figure 3. Scatter plot of the ratio of total NNAL (in pmol/mg creatinine) to cotinine (in pmol/mg creatinine) by cotinine and fitted model A for females and males, overall and within categories of smoking intensity. Dot line is fitted model A with linear and quadratic terms for males.

differs by sex (P = 0.01; Fig. 4). A post hoc test of homogeneity of slopes for the very low addiction category compared with higher addiction categories is rejected (P < 0.01). Results are consistent within each component variable of the FTND. There is a greater decline in the higher ''addictive'' categories, including CPD (P = 0.01), time to first cigarette on awaking (P = 0.07), difficulty in refraining from smoking (P = 0.55), difficulty giving up first morning cigarette (P = 0.10), increased frequency during the morning (P = 0.36), and smoke when ill (P < 0.01).

Ln(total NNAL/cotinine) declines with ln(cotinine) within age groups, with slopes homogeneous (P = 0.10; Fig. 5). Patterns differ by sex (P < 0.01). Estimates of β_1 for males, −0.46, −0.38, −0.43, and −0.62, respectively, suggest an increased rate of decline in the oldest age group. A post hoc test of homogeneity of slopes for subjects over age 60 is rejected (P = 0.02).

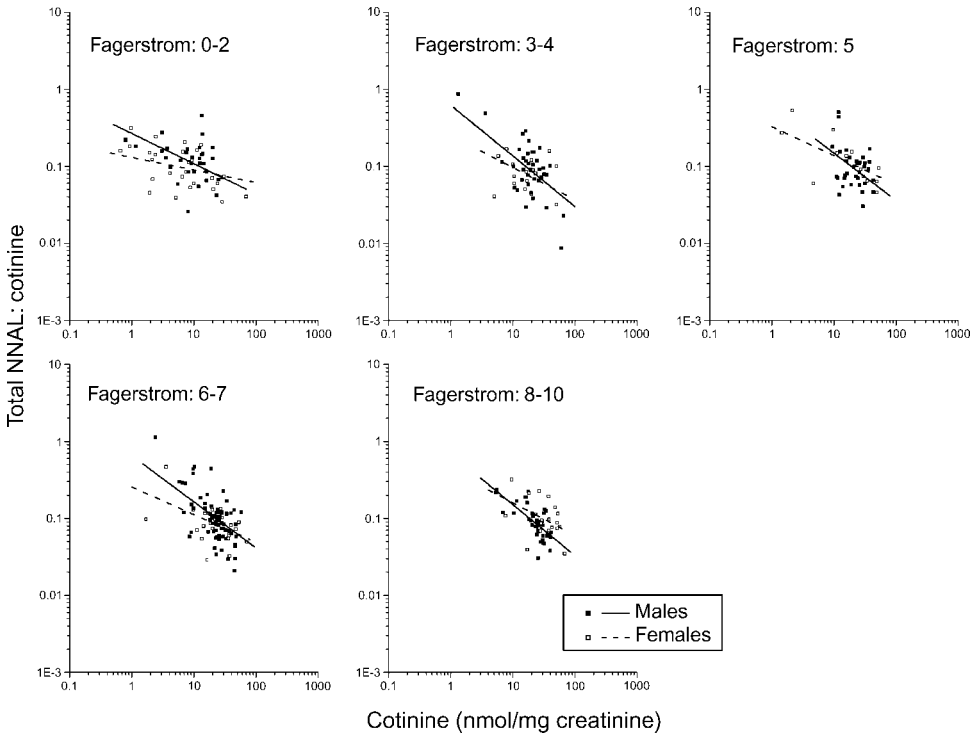

Figure 4. Scatter plot of the ratio of total NNAL (in pmol/mg creatinine) to cotinine (in pmol/mg creatinine) by cotinine and fitted model A for females and males within score of the FTND, grouped into levels of addiction (0-2, very low; 3-4, low; 5, medium; 6-7, high; 8-10, very high).

Discussion

Previous reports suggest a linear relationship between cotinine and CPD under 20 to 25 CPD (4, 16-27). At higher CPD, the relationship has been observed to increase without diminution (19, 23, 25, 26), increase but at a diminished rate (17, 19-21, 24, 27), or increase to a plateau and possibly even decline (4, 16, 19, 22). In our data, urinary cotinine concentration diminished at higher CPD. Using log-log scales, the relationship was linear but varied within categories of FTND score and age. Trends were greater in females, and were significantly reduced in subjects with high and very high addiction levels, and in older subjects. Confounding by these or other host factors may help explain the diverse relationships observed between CPD and cotinine in the various studies.

Our study is the first detailed evaluation of the ratio of NNAL to cotinine and its relationship with cotinine. The ratio declined with increasing cotinine, with the rate of decline greater in subjects with greater cigarette consumption, with increased nicotine addiction, at older ages, and in males. One possible explanation for the general pattern is that enzymes involved in other pathways of NNK metabolism are induced at higher levels of smoking intensity, thus decreasing the flux of NNK metabolites through the NNAL pathway. We have previously observed decreased levels of total NNAL in the urine of smokers who were exposed to indole-3-carbinol presumably due to induction of hepatic cytochrome *P*450 1A2 (28, 29). Explanations for the variations in the regression of ln(total NNAL/cotinine) on ln(cotinine) by the various host factors need further development.

We standardized total NNAL by cotinine, rather than CPD, because cotinine better reflects ''internal'' tobacco exposure (23). This minimizes bias due to misclassification of smoking rate and minimizes the possible effect of a decline in ''nicotine boost'' (i.e., an increase in blood plasma nicotine per cigarette) with increasing CPD (30). Our results therefore do not likely reflect misclassification of tobacco exposure by CPD or nicotine satiation with increasing CPD but likely reflect host factor–dependent biological effects linked to NNK metabolism.

The effects of host factors on the regression of ln(total NNAL/cotinine) on ln(cotinine) (Figs. 3-5) are broadly similar to analyses of cigarette smoking risks and effect modifications in two lung cancer case-control studies (31). The analysis was based on a linear relationship for the excess OR with pack-years and included a function for the modification of the excess OR/pack-year by CPD. Results indicated that for a fixed total cigarette consumption there was a decreasing exposure rate effect above 15 CPD (i.e., for equal total exposure risk decreased with CPD). In addition, CPD effects were greater for older subjects, which was similar to our finding that the declining trend of ln(total NNAL/cotinine) on ln(cotinine) was greatest at ages >60 years. In the epidemiologic analysis, CPD had less effect on risk in subjects with putatively ''lower risk'' smoking behavior (i.e., subjects who inhaled less frequently or into the mouth and throat compared with subjects who inhaled frequently or moderately or deeply into the chest). Although comparable inhalation information was not available, we found lower rates of decline in the regression trends with low CPD and with low FTND scores. Finally, in the lung cancer analysis, although not statistically significant, CPD had a smaller effect on risk in females compared with males, which was comparable with our results of smaller declines in regression trends in females.

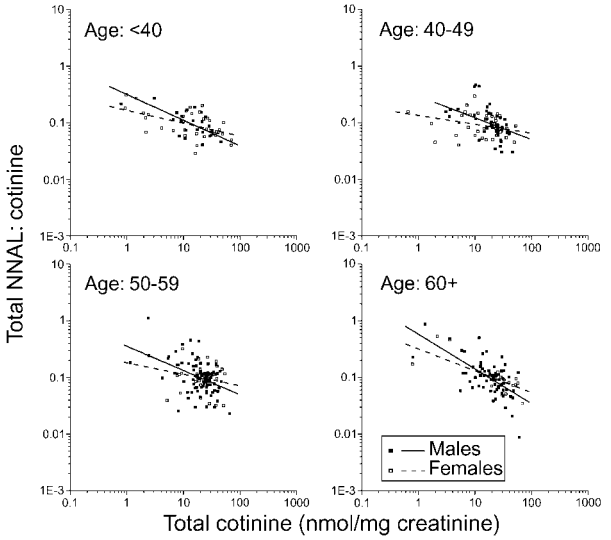

Figure 5. Scatter plot of the ratio of total NNAL (in pmol/mg creatinine) to cotinine (in pmol/mg creatinine) by cotinine and fitted model A for females and males within categories of age.

In summary, we find a linear relationship between ln(cotinine) and ln(intensity) within FTND addiction score and within age group. The increasing trend was significantly smaller for subjects with high nicotine dependence, for older subjects, and for males compared with females. The regression of ln(total NNAL/cotinine) on ln(cotinine) showed a declining trend, suggesting reduced uptake of NNK per unit cotinine with increasing cotinine. The declining trend was greater with increased CPD, with high nicotine dependence and at older ages, and in males. Variations in the ratio of total NNAL to cotinine by host characteristics were generally consistent with an epidemiologic analysis of effect modification of lung cancer and cigarette smoking (31).

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