

Urine cotinine underestimates exposure to the tobacco-derived lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in passive compared to active smokers

Neal Benowitz, MD^{1,2}, Maciej Lukasz Goniewicz, PhD^{1,2,3}, Mark D. Eisner MD, MPH⁴, Eduardo Lazcano-Ponce, D.Sc.⁵, Wioleta Zielinska-Danch, PhD³, Bartosz Koszowski, M.Sc.³, Andrzej Sobczak, PhD³, Christopher Havel¹, Peyton Jacob III, PhD¹

¹Center for Tobacco Control Research and Education, University of California, San Francisco, USA, ²Division of Clinical Pharmacology and Experimental Therapeutics, Departments of Medicine and Bioengineering and Therapeutic Sciences, University of California, San Francisco, USA, ³Department of General and Analytical Chemistry, Medical University of Silesia, Sosnowiec, Poland, ⁴Division of Occupational and Environmental Medicine & Division of Pulmonary and Critical Care Medicine, University of California San Francisco, USA, ⁵Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública de México, México, D.F., Mexico

Corresponding Author:

Neal L. Benowitz, MD
Chief, Division of Clinical Pharmacology and
Experimental Therapeutics
University of California, San Francisco, Box 1220
San Francisco, California 94143-1220
Tel. (415) 206-8324
Fax (415) 206-4956
email: NBenowitz@MedSFGH.ucsf.edu

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
Copyright © 2010 American Association for Cancer Research

Key words: cotinine, NNAL, smokers, tobacco smoke, exposure

Abstract

Objectives: Cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are widely used biomarkers for tobacco-derived nicotine and the lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), respectively. The discrepancy between cotinine levels in relation to disease risk comparing active vs. passive smoking suggests a non-linear tobacco smoke dose-response and/or that cotinine is not providing an accurate measure of exposure to tobacco smoke toxic constituents from secondhand smoke.

Methods: Cotinine and NNAL were measured in urine of 373 active smokers and 228 passive smokers.

Results: Average cotinine levels were 1,155 (IQR 703-2,715) for active smokers and 1.82 (0.45-7.33) ng/mg creatinine for passive smokers. Average NNAL levels were 183 (103-393) and 5.19 (2.04-11.6) pg/mg creatinine, respectively. NNAL/cotinine ratio in urine was significantly higher for passive smokers when compared to active smokers (2.85×10^3 vs. 0.16×10^3 , $p < 0.0001$).

Conclusions: Passive smoking is associated with a much higher ratio of NNAL/cotinine in the urine compared to active smoking.

Impact: Cotinine measurement leads to an underestimation of exposure to the carcinogen NNK from second-hand smoke when compared with active smoking.

Introduction

Cotinine, the major proximate metabolite of nicotine, is widely used as a biomarker of tobacco exposure.(1, 2) Measurement of cotinine in blood, saliva or urine, has been used to support epidemiologic findings of causal relationships between second-hand smoke (SHS) exposure and lung cancer, cardiovascular disease, and aggravation of chronic obstructive pulmonary disease in adults, and asthma in children.(3-6)

If one compares concentrations of cotinine in people exposed to SHS compared to active smoking, the relative exposure with SHS exposure is typically 1% or less, comparing blood or urine cotinine levels in SHS vs. active smokers.(1) In contrast, the relative risk of lung cancer and cardiovascular disease with SHS exposure compared to active smoking is much higher than the relative cotinine levels. For example the odds ratio for cigarette smoking and lung cancer is 1.25 for secondhand smoke exposure and 10 for active smoking, translating into a relative attributable risk ratio of 36.(7) The odds ratio for cardiovascular disease is about 1.3 with SHS and 2 with active smoking, translating into a relative attributable risk ratio of 3.3.(8) The discrepancy between relative cotinine levels and disease risk with SHS vs. active smoking suggests that there is a non-linear tobacco smoke dose-response and/or that cotinine is not providing an accurate measure of exposure to tobacco smoke toxic constituents.

Among the most important tobacco smoke toxins are tobacco-specific nitrosamines (TSNAs), which are derived from nicotine and other tobacco alkaloids mostly during tobacco curing.(9) These compounds are known animal and human carcinogens. The most potent carcinogenic TSNA is 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNK is metabolized in the human body to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which is further conjugated to form NNAL N- and O-glucuronides (NNAL-Gluc). The presence of NNAL in urine is highly specific for tobacco exposure and provides a biochemical link between both active and passive smoking and lung cancer.(3)

There are several reasons to suspect that cotinine levels underestimate exposure to NNK. As SHS ages, concentrations of nicotine decline faster than many other gaseous and particulate

components of smoke due to absorption of nicotine on surfaces such as walls and carpets.(10) In addition NNK levels increase as SHS ages, presumably related to the reaction of nicotine with nitric oxide in SHS.(11, 12) Thus exposure to SHS over a period of time, in between emissions from individual cigarettes, would be expected to result in lower relative intake of nicotine vs. NNK as compared to that obtained by the active smoker from mainstream smoke. Additionally, the half-life of NNAL is much longer (10 days) than that of cotinine (16 hours).(2, 13) As a result with intermittent exposure to SHS cotinine levels will decline between exposures to a much greater extent than NNAL, which would further increase the ratio of NNAL/cotinine in passive vs. active smokers.

The aim of our study was to examine the hypothesis that cotinine does not provide an accurate assessment of exposure to the tobacco smoke carcinogen NNK in passive smokers. We compared the relative concentrations of NNAL and cotinine in active vs. passive smokers.

Materials and Methods

Study design and Subjects

A descriptive study was conducted in smoking and nonsmoking subjects from the USA, Poland and Mexico, each of who provided a urine sample for measurement of concentration of NNAL and cotinine. The subjects included 373 smokers and 228 nonsmokers with evidence of exposure to SHS. Detailed characteristics of study groups are presented in Table 1.

Adult daily smokers were recruited in three different studies (Study A-C). The groups were selected to include both regular daily smokers and occasional smokers. Study A was a study of tobacco smoke biomarkers comparing African American and white smokers in San Francisco, USA (N = 128). Study B assessed effect of smoking topography on tobacco biomarkers among daily smokers recruited in Silesia region, Poland (N=187, Koszowski and Sobczak). Study C compared urine biomarkers in daily compared to occasional smokers in Pittsburgh, USA (N = 58, Shiffman).

Nonsmokers exposed to SHS had participated in two previously published (Study D and F) and one not published (Study E) studies in which urine was collected for the assessment of SHS exposure. Subjects were selected to range from very light to heavy SHS exposure. Study D was a U.S. cohort study of non-smoking adults with chronic obstructive lung disease (COPD), who collected samples in their homes and mailed samples to the investigators (N = 72).(14) Among recruited subjects there were no current smokers, although almost half of them had history of smoking (N=35) (1,2). Only subjects who had biochemical evidence of SHS exposure (cotinine and NNAL levels above the limit of quantitation) were included. Study group E was a Polish cohort of non-smoking adults with urine samples to assess second-hand exposure to tobacco smoke in home and work environments. Subjects provide morning spot samples during screening medical tests (N=108, Zielinska-Danch). Study F included volunteers from central Mexico who provided a urine sample after being in a discotheque in which smoking was ongoing for at least one hour (N = 81).(15)

Analytical Chemistry

Cotinine (unconjugated) was analyzed by liquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry (LC-MS/MS) by a method similar to the one described by Bernert et al.(16) Total NNAL (after hydrolysis of NNAL glucuronide) was analyzed by LC-MS/MS as described by Jacob et al.(17) The limits of quantification were 0.05 ng/mL and 0.25 pg/mL for cotinine and NNAL, respectively.

Data analysis

Non-parametric Kruskal-Wallis analysis of variance was used to compare biomarker levels and their ratios among study groups. Pearson correlations of log transformed urine cotinine and NNAL concentrations were performed. All analyses were performed using STATISTICA data analysis software system v. 8 (StatSoft, Inc., USA).

Results

Geometric mean urine cotinine and NNAL concentrations and the ratio of NNAL/cotinine for each of the study groups are shown in Table 1, and comparisons between active and passive smokers in Fig. 1. The distribution of the NNAL/cotinine ratio among all subjects is shown in Fig. 2. The average ratio of NNAL/cotinine was almost 18 times higher in passive smokers (2.85, IQR 1.32 – 6.14 X 10³) compared to active smokers (0.16, IQR 0.09 – 0.26 x 10³)(*p*<0.0001), and there was relatively little overlap in the ratio in the active vs. passive smoking groups. The two subjects with the highest NNAL/cotinine ratios (361 and 107 x 10³) were from passive smoker groups D and E, respectively; and their high ratios were due to extraordinarily high levels of urine NNAL.

Among active smokers urine cotinine/creatinine ratios were significantly higher for group A compared to B and C (*p* < 0.05) and urine NNAL/creatinine significantly higher in group C compared to A and B (*p* < 0.05). Among smokers the urine NNAL/cotinine ratio was significantly higher in groups B and C compared to group A (*p* < 0.05). Within group A, there was no significant difference in the NNAL/cotinine ratio comparing African American and white smokers. Among passive smokers group F had significantly higher urine cotinine and NNAL levels and lower NNAL/cotinine ratios compared to groups D and E (all *p* < 0.05).

Among active smokers log transformed concentrations of cotinine and NNAL urine were highly correlated: group A, *r* = 0.79; group B, *r* = 0.80; group C, *r* = 0.79; all smokers, *r* = 0.76 (all *p* < 0.05). Among passive smokers these biomarkers were also highly correlated: group D, *r* = 0.71; group E, *r* = 0.74; group F, *r* = 0.67; all passive smokers, *r* = 0.79 (all *p* < 0.05)

Discussion

The main and novel finding of our study is that the ratio of NNAL to cotinine is much higher in passive compared to active cigarette smokers. This finding supports the idea that passive smoking leads to relatively higher exposure to the carcinogen NNK in relation to nicotine compared to active smoking. Thus the use of urine cotinine to estimate exposure to the tobacco smoke carcinogen NNK in passive smokers with the assumption of a similar relationship between nicotine and NNK as that seen in active smokers, leads to an underestimation of exposure and

potential cancer risk. Our data on absolute concentrations of NNAL and cotinine in urine among active and passive smokers are similar to those reported by other researchers,(1, 18) however to the best of our knowledge no one has published a formal comparison of ratios in active and passive smokers.

Our study focuses on NNAL, which is a highly specific biomarker of tobacco smoke exposure. We do not know if cotinine measurement also underestimates exposure to other tobacco smoke toxins based on biomarker measures in humans because the other toxins are not specific to tobacco exposure. However, studies of the concentrations of nicotine and other tobacco smoke constituents in the air immediately after smoking and then followed over time indicate that nicotine levels decline much faster than do most other smoke constituents(10). Thus it is likely that measurement of cotinine, which reflects intake of nicotine, also underestimates exposure to other tobacco smoke toxins. Epidemiologic data comparing risks of lung cancer and cardiovascular disease in SHS exposed vs active smokers show much higher risk for SHS compared to active smokers based on relative cotinine levels.(7, 8) Thus cotinine underestimates risks of tobacco-related diseases in passive smokers compared to active smokers.

On average for U.S. cigarettes the mainstream / sidestream smoke ratios for nicotine and NNK are 2.31 and 0.40, respectively.(19) Given these ratios and based on exposure to fresh sidestream smoke, one would expect that passive smokers would be exposed to relatively more nicotine than NNK compared to active smokers, which is opposite to what we observed. As described above, as SHS ages nicotine levels decline while NNK levels increase, which most likely explains our observations.

Our study has potential limitations with respect to generalizability. Our subjects were not representative of the general U.S. population. Our active smokers came from both the U.S. and Poland. Our secondhand smoke exposed subjects were also multinational, with different levels of SHS exposure. These included heavily exposed (Mexican discotheques), moderately exposed (Polish workers) and lightly exposed (COPD subjects in the US). The duration of exposure to SHS was also different in these three groups. The Mexico subjects were exposed for a short period of time, the Polish and COPD subjects were presumably exposed over a longer period of

time. Furthermore, it is unknown if this is an effect of COPD on the absorption of nicotine or NNK.

Comparison of the urine NNAL/cotinine ratio within the three groups of smokers indicated that Polish regular smokers had a significantly higher ratio than US regular smokers. These groups had similar NNAL levels but the US smokers had on average higher cotinine levels. This difference between groups of smokers could be due to the difference in racial composition (the US group included nearly half African Americans, who metabolize cotinine and possibly NNAL more slowly than whites, (20, 21) and/or due to difference in NNK levels in American vs Polish cigarettes. However we found no difference in the NNAL/cotinine ratio comparing African American to white smokers, suggesting that racial differences in metabolism does not explain our findings. The NNK content of cigarette tobacco and the NNK yield of cigarettes by machine testing are known to differ in different countries.(22, 23) However we were unable to locate any published data on NNK content of Polish cigarettes. Of note is that our occasional U.S. smokers had an NNAL/cotinine ratio similar to Polish regular smokers.

Among the passive smokers the two groups of lightly exposed smokers in the US and Poland had similar ratios, but the heavily exposed Mexican group had a significantly higher ratio than either of the other two groups. Cigarettes from Mexico are reported to have lower NNK content and yield than U.S. cigarettes.(22, 23) Despite lower NNK levels in the tobacco, the NNAL/cotinine ratios were higher in Mexican passive smokers, indicating that country differences cannot explain our results. Considering all of our groups of smokers and nonsmokers, there appears to be a pattern going from passive smokers to active smokers such that the heavier the exposure the lower the NNAL/cotinine ratio.

In our interpretation of the study findings we make the assumption that urine NNAL levels quantitatively reflect systemic NNK exposure, which is expected since NNAL is a metabolite of NNK. In active smokers urine NNAL is strongly correlated with mouth-level exposure to NNK, as assessed by measuring the latter in cigarette butts.(24) The possibility of dose-dependent metabolism of NNK such that there is saturation of metabolism at high doses with relatively less excretion of NNAL might be considered as a potential confounder. We are

aware of only one study that has examined dose-dependent metabolism of NNK, a study carried out in rodents.(25) This study found that urine recovery of NNAL was greater with higher compared to lower doses of NNK.If this is also the case for people it would bias against our findings of higher NNAL/cotinine ratios in those exposed to lower compared to higher levels of tobacco smoke. Thus, dose-dependent metabolism of NNK does not appear to explain our findings.

In conclusion, passive smoking is associated with a much higher ratio of NNAL/cotinine in the urine compared to active smoking. This finding is robust and is seen even with the inclusion of subjects from different countries and with different levels of active and passive smoke exposures. Even the most heavily exposed passive smokers had much lower ratios than occasional light active smokers, supporting the idea that the use of cotinine measurement leads to an underestimation of exposure to the carcinogen NNK from SHS when compared to active smoking.

Acknowledgments

Research supported by National Institutes of Health grants NCI CA78603, P30 DA12393, and NIH R01 HL677438 (MDE), as well as the Flight Attendants Medical Research Institute, K24 HL 097245 (MDE), R25CA113710, and Medical University of Silesia KNW-2-185/09 (WZD, AS) and KNW-2-185/09 (BK).

We thank Faith Allen, Sandy Tinetti, Katherine Dains for assistance in data management, Lisa Yu and Tricia Mao for assistance with laboratory analysis, and Marc Olmsted for editorial assistance.

Figure Legends

Figure 1

Comparison of geometric means of cotinine, NNAL and NNAL/cotinine ratios among self-reported active (N=373) and passive smokers (N=228) (bars show interquartile ranges)

Figure 2

Distribution of urine NNAL/Cotinine ratio among self-reported active (N=373) and passive smokers (N=228)

References

1. Benowitz NL. Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiol Rev* 1996; 18:188-204.
2. Benowitz NL, Hukkanen J, Jacob P, 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol* 2009:29-60.
3. Hecht SS. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* 1999; 91:1194-210.
4. Boffetta P, Clark S, Shen M, Gislefoss R, Peto R, Andersen A. Serum cotinine level as predictor of lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2006; 15:1184-8.
5. Strachan DP, Jarvis MJ, Feyerabend C. The relationship of salivary cotinine to respiratory symptoms, spirometry, and exercise-induced bronchospasm in seven-year-old children. *Am Rev Respir Dis* 1990; 142:147-51.
6. Whincup PH, Gilg JA, Emberson JR, et al. Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ* 2004; 329:200-5.
7. Department of Health and Human Services PHS. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. DHHS (CDC) Publication No. 87-8398. Washington DC: US Government Printing Office; 2006.
8. Institute of Medicine. Secondhand Smoke Exposure and Cardiovascular Effects - Making Sense of the Evidence. Washington DC: National Academy Press; 2010.
9. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem Res Toxicol* 1998; 11:559-603.
10. Singer BC, Hodgson AT, Guevarra KS, Hawley EL, Nazaroff WW. Gas-phase organics in environmental tobacco smoke. 1. Effects of smoking rate, ventilation, and furnishing level on emission factors. *Environ Sci Technol* 2002; 36:846-53.
11. Schick SF, Glantz S. Concentrations of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in sidestream cigarette smoke increase after release into indoor air: results from unpublished tobacco industry research. *Cancer Epidemiol Biomarkers Prev* 2007; 16:1547-53.
12. Sleiman M, Gundel LA, Pankow JF, Jacob P, 3rd, Singer BC, Destailats H. Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. *Proc Natl Acad Sci U S A* 2010; 107:6576-81.
13. Goniewicz ML, Havel CM, Peng MW, et al. Elimination kinetics of the tobacco-specific biomarker and lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Cancer Epidemiol Biomarkers Prev* 2009; 18:3421-5.
14. Eisner MD, Jacob P, 3rd, Benowitz NL, Balmes J, Blanc PD. Longer term exposure to secondhand smoke and health outcomes in COPD: impact of urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Nicotine Tob Res* 2009; 11:945-53.

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
Copyright © 2010 American Association for Cancer Research

15. Lazcano-Ponce E, Benowitz N, Sanchez-Zamorano LM, et al. Secondhand smoke exposure in Mexican discotheques. *Nicotine Tob Res* 2007; 9:1021-6.
16. Bernert JT, Jr., Turner WE, Pirkle JL, et al. Development and validation of sensitive method for determination of serum cotinine in smokers and nonsmokers by liquid chromatography/atmospheric pressure ionization tandem mass spectrometry. *Clin Chem* 1997; 43:2281-91.
17. Jacob P, 3rd, Havel C, Lee DH, Yu L, Eisner MD, Benowitz NL. Subpicogram per milliliter determination of the tobacco-specific carcinogen metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in human urine using liquid chromatography-tandem mass spectrometry. *Anal Chem* 2008; 80:8115-21.
18. Hecht SS. Carcinogen derived biomarkers: applications in studies of human exposure to secondhand tobacco smoke. *Tob Control* 2004; 13 Suppl 1:i48-56.
19. Borgerding MF, Bodnar JA, Wingate DE. The 1999 Massachusetts Benchmark Study Final Report. A Research Study Conducted after Consultation with the Massachusetts Department of Public Health. Massachusetts: Department of Health; 2000.
20. Perez-Stable EJ, Herrera B, Jacob P, 3rd, Benowitz NL. Nicotine metabolism and intake in black and white smokers. *JAMA* 1998; 280:152-6.
21. Richie JP, Jr., Carmella SG, Muscat JE, Scott DG, Akerkar SA, Hecht SS. Differences in the urinary metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in black and white smokers. *Cancer Epidemiol Biomarkers Prev* 1997; 6:783-90.
22. Ashley DL, Beeson MD, Johnson DR, et al. Tobacco-specific nitrosamines in tobacco from U.S. brand and non-U.S. brand cigarettes. *Nicotine Tob Res* 2003; 5:323-31.
23. Wu W, Zhang L, Jain RB, Ashley DL, Watson CH. Determination of carcinogenic tobacco-specific nitrosamines in mainstream smoke from U.S.-brand and non-U.S.-brand cigarettes from 14 countries. *Nicotine Tob Res* 2005; 7:443-51.
24. Ashley DL, O'Connor RJ, Bernert JT, et al. Effect of differing levels of tobacco-specific nitrosamines in cigarette smoke on the levels of biomarkers in smokers. *Cancer Epidemiol Biomarkers Prev* 2010; 19:1389-98.
25. Morse MA, Eklind KI, Toussaint M, Amin SG, Chung FL. Characterization of a glucuronide metabolite of 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its dose-dependent excretion in the urine of mice and rats. *Carcinogenesis* 1990; 11:1819-23.

Table 1. Characteristics of study groups (n=601)

Study	Active Smokers (n=373)			Passive Smokers (n=228)		
	A	B	C	D	E	F
Demographic Data						
Sample size	130	187	59	72	108	81
Subjects with detectable cotinine levels (%)	129 (99%)	187 (100%)	58 (98%)	54 (75%)	108 (100%)	80 (99%)
Subjects with detectable NNAL levels (%)	128 (98%)	187 (100%)	59 (100%)	48 (67%)	106 (98%)	77 (95%)
Valid subjects	128	187	58	45	106	77
Sex (male)	74 (58%)	83 (44%)	26 (45%)	19 (42%)	50 (47%)	27 (35%)
Race-ethnicity (White, non-Hispanic)	67 (52%)	187 (100%)	33 (57%)	42 (93%)	106 (100%)	N.A.
Age (mean±S.D.)	38.2±10.9	36.3±13.8	N.A.	64.6±5.8	34.6±16.6	25.7±7.4
Nationality	USA	Poland	USA	USA	Poland	Mexico
Cigarettes per day (mean±S.D.)	18.4±8.2	15.0±8.4	6.9±7.1	-	-	-
Analytical Data (geometric mean, IQR)						
Cotinine [ng/mL]	1,993 (1,180-3,604)	928 (646-1,942)	389 (127-1,606)	0.57 (0.15-2.07)	0.93 (0.39-1.74)	12.6 (5.60-18.8)
Cotinine [ng/mg creatinine]	2,471 (1,662-4,393)	882 (542-1,914)	514 (135-1,510)	0.85 (0.18-4.15)	0.71 (0.32-1.47)	10.5 (4.81-16.7)
NNAL [pg/mL]	174 (76.7-367)	192 (119-411)	91.1 (36.5-231)	3.13 (0.92-8.59)	4.00 (1.73-7.61)	13.9 (8.09-24.5)
NNAL [pg/mg creatinine]	223 (134-386)	182 (102-418)	120 (51.5-366)	4.69 (1.15-10.3)	3.04 (1.51-4.76)	11.5 (6.83-17.5)
NNAL/cotinine Ratio (×10 ³)	0.09 (0.06-0.13)	0.21 (0.13-0.31)	0.23 (0.12-0.52)	5.50 (2.65-11.7)	4.31 (2.44-7.36)	1.10 (0.60-2.14)

Note: IQR, interquartile range; N.A., data not available; S.D., standard deviation;

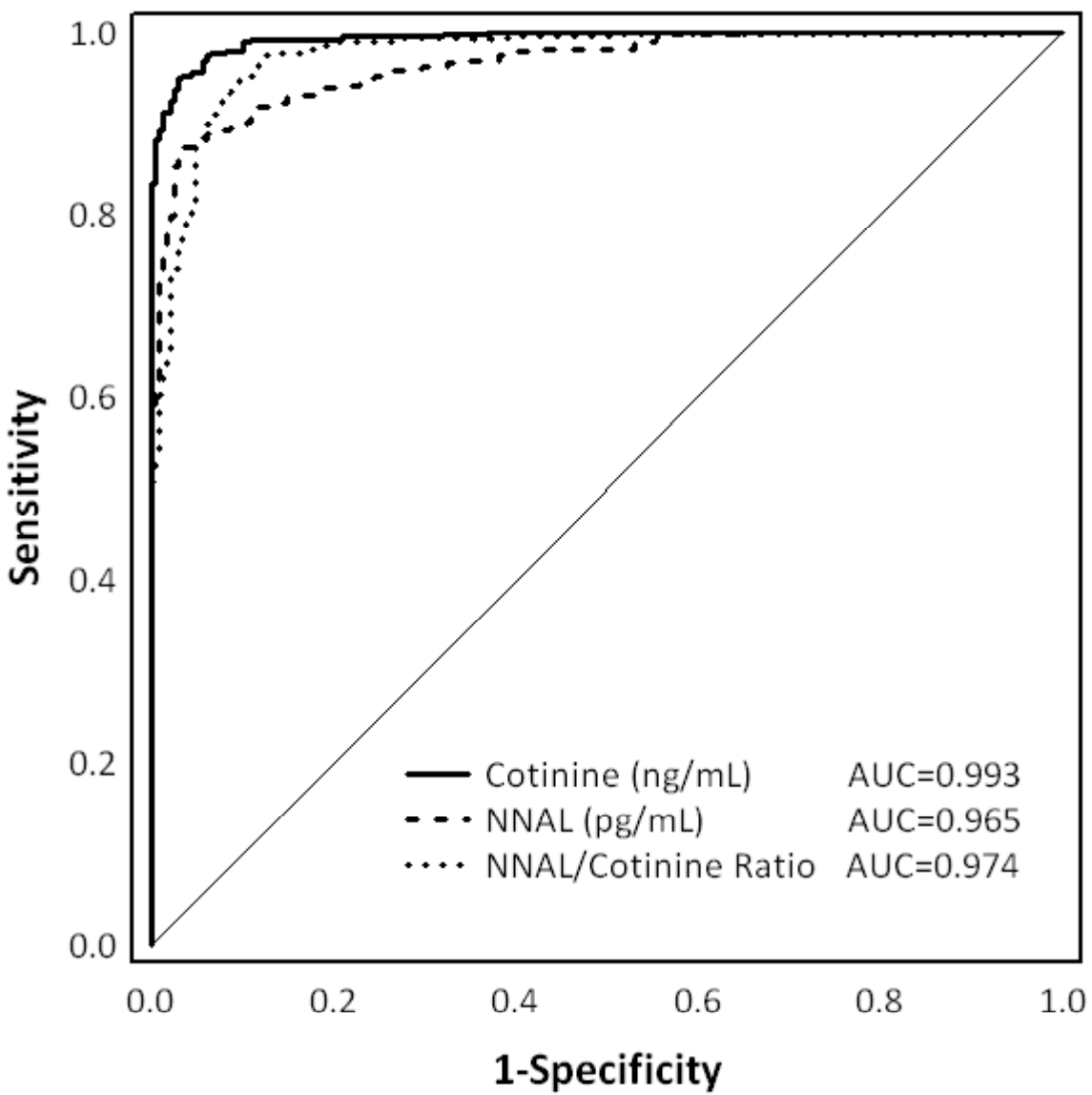
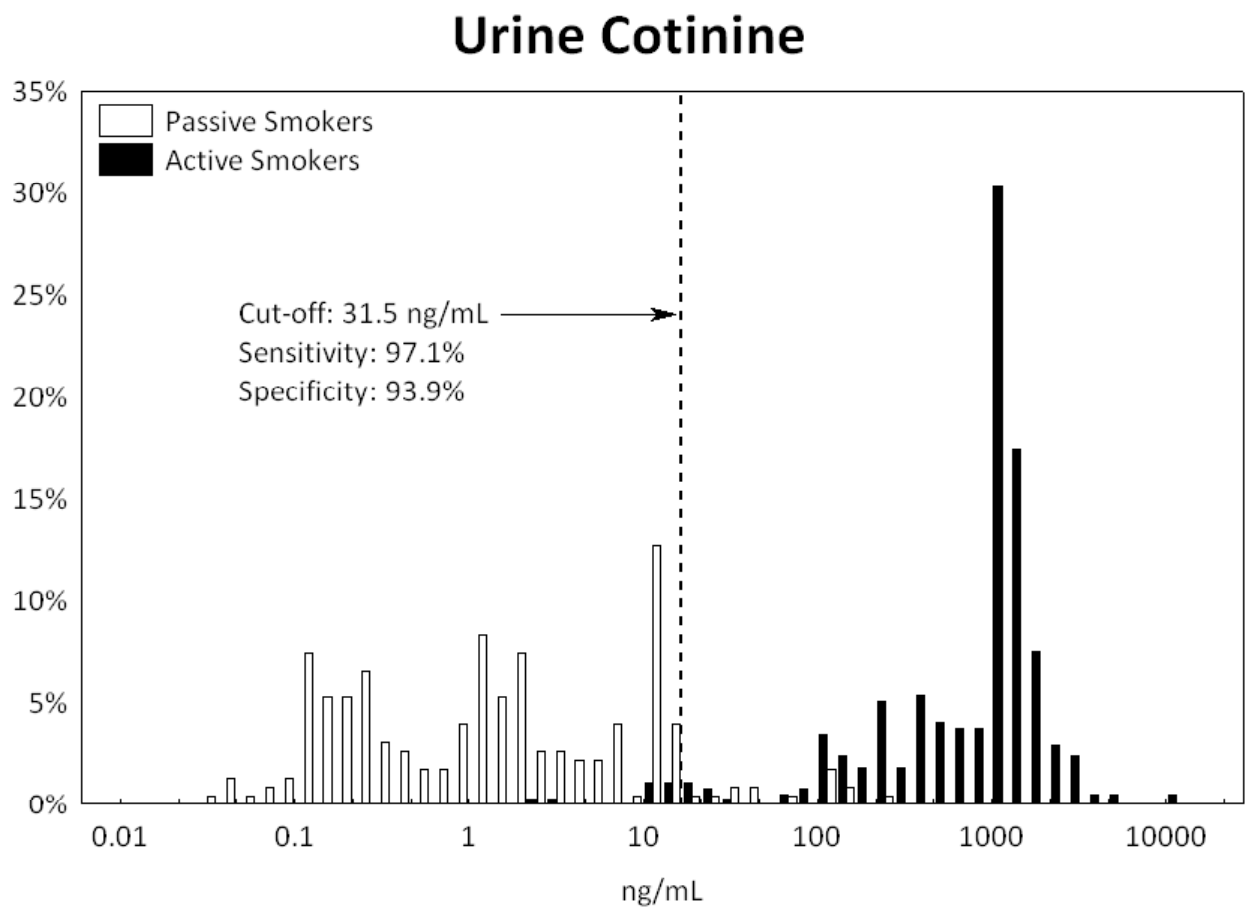


Fig. 1

Fig. 2



Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

Urine cotinine underestimates exposure to tobacco-derived lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in passive compared to active smokers

Neal L. Benowitz, Maciej Goniewicz, Mark Eisner, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst August 30, 2010.

Updated version Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-10-0497](https://doi.org/10.1158/1055-9965.EPI-10-0497)

Author Manuscript Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cebp.aacrjournals.org/content/early/2010/08/27/1055-9965.EPI-10-0497>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.