Differences in the Urinary Metabolites of the Tobacco-specific Lung Carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone in Black and White Smokers

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Abstract

Incidence and mortality rates for lung cancer in the United States are significantly greater in blacks than in whites. This disparity cannot be explained by differences in smoking behavior. We hypothesize that the observed racial differences in risk may be due to differences in the metabolic activation or detoxification of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). To test this, different biomarkers of NNK exposure and metabolism, including the urinary metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and the presumed detoxification product [4-(methylnitrosamino)-1-(3-pyridyl)but-1-yl]-β-O-D-glucosiduronic acid (NNAL-Gluc), were examined along with questionnaire data on lifestyle habits and diet in a metabolic epidemiological study of 34 black and 27 white healthy smokers. Results demonstrated that urinary NNAL-Gluc:NNAL ratios, a likely indicator of NNAL glucuronidation and detoxification, were significantly greater in whites than in blacks (P < 0.02). In addition, two phenotypes were apparent by probit analysis representing poor (ratio <6) and extensive (ratio ≥6) glucuronidation groups. The proportion of blacks falling into the former, potentially high-risk group was significantly greater than that of whites (P < 0.05). The absolute levels of urinary NNAL, NNAL-Gluc, and cotinine were also greater in blacks than in whites when adjusted for the number of cigarettes smoked. None of the observed racial differences could be explained by dissimilarities in exposure or other sociodemographic or dietary factors. Also, it is unlikely that the dissimilarities are due to racial differences in preference for mentholated cigarettes, because chronic administration of menthol to NNK-treated rats did not result in either increases in urinary total NNAL or decreases in NNAL-Gluc:NNAL ratios. Altogether, these results suggest that racial differences in NNAL glucuronidation, a putative detoxification pathway for NNK, may explain in part the observed differences in cancer risk.

Introduction

Lung cancer rates in the United States vary greatly between races, and among the major racial/ethnic groups, blacks have the highest age-adjusted incidence and mortality rates (1, 2). This racial disparity represents a significant public health problem, with incidence rates varying from 122/100,000 for black males to 77.9/100,000 for white males (1). To date, there is little information available on the specific factors responsible for the observed differences in lung cancer between the races. In a recent analysis based on Surveillance, Epidemiology and End Results (SEER) Registry data, lung cancer incidence in blacks was actually lower than that in whites after adjustment for population density and education, suggesting that differences in socioeconomic factors such as smoking prevalence or diet could be responsible for the observed racial differences in lung cancer rates (3). However, whereas tobacco smoking is the major risk factor for lung cancer in both blacks and whites, available data on smoking behavior suggest that racial differences in tobacco smoke exposure do not account for the differences in cancer rates. The proportion of ever smokers among blacks (57.7%) is the same as that observed among whites (59.3%; Ref. 4). In addition, although the proportion of current smokers among blacks (40.4%) is greater than that among whites (32.9%), blacks tend to smoke far fewer numbers of cigarettes (4, 5). Only 40.8% of black smokers are considered heavy smokers (≥15 CPD4) compared to 70.9% of white smokers (4). In the absence of differential exposures, it is possible that racial differences in cancer susceptibility are responsible for the differences in cancer incidence rates. However, few case-control studies on lung cancer risk comparing blacks and whites have been reported.

We hypothesize that the observed racial differences in cancer incidence are due to variations in carcinogen metabolism, resulting in differences in the exposure of individuals and target tissues to activated tobacco smoke carcinogens. Of par...
ticular interest in the present study is the tobacco-specific nitrosamine NNK. Chemical and animal studies, together with epidemiological observations linking tobacco use with enhanced cancer risk, provide strong evidence that NNK is a causative factor for lung cancer in smokers (6). NNK is found in substantial concentrations in tobacco smoke and induces adenocarcinoma of the lung in mice, rats, and hamsters whether administered orally, topically, or by s.c. or i.p. injection (6). Indeed, tumors are induced at total doses similar to those to which human smokers are exposed.

NNK requires metabolic activation to trigger its carcinogenic effects (7). Activation occurs through α-hydroxylation to reactive species that can methylate or pyridyloxobutylate DNA (Fig. 1). These DNA adducts have been detected in rodent and human tissues (8–12), and in mouse lung, they are associated with Ki-ras activation (13–14).

The major metabolic pathway for NNK in most tissues is the conversion to NNAL by carbonyl reduction (Fig. 1; Ref. 7). Like NNK, NNAL is a powerful lung carcinogen in animal models, and its carcinogenicity is dependent on activation by α-hydroxylation. The majority of NNAL is glucuronidated to form NNAL-Gluc, a putative detoxification product of NNK and NNAL metabolism (15). In animal models, urinary total NNAL (NNAL + NNAL-Gluc) levels are highly correlated with the dose of NNK (16).

Recently, a method was reported for the analysis of the two major NNK metabolites, NNAL and NNAL-Gluc, in the urine of smokers (17) as well as that of nonsmokers who have been passively exposed to environmental tobacco smoke (18). In these studies, it was proposed that measurement of total NNAL could serve as a potential biomarker of NNK dose and metabolism. In addition, the molar ratio of NNAL-Gluc:NNAL may be indicative of an individual’s capacity to glucuronidate NNAL. Because NNAL-Gluc is a probable detoxification product of NNAL and NNK, the NNAL-Gluc:NNAL ratio could serve as an index of detoxification capacity. Recently, we reported on the intraindividual and interindividual variation in urinary NNAL and NNAL-Gluc levels in healthy smokers (19).

Results verified the utility of the NNAL-Gluc:NNAL ratio as a potential biomarker and suggested that phenotypic differences exist for NNAL glucuronidation capacity in human populations (19). Based on these studies, 85% of smokers exhibited a low NNAL-Gluc:NNAL ratio (<6), and the remaining 15% exhibited a high ratio (>6). It was proposed that individuals in the low-ratio group would have a relatively lower capacity to detoxify NNAL and NNK and thus would be at greater risk for lung cancer. However, it must be noted that the confirmation of NNAL-Gluc as a detoxification product and the association of the low-ratio phenotype with disease risk remain to be confirmed.

In humans, the balance between metabolic activation and detoxification of NNK varies between individuals and is likely to affect one’s risk for cancer on exposure to NNK. Thus, the goal of the present research was to use these newly developed biomarkers of NNK metabolism in black and white smokers to determine whether racial differences in the metabolic activation or detoxification of NNK occur and can account, in part, for the observed differences in cancer incidence. Because differences in metabolism can result from either genetic or environmental factors, detailed questionnaire data on lifestyle habits, sociodemographics, and diet were also obtained.

Materials and Methods

Study Subjects. All subjects were healthy adult smokers ranging in age from 21–50 years. Subjects were recruited in the city of Mount Vernon, New York, a community of 66,153 residents located 13 miles north of Manhattan, New York City (20). In 1990, 55% of the population were black, 40% were white, and 7% were of Hispanic origin, and 9% of all families had incomes below the poverty line. Recruitment was carried out from 1992–1994 using flyers, public lectures, newspaper and television advertisements, recommendations from community leaders, and word of mouth. To be eligible for participation, each subject was free of chronic disease, and English-speaking.

Two interview clinics were established in Mount Vernon, one at Grace Baptist Church and the other at Mount Vernon Hospital, at which all interviewing and sample collections were performed. After providing informed consent, subjects were given a questionnaire requesting detailed information on sociodemographics, tobacco and alcohol use, occupational, family and medical histories, environmental exposure, and lifestyle habits. In addition, a semiquantitative National Cancer Institute food frequency questionnaire (21) was administered to provide information on dietary intake.

Subjects were participating in a larger study of ethnic differences in carcinogen metabolism that included protocols for assessing caffeine metabolism. Thus, subjects were asked to fast and abstain from smoking starting at 12 a.m. and abstain from caffeine for 24 h. At 9 a.m., they were given a cup of coffee and asked to collect their urine for the next 3 h. During this period, the questionnaire was administered, and a blood sample was collected. Some subjects were recalled for a second analysis 4–16 months after the first analysis.
Collection of Blood and Urine. Urine samples were placed on ice immediately after collection, and within 4 h, they were aliquoted and frozen at -20°C until analysis. Blood was collected from an antecubital vein into tubes containing EDTA as an anticoagulant and immediately placed on ice. Within 4 h, blood was processed by centrifugation at 2100 × g for 15 min at 4°C, and plasma was removed, aliquoted, and frozen at -20°C. The remaining RBCs were washed three times in ice-cold 0.9% (w/v) saline and stored in the original blood tube at -20°C until analysis.

Analysis of Creatinine and Cotinine. Urinary cotinine was measured by GC-MS (22). In brief, cotinine was extracted from urine samples with CH2Cl2:isopropyl alcohol (80:20) containing 2% (w/v) ammonium hydroxide. After evaporation of the organic solvent, cotinine was measured by GC-MS using deuterated cotinine as the internal standard. Urinary creatinine was measured using a Kodak Ektachem 500 clinical chemistry analyzer.

Analysis of Urine for NNAL and NNAL-Gluc. Urine was thawed, and a 20–25-ml aliquot was withdrawn for analysis as described recently by Carmella et al. (19).

Effect of Menthol on NNK Biomarkers in F-344 Rats. Male F-344 rats, -250 g each, were maintained on NIH-07 diet alone (control group, n = 5) or on NIH-07 diet containing 5000 ppm (-)menthol (menthol group, n = 5). All rats were given 2 ppm NNK in drinking water throughout the study. After 15 days, the rats were placed in metabolism cages, and 24 h urine was collected. Blood (0.3–0.5 ml) was withdrawn from the orbital sinus. Urine was analyzed for NNAL and NNAL-Gluc. Blood was analyzed for HPB-releasing hemoglobin adducts.

Statistical Methods. Data are expressed as mean ± SD unless otherwise indicated. Comparison of group means was performed using Student's t test or ANOVA, followed by Scheffe's post-hoc test where appropriate (23). Normality of data was assessed using either the Kolomogorov-Smirnov (23) or Martinez-Iglewicz (24) tests. In cases in which the data deviated from normal, the nonparametric Mann-Whitney U test (23) was used to detect differences in group medians. Correlations were determined by calculation of Pearson correlation coefficients (23). Probit transformations of the NNAL-Gluc:NNAL ratio data were conducted by plotting NNAL-Gluc:NNAL ratios against their corresponding percentage area under the normal probability curve on probability paper (25). By using probit transformation, a straight line would result for data that are normally distributed or log-distributed. A broken line indicates a deviation from normality. Prevalence data were compared by χ² analysis (23). All statistical analyses were performed using NCSS statistical software (NCSS, Kaysville, UT).

Results

Study Subject Characteristics. A description of the study subject characteristics is provided in Table 1. Subjects consisted of 34 blacks and 27 whites ranging in age from 21–50 years, with a mean of 33.4 years for blacks and 32.1 years for whites. Overall, 48% of subjects were males and 52% were females. Indicators of sociodemographic status were derived from the questionnaire data (Table 1). There were no significant differences in the age, sex, ratio, marital status, education, or number of residents/bedroom between the races, although the sample size was too limited to allow for the detection of small differences in these variables.

A summary of smoking status parameters for the study subjects is provided in Table 2. No racial differences occurred in the mean age of starting smoking and total years smoking. Whites smoked on the average 8 more CPD than blacks (P < 0.0003) but smoked cigarettes of a slightly lower nicotine content (P < 0.0003). Using CPD and tar and nicotine/cigarette values, the daily exposure of study subjects to tar and nicotine was estimated. Based on these calculations, whites were apparently exposed to 36% more nicotine and 48% more tar per day than blacks. The prevalence of smoking menthol cigarettes was significantly greater in blacks (73.5%) than in whites (18.5%).

Food frequency and alcohol intake data are provided in Table 3. No racial differences in intake were observed for any of the major food groups examined.

Urinary Cotinine Levels. Urinary cotinine levels were examined in all subjects (Table 4). The active smoking status of the study subjects was confirmed, because cotinine levels ranged from 130–6770 ng/mg creatinine. Overall, cotinine levels were correlated with CPD (r = 0.32; P < 0.006). No racial differences were apparent in mean cotinine levels. However, when cotinine was expressed on a per CPD basis, mean cotinine was 2-fold higher in black smokers than in white smokers (P < 0.0001). Cotinine results were also calculated separately for smokers of 0–5, 6–10, 11–15, 16–20, and 21+ CPD (Fig. 2).
Cotinine levels were 75% greater in blacks than in whites in the 16–20 CPD group and 48% greater in the 21+ CPD group (P < 0.05). No statistical differences were observed between the races for smokers of fewer than 16 CPD.

**Urinary NNAL and NNAL-Gluc.** Levels of urinary NNAL and NNAL-Gluc are summarized in Table 5. Concentrations are expressed on a per milligram of creatinine basis to account for urine dilution, which differed between individuals. As observed previously (17, 19), urinary levels of NNAL-Gluc are 2.5- to 4-fold greater than those of NNAL. Whereas no racial differences were observed for NNAL-Gluc, NNAL levels were 2-fold greater in blacks than in whites (P < 0.01). A similar 2-fold increase in NNAL concentration was also observed when expressed on a picomole/milliliter urine basis. Mean total NNAL (NNAL + NNAL-Gluc) levels were 35% greater in blacks than in whites, but the difference was not statistically significant (P = 0.13).

To analyze urinary NNAL-Gluc and NNAL levels in relation to the extent of exposure, the levels of metabolites were expressed per CPD (Table 5). Significantly higher levels of all metabolites were observed in blacks than in whites expressed in this fashion (P < 0.05). Total NNAL results were also calculated separately for smokers of 0–5, 6–10, 11–15, 16–20, and 21+ CPD (Fig. 3). Total NNAL levels were 2-fold greater in blacks than in whites in the 16–20 CPD group (P < 0.05) and 2.7-fold greater in the 21+ CPD group. No differences were observed between the races for smokers of fewer than 16 CPD. A significant correlation was observed between total NNAL and CPD for blacks (r = 0.38; P < 0.02) but not for whites (r = 0.22).

To examine urinary NNK metabolites in relation to the extent of internal exposure to tobacco smoke components, the relationship of NNAL-Gluc to cotinine was also examined. In all subjects, cotinine levels were correlated with NNAL-Gluc (r = 0.36), NNAL (r = 0.56), and total NNAL (r = 0.48). When NNAL-Gluc and NNAL were expressed on a per milligram of cotinine basis, racial differences were observed only for NNAL, in which levels were 60% greater in blacks than in whites (P < 0.05; Table 5).

**Racial Differences in the Metabolic Ratio of NNAL-Gluc:** NNAL:NNAL-Gluc ratios were calculated for all study subjects. Although these ratios were unrelated to other smoking parameters, including CPD and urinary cotinine lev-
the data were analyzed in this fashion to examine racial differences (inset). Clearly demonstrated two distinct groups consisting of individuals with high (>6) and low (<6) ratios (Fig. 5, inset). Thus, phenotypic differences were apparent in this population. When the data were analyzed in this fashion to examine racial differences, the percentage of subjects falling into the high-ratio group was significantly greater among whites (26%) than among blacks (6%) (Fig. 5; P < 0.05). In addition, greater than 20% of all black subjects and no white subjects had NNAL-Gluc:NNAL ratios of ≤2. No apparent relationships were observed between NNAL-Gluc:NNAL ratio subgroups and other smoking-related parameters or indicators of smoke exposure. To investigate the stability of these proposed phenotypes within individuals, five subjects (two with a high ratio and three with a low ratio) were retested after 4–16 months. All subjects remained in the same phenotype category after retesting, suggesting that these phenotypes are consistent within individuals over long periods of time (19). Likewise, no differences in phenotype were observed when six subjects were tested daily over a period of 3 days or when 24 h urine samples were compared to random urine samples throughout the day (19).

**Menthol Study in Rats.** Body weight data along with urinary NNK metabolite and blood HPB-releasing adduct levels in menthol-treated rats are provided in Table 6. Menthol supplementation did not seem to affect food intake, because body weight was the same in the control and menthol groups. Increases of 24% for NNAL-Gluc levels and 32% for NNAL-Gluc:NNAL ratios were observed in menthol-treated animals. All other urine and blood measurements were unchanged.

**Discussion**

A key finding in this investigation is the racial difference in the proportion of subjects falling into the high- and low-NNAL-Gluc:NNAL ratio phenotypes. In a previous report, we suggested that the NNAL-Gluc:NNAL ratio may be an important factor in assessing the risk for cancer in smokers, because NNAL-Gluc is a likely detoxification product of NNAL and NNK (16). Examination of the NNAL-Gluc:NNAL ratio data in this study suggests that two phenotypes exist, representing a high-ratio group (extensive glucuronidators) and a low-ratio group (poor glucuronidators). Accordingly, individuals in the high-ratio group may be partially protected against the carcinogenic effects of NNK and NNAL, whereas those in the low-ratio group may be at greater risk. The percentage of whites represented in the high-ratio group was significantly higher than that of blacks. Thus, a greater proportion of blacks falling into the low-ratio group may be indicative of a greater risk for lung cancer. Altogether, the results suggest that a decreased capacity to detoxify NNK and NNAL by glucuronidation may be one factor leading to greater risk for lung cancer at the same levels of smoking in black versus white populations.

The suggestion that NNAL-Gluc represents a detoxified product of NNK and NNAL results from glucuronidation being one of the major detoxification reactions for a wide variety of xenobiotics and carcinogens, resulting in products that are water-soluble and easily excreted. This mechanism is supported by the results of a recent study in which F-344 rats were treated with NNAL-Gluc and the excretion of urinary metabolites was examined (26). Of the total dose administered, almost 59% was excreted within 6 h and 94% was excreted after 24 h. Furthermore, 76% of the dose was excreted as unchanged NNAL-Gluc, and only 11% appeared as products of NNK or NNK α-hydroxylation. In contrast, α-hydroxylation of NNK in F-344 rats is extensive, representing about 60% of the dose, as determined by analysis of urinary metabolites (27, 28).

The possibility must be noted that glucuronidation of NNAL could also serve as an active transport system delivering a small percentage of NNAL from the liver to the lung. Indeed, β-glucuronidase activity has been reported in tissue samples of...
human lung (29). The notion that such β-glucuronidase activity occurs in vivo was supported by the analysis of urinary products of NNAL-Gluc administered to rats in the above-mentioned study (26). Whereas NNAL-Gluc itself represented the major urinary metabolite, 17% of the excreted products were NNAL, NNK, or α-hydroxylation reaction products of NNAL or NNK. The occurrence of these products, although much lower than that observed with NNK, nevertheless suggests that a small percentage of NNAL-Gluc was converted to NNAL and, in turn, metabolized to activated products.

Given the different possible roles of glucuronidation reactions in carcinogenesis, DNA-adduct studies and carcinogenicity bioassays are required to confirm the role of NNAL-Gluc as a detoxification product. To date, such studies have not been reported.

The finding that blacks smoked, on the average, 8 fewer CPD than whites is consistent with other studies both in this community (30) and elsewhere (4, 5). Despite a lower exposure to tar and nicotine in black smokers, we observed higher urinary cotinine levels in blacks than in whites when adjusted for the number of cigarettes smoked. These results were consistent with several previous reports (31, 32) of serum cotinine in black and white smokers. In these studies, as well as in the present report, there was no evidence for a reporting bias in either group. Altogether, these studies suggest that racial differences in nicotine metabolism exist. Racial differences have previously been noted for the metabolism of a number of drugs and xenobiotics such as phenytoin (33), acetaminophen (34), and certain oral contraceptives (35). Differences in nicotine metabolism may account for the tendency of blacks to be light smokers; a similar internal exposure to nicotine is obtained from a fewer number of cigarettes smoked by blacks compared to whites. Such a phenomenon could be of particular importance in understanding the observed racial differences in the success rates of smoking cessation programs.

An interesting important finding in this study is the observation that urinary NNAL levels are greater in blacks than in whites. These ethnic differences in NNAL as well as NNAL-Gluc and total NNAL are even greater when adjusted for the number of cigarettes smoked. In fact, a correlation between CPD and total NNAL was observed in blacks only. Thus, like cotinine, NNAL exposure seems to be greater in black smokers than in white smokers. It is interesting to note that the differences for both cotinine and NNAL occur only for individuals smoking greater than 16 CPD. This relationship between cotinine and NNAL could be a result of a greater internal exposure to tobacco smoke/cigarette in blacks compared to whites, perhaps due to differences in smoking behavior. However, this is unlikely, because NNAL/cotinine ratios were significantly greater in blacks than in whites. In addition, Wagenknecht et al. (31) found no racial differences in serum thiocyanate levels in black versus white smokers when the quantity smoked was taken into account, despite finding significant differences in cotinine levels.

The significance of the finding of increased NNAL and NNAL-Gluc in the urine of black smokers relative to that of white smokers is unknown. One explanation is an increased overall exposure to NNK, resulting in greater urinary excretion of metabolites. Alternatively, it can be argued that these changes are due to a more efficient conversion of NNK to NNAL and/or excretion of NNAL in urine and may be indicative of a decrease in NNK activation. To clarify these questions regarding NNK and NNAL metabolism, it is important to account for all of the major NNK metabolites in urine. However, at the present time, methods have not been reported for the
analysis of α-hydroxylation and N-oxidation products in the urine of human smokers.

It is of interest to note that the use of mentholated cigarettes was greater in blacks (74%) than in whites (18%). Similar racial trends in mentholated cigarette usage have been observed previously (4, 5). Although these differences suggest that mentholated cigarette usage may be in part responsible for the increased risk for lung cancer in blacks, most case-control studies have found no increased risk of lung and oral cancers for users of mentholated cigarettes compared to nonmentholated cigarettes (36, 37). Another study found no effect of mentholation on the risk of lung cancer in men, whereas a slight increased risk was observed in women (38).

To examine the possibility that menthol exposure may alter NNK metabolism, urinary NNK metabolites and blood HPB-releasing adducts were measured in NNK-treated rats fed either control or menthol-supplemented diets. Menthol has little effect on NNK metabolites, with the exception of a slight enhancement of NNAL-Gluc:NNAL ratios and an increase in NNAL-Gluc excretion. Because the observed changes are inconsistent with the racial differences observed in the human study, it is unlikely that these differences can be attributed to use of mentholated cigarettes.

An important aspect in the present study is the subject recruitment strategy. Mount Vernon represents an ideal community for such a study due to its equal representation of blacks and whites and relative racial equality in socioeconomic status. The Mount Vernon community has been the site of previous biracial studies on lifestyle factors and health (30). This is particularly important in light of a recent study that suggested that differences in socioeconomic factors can explain the observed racial differences in lung cancer incidence (3). The metabolic differences observed in the present study do not seem to be the result of differences in socioeconomic status, based on the questionnaire data obtained from the study participants. In addition, diet does not seem to play a major role, because little differences were found in the dietary factors examined. However, environmental influences cannot be discounted because of the relatively low power in this study to detect differences in dietary habits.

Concern has been expressed regarding the impact of heterogeneity among ethnic and racial subpopulations on studies dealing with the epidemiology of cancer in these groups (39, 40). Indeed, it is recognized in the present study that metabolic differences are being examined among groups that are defined by political and cultural means in addition to ethnicity. However, despite the likely genetic heterogeneity, clear differences have been observed in cancer risk and, in this study, in metabolic parameters that may be important in regulating risk. In light of the nature of the populations under study, cultural, dietary, behavioral, and other like factors in addition to genetics must be addressed in identifying the underlying mechanisms responsible for the observed differences.

Altogether, these results suggest that specific metabolic differences occur in the activation and/or detoxification of NNK between blacks and whites. Of particular interest is the finding of greater NNAL-Gluc:NNAL ratios in whites than in blacks. The potential use of the NNAL-Gluc:NNAL ratio data as a biomarker is supported by the long-term stability of these ratios in free-living subjects and the lack of variability due to tobacco smoke exposure. However, although it is likely that high NNAL-Gluc:NNAL ratios are consistent with a decreased risk for lung cancer, case-control studies are required to confirm this hypothesis. Additional studies of this nature are required before the differences noted in this study can be said to contribute to the racial differences in lung cancer risk.

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References


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