Published OnlineFirst March 23, 2011; DOI:10.1158/1055-9965.EPI-10-1330

Cancer Epidemiology, Biomarkers & Prevention

Research Article

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Comparison of Serum Cotinine Concentration within and across Smokers of Menthol and Nonmenthol Cigarette Brands among Non-Hispanic Black and Non-Hispanic White U.S. Adult Smokers, 2001–2006

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Abstract

Background: The Food and Drug Administration (FDA) is examining options for regulating menthol content in cigarettes. There are many pharmacologic properties of menthol that may facilitate exposure to tobacco smoke, and it has been suggested that the preference for menthol cigarettes in black smokers accounts for their higher cotinine levels.

Objective: To assess cigarettes smoked per day–adjusted cotinine levels in relation to smoking a menthol or nonmenthol cigarette brand among non-Hispanic black and white U.S. adult smokers under natural smoking conditions.

Method: Serum cotinine concentrations were measured in 1,943 smokers participating in the 2001 to 2006 National Health and Nutrition Examination Surveys (NHANES). The effect of smoking a menthol brand on cigarettes smoked per day–adjusted serum cotinine levels in these two populations was modeled by adjusting for sex, age, number of smokers living in the home, body weight, time since last smoked, and FTC (Federal Trade Commission)-measured nicotine levels. The 8- or 12-digit Universal Product Code (UPC) on the cigarette label was used to determine the cigarette brand and whether it was menthol.

Results: Smoking a menthol cigarette brand versus smoking a nonmenthol cigarette brand was not associated ($P \geq 0.05$) with mean serum cotinine concentration in either black or white smokers.

Conclusions: The higher levels of cotinine observed in black smokers compared with white smokers are not explained by their higher preference for menthol cigarette brands.

Impact: Further studies like ours are needed to improve our ability to understand health consequences of future changes in tobacco product design. *Cancer Epidemiol Biomarkers Prev; 20(7); 1329–40. ©2011 AACR.*

Introduction

Cotinine is the primary proximate metabolite of nicotine. On an average, 72% of nicotine is converted to cotinine, ranging from 55% to 92% (1). The half-life cotinine is 16 to 19 hours and its ready availability in saliva, blood, and urine makes it widely practical as a biomarker of nicotine uptake and exposure to both active and secondhand tobacco smoke. For smokers with a fairly consistent smoking pattern (about 80% of adult smokers report smoking each day; ref. 2), serum cotinine levels reach a steady state, varying only by 15% to 20% over the course of the day with lower levels usually in the morning as there is typically minimal exposure to cigarette smoke overnight (1). Racial and ethnic differences in the number of cigarettes smoked per day (cpd; refs. 3–5) and in serum cotinine concentration per cigarette smoked have been well established (6–11). In U.S. studies, non-Hispanic black smokers (hereafter referred to as black) have consistently been found to have higher serum cotinine concentrations per cigarette smoked than non-Hispanic white smokers (hereafter referred to as white; refs. 7,10). The reasons for these differences are not well understood but may include a combination of factors,

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doi: 10.1158/1055-9965.EPI-10-1330

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Published OnlineFirst March 23, 2011; DOI:10.1158/1055-9965.EPI-10-1330

among them cigarette characteristics (e.g., menthol/nonmenthol, mainstream smoke levels of nicotine), smoking topography (e.g., puff volume, depth of inhalation, retention time of smoke in the lungs), and differences in nicotine metabolism or elimination among individual smokers.

There are over 1,000 brands and subbrands of cigarettes that are sold in the United States (12). Most recent Federal Trade Commission (FTC) data show that menthol brands represented about 26% to 27% of market share of cigarettes between 2003 and 2005. The leading menthol cigarette brands sold in the United States during that period were Newport, Marlboro Menthol, Kool, and Salem; however, there are many other menthol cigarette brands that are sold in the United States. The leading menthol brands, similar to nonmenthol brands, have a variety of subbrands. These menthol subbrands of the same brand vary in FTC-measured nicotine levels. For example, the leading menthol brand Newport has subbrands which range in FTC-measured[1] nicotine levels from 0.8 mg (Newport Slim Light) to 1.4 mg (Newport); Marlboro Menthol has subbrands in which nicotine yields vary from 0.5 mg (Marlboro Menthol Ultra Light) to 1.2 mg (Marlboro Menthol 100s); Kool from 0.2 mg (Kool Ultra) to 1.4 mg (Kool Super Longs); and Salem from 0.5 mg (Salem Ultra Lights) to 1.4 mg (Salem). Similarly, these menthol brands and its subbrands also have different concentrations of the additive menthol in it; however, menthol is also present at low levels in many nonmenthol brands. In a study conducted by Celebucki and colleagues (13), the authors found that subbrands of Newport ranged in menthol per cigarette and in menthol per gram of tobacco. In addition to the type of cigarettes smoked (menthol or nonmenthol, amount of menthol, amount of nicotine), cigarettes are smoked differently (e.g., puff volume, depth of inhalation, retention time of smoke in the lungs, potential blocking ventilation holes) and differences in nicotine metabolism or elimination among individual smokers and between racial groups exist.

Documenting and quantifying differences in serum cotinine concentration between smokers of menthol and nonmenthol brands (within and between race comparisons) are best done under natural smoking conditions as opposed to conditions set in a laboratory. Serum cotinine variability has been extensively studied in relation to race/ethnicity. Number of cigarettes smoked per day, and to a smaller degree, cigarette types like menthol have also been studied. However, these 3 factors are highly interrelated, and their independent effects on cotinine levels have not been well studied.

We report here an assessment of serum cotinine levels using models based on nationally representative data that simultaneously include number of cigarettes smoked per day, race, and smoking a menthol or nonmenthol cigarette brand.

Cotinine is a biomarker of current exposure to nicotine. Because the Food and Drug Administration (FDA) is examining options for regulating menthol cigarettes, it is important to determine whether smoking a menthol brand is associated with higher nicotine uptake under natural smoking conditions. Such information may help to understand reasons for the disparities between the risk of smoking-related diseases and aspects of nicotine dependence such as quit rate between black smokers and white smokers in the United States.

Methods

We measured serum cotinine concentrations among a nationally representative sample of white and black smokers according to the type of cigarettes they smoked in the past 2 days. Specifically, we determined serum cotinine concentrations as a function of self-reported cigarettes per day among the 2 racial groups by type of cigarette. Cigarette type was determined by the brand they smoked at the time of the home interview and categorized as menthol or nonmenthol, as well as by pack descriptors and data reported annually to the Federal Trade Commission (FTC) for mainstream smoke nicotine yield. The serum cotinine concentration was first preadjusted for the day the last cigarette was smoked (today or yesterday), the number of smokers who smoked inside the home in the past 7 days, whether the subject physically showed the cigarette pack to the interviewer in the home interview, age, and body weight, as subsequently described.

Description of NHANES

The National Health and Nutrition Examination Survey (NHANES) consists of a number of questionnaires administered in the household followed by standardized physical examinations and additional tobacco use questions administered in specially equipped mobile examination centers (MEC), which on an average occur about 2 weeks after the household interview. The NHANES target population is the civilian, noninstitutionalized U.S. population. This nationally representative sample permits calculation of national estimates. Related to our study, NHANES oversamples low-income persons, persons 60+ years of age, and non-Hispanic blacks. We used NHANES data collected between January 2001 and December 2006. The overall response rate to NHANES for 2001 to 2006 was 78%.

[1]In 2008, the FTC rescinded guidance issued in 1966 that generally permitted statements concerning tar and nicotine yields if they were based on the Cambridge Filter Method, sometimes called the FTC method. At the time, the Commission believed that giving consumers uniform, standardized information about tar and nicotine yields of cigarettes would help them make informed decisions about the cigarettes they smoked. In 2008, however, the scientific consensus was that machine-based measurements of tar and nicotine yields based on the Cambridge Filter Method did not provide meaningful information on the amounts of tar and nicotine smokers received from cigarettes, thus the FTC method was flawed. The FTC method is no longer valid to provide information to consumers about tar and nicotine yields in cigarettes.

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The MEC tobacco questionnaire, administered via computer-assisted personal interview (CAPI), asked participants, "During the past 5 days, on the days {you/he/she} smoked, how many cigarettes did {you/he/she} smoke each day?" This number was our independent variable. Cigarettes smoked per day was not a calculated variable. It is a directly reported respondent impression of the "average" number of cigarettes smoked, on the days they smoked cigarettes. NHANES did not ask for the numbers of cigarettes smoked on each of the last 5 days but did ask when they smoked their last cigarette (today, yesterday). Finally, another MEC questionnaire item asked about when the respondent smoked last: "When did {you/he/she} smoke {your/his/her} last cigarette?" Possible responses were "today," "yesterday," or "3 to 5 days ago." Those who answered "3 to 5 days ago" were excluded from the analyses.

The analytic sample for this study included smokers aged 20 years and older who had smoked on the day of or on the day preceding the MEC visit, who were recoded by NHANES as non-Hispanic white or non-Hispanic black/African American, who had a serum cotinine measurement and provided tobacco use information in the MEC. We excluded smokers who had used any other tobacco product (pipes, cigars, chewing tobacco, or snuff) or nicotine patches, gum, or other nicotine products during the 5 days preceding the MEC visit.

Of the 11,171 white or black adults aged 20 years and older who completed the NHANES home interview, 10,504 (94.0%) visited the MECs; 9,668 answered the MEC tobacco questionnaire. Of these, 2,188 had smoked cigarettes during the past 5 days and had a serum cotinine measurement. Of these, 2,095 had smoked on the day of or the day preceding the MEC exam; 2,034 reported using no sources of nicotine other than cigarettes. Among these, 91 were excluded due to missing cigarette brand information. The final analytic sample consisted of 1,943 individuals.

Menthol cigarette brand

During the CAPI household interview, respondents were asked whether they now smoke cigarettes every day, some days, or not at all. Respondents who indicated they smoke every day or some days were asked to show their cigarette pack for the cigarette brand they usually smoke. Interviewers then entered the 8- or 12-digit Universal Product Code (UPC) into the computer, which then displayed the brand name from a stored list for verification by the respondent. If the respondent's brand was not displayed or the respondent did not show the pack, the brand (reported by the respondent) was selected from a list of brands/types. If the respondent's usual brand was not on the computer list, the interviewer asked the respondent about the usual brand's characteristics to help classify the brand according to filter, menthol, length, and packaging categories. Approximately 80.0% ($n = 1,546$) of study participants showed their cigarette pack and about 20.0% ($n = 397$) provided information about the usual brand's characteristics. Using this method, we determined whether the cigarette brand currently smoked by the respondent was menthol or nonmenthol.

Individual level measures

Demographics and exposure to secondhand smoke were measured by using CAPI. Most interviews were conducted in the home. Race and ethnicity were based on self-report. Age at interview was categorized as 20 to 24, 25 to 44, 45 to 64, or 65 or more years. Each respondent's weight in kilograms, measured by using a digital scale, was categorized as less than 60, 60 to 69.99, 70 to 79.99, and 80 kg or more. Reported exposure to secondhand smoke at home was based on the following questions posed to 1 member of the household (usually the head of the family or spouse of the head): "Does anyone who live here smoke cigarettes in the home?" The number of household members who smoked cigarettes in the home was categorized as 0 or 1 (not exposed or exposed).

Source for cigarette nicotine data

In addition to cigarette brand characteristics obtained directly from the cigarette pack or from the smoker's report, we obtained machine-generated nicotine levels from annual reports to the FTC (12). These were categorically coded in NHANES at the time of the UPC match, if any. FTC machine–determined levels were linked to each respondent's brand by first matching the brand name and characteristics provided by the participant to the brand characteristics (brand name, package type, and menthol) in the FTC listing of mainstream smoke yields by brand and variety (12). Respondent's brand was matched to the FTC data for the year of the NHANES interview or the most recent year available prior to the year of the NHANES interview (14). These were also augmented by the merging of data from the FTC (15). The augmented data contained secondary sources for brand nicotine in addition to brand name, length, filter, package type, strength, and menthol. A combined outcome was created by selecting the UPC outcome for each cigarette attribute, if a match with the UPC database occurred and there was useable data, otherwise the original NHANES determination was used. We conducted analyses using FTC nicotine levels as a continuous variable. For illustration purposes, we used 0.8 and 1.1 mg of FTC machine–measured nicotine levels.

Serum cotinine measurement

Biochemical determination of tobacco exposure was performed by measuring serum cotinine levels in blood specimens obtained by venipuncture in the MEC. The cotinine assay involved isotope dilution, liquid chromatography, and tandem mass spectrometry. Cotinine data are reported in nanograms per milliliter. The limit of detection (LOD) for this procedure was 0.015 ng/mL (16). No smoker in the study had serum cotinine concentrations below LOD.

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Statistical analysis

Statistical analysis was carried out in 2 stages.

Stage 1: Preadjustment and removal of nuisance variation. First, serum cotinine levels were adjusted for sources of nuisance variation within each of the 4 race/ethnicity times sex categories. Nuisance variables were as follows: time since last smoked (today), whether the respondent showed his/her cigarette pack (yes), and number of smokers in the home (only the respondent). We did not adjust for cigarettes smoked per day in stage 1, as this was the focus of the stage 2 analysis. Nonlinear and quadratic functions of age, sex, and body weight were also used to improve the adjustment for those not in the appropriate reference category. Predicted serum cotinine levels for respondent covariate combinations not in the reference categories were calculated by setting the covariates to these reference levels before calculating the predicted values. The ratio of predicted cotinine values for reference covariate levels to predicted cotinine values for observed covariate levels was calculated. Adjusted cotinine values were calculated by multiplying the observed cotinine values by this ratio. We also preadjusted for time since last cigarette. We preadjusted for the decay by using regression to predict within each race and sex what the cotinine would have been had they been measured on the day they smoked their last cigarette (i.e., today). Those results, for all adjustment factors, were generally consistent in the direction of the change in the coefficient signs across all 4 races by sex strata, which lends some additional internal validity to the approach. The amount of adjustment was data driven through the coefficient magnitude within each race and sex. The procedure simultaneously accounted for other factors such as age and body weight. The resulting models were adequately fit and highly consistent. People who smoked their last cigarette 3 to 5 days ago were excluded from the analyses because of considerably more variability in serum cotinine concentration than those who smoked the day blood was collected or the day before.

Stage 2: Exponential models for cigarettes per day by menthol brand status. In the second stage, nuisance-adjusted cotinine values were regressed on cigarettes per day and cigarette menthol status, controlling for FTC-measured nicotine levels, respondent body weight, and gender. Survey weights were used to adjust for differing probabilities of selection, nonresponse, and to adjust the sample to reflect the demographic distribution of the U.S. population. SAS was used for all analyses. We assessed the adequacy of the fit of the exponential regression models by using plots of the residuals versus the predicted values.

Determination of adjusted serum cotinine levels by the number of cigarettes smoked per day and menthol brand status involved fitting nonlinear exponential regression models of the form: $\ln(\text{adjusted cotinine} + 1.0) = \beta_0 - \beta_1 \exp(-\beta_2 X) + \text{error}$, where $\ln(\cdot)$ is the natural logarithm; X is the number of self-reported cigarettes smoked per day; β_0, β_1, and β_2 are parameters that describe the exponential relationship; and *error* is the residual error left unexplained by the model. This exponential equation models serum cotinine as a monotonically increasing function of the number of cigarettes smoked, with cotinine increasing at a decreasing rate toward an upper asymptote. The variable β_0 represents the upper bound (maximum achievable level) of ln(adjusted cotinine + 1.0) at the highest levels of daily smoking, and β_1 and β_2 work together to control the span and steepness curvature of how cotinine increases with daily consumption.

The base model, stratified by race (separate models were run by race), included the 3 parameters described above. After fitting the base model, 2 different covariate adjusted models were fit. Model 1 investigated the relationship between serum cotinine and cigarettes smoked per day after adjustment for FTC nicotine levels, body weight, and gender. Model 2 added cigarette menthol status to the model 1 variables.

In a preliminary investigation, we analyzed the data with and without the stage 1 adjustment and the models were similar, except that the stage 1 adjustment resulted in serum cotinine intercepts closer to the origin, as would be expected if all nuisance factors were accounted for when cigarettes per day is near 0.

Results

Table 1 shows the sociodemographic characteristics and the type of cigarettes smoked for white and black smokers. χ^2 tests of the association between race and sociodemographic and cigarette characteristics showed that the distributions were statistically different ($P < 0.01$) across the 2 racial groups. While white smokers had a similar proportion of men and women (51.8% men, 48.2% women), black smokers were predominantly men (61.9%). Also, age distribution differences were observed among smokers by race. Only 19.5% of white smokers were living below the poverty level, whereas about 31.7% of black smokers were living below the poverty level. Differences in body weight were also observed; a higher proportion of black smokers (50.3%) weighed 80 kg or more compared with 43.4% of white smokers. A higher proportion of black smokers were exposed to secondhand smoke in the home (78.9%) compared with white smokers (69.6%).

As expected, only a minority (19.4%) of the sample of white smokers smoked menthol cigarettes, whereas the majority (73.9%) of black smokers smoked a menthol brand. Accordingly, black smokers smoked cigarette brands that were on an average higher in FTC-measured nicotine than white smokers, as the specific menthol brands smoked by black smokers (e.g., Newport) had higher FTC machine–determined deliveries of nicotine than nonmenthol brands smoked by white smokers (e.g., Marlboro Light). About 3 of 4 white and black smokers smoked their last cigarette the same day their blood was

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Table 1. Study sample distribution (not weighted) of 1,943 smokers aged 20 years or older

	χ^2 test of association between race And characteristic	No. of non-Hispanic			
		Whites ($n = 1,379$)		Blacks ($n = 564$)	
		n	%	*n*	%
Sex					
Male	$P < 0.01$	714	51.8	349	61.9
Female		665	48.2	215	38.1
Age, y					
20–24		183	13.3	47	8.3
25–44	$P < 0.01$	567	41.1	226	40.1
45–64		484	35.1	226	40.1
65+		145	10.5	65	11.5
Poverty level					
At/Above	$P < 0.01$	1,057	80.5	362	68.3
Below		256	19.5	168	31.7
Weight, kg					
00–60		232	17.1	73	13.3
60–70	$P < 0.01$	268	19.7	83	15.1
70–80		270	19.9	117	21.3
80+		590	43.4	276	50.3
Exposure to secondhand smoke in the home					
No exposure	$P < 0.01$	417	30.4	117	21.1
Exposed		956	69.6	438	78.9
Type of cigarettes smoked					
Menthol	$P < 0.01$	264	19.4	413	73.9
Nonmenthol		1,095	80.6	146	26.1
FTC nicotine, mg (nic)					
nic < 0.8		278	23.5	28	5.4
0.8≤nic<1.1	$P < 0.01$	526	44.4	132	25.6
nic ≥ 1.1		380	32.1	356	69.0
Smoked last cigarette					
Today	$P = 0.58$	1,058	76.7	426	75.5
Yesterday		321	23.3	138	24.5
Smokes everyday or some days					
Everyday	$P = 0.27$	1,259	91.3	506	89.7
Some days		120	8.7	58	10.3
CPD on days smoked					
1–3		74	5.4	64	11.4
4–9	$P < 0.01$	191	13.9	200	35.5
10–16		408	29.6	160	28.4
17+		706	51.2	140	24.8

drawn. About 9 of 10 white and black smokers reported smoking every day. Finally, black smokers smoked fewer cigarettes per day than white smokers.

Figure 1 illustrates cumulative percentages of FTC-measured nicotine levels of the cigarettes smoked by white and black smokers. Menthol cigarettes smoked by black smokers (1.24 mg) were on an average higher in FTC nicotine levels to the menthol cigarettes (0.94 mg) smoked by white smokers ($P < 0.01$). Nonmenthol cigarettes smoked by black smokers (1.01 mg) were on an average higher in FTC nicotine levels to the nonmenthol cigarettes (0.88 mg) smoked by white smokers ($P < 0.01$). Finally, for white smokers, the menthol cigarettes (0.94 mg) they smoked were on an average higher in FTC nicotine levels than the nonmenthol cigarettes (0.88 mg) they smoked ($P < 0.05$).

Unadjusted analysis shows that at the lowest cigarette smoking level (1–3 cpd), black smokers had geometric mean serum cotinine concentrations (94.4 ng/mL) almost 3 times that of white smokers (32.7 ng/mL; Table 2). The median number of cigarettes smoked in whites was 18 and the median in blacks was 10 (results not shown).

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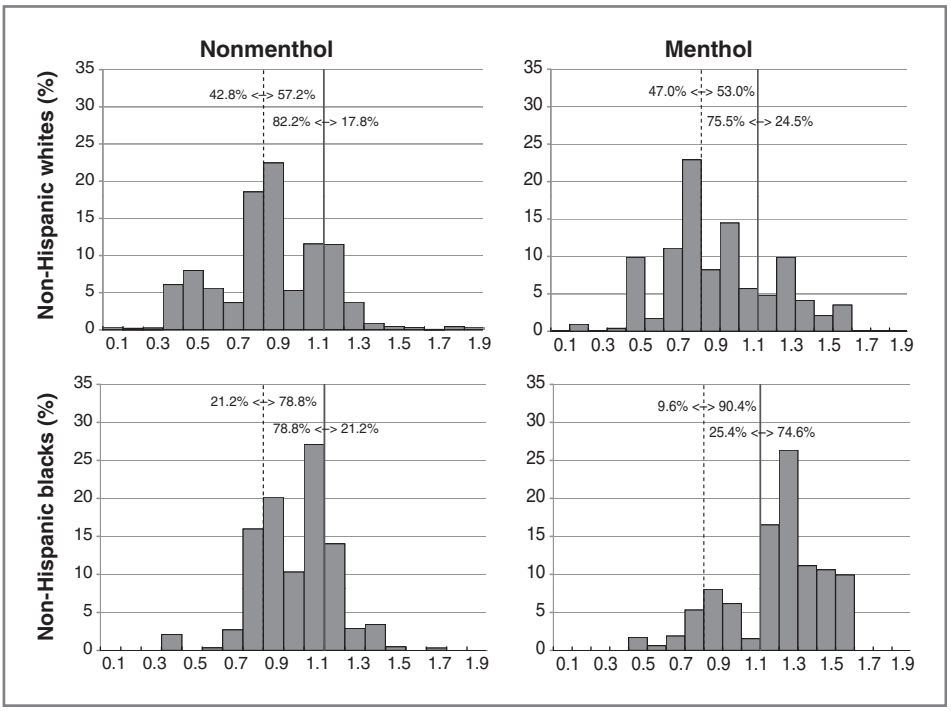

Figure 1. FTC-measured nicotine levels of nonmenthol and menthol brands smoked by non-Hispanic white and non-Hispanic black cigarette smokers, NHANES 2001 to 2006. Note: the lines in the graphs were chosen to roughly intersect the middle of the distributions of nicotine on the 4 groups (2 races × menthol status yes/no). The range 0.8 to 1.1 at which lines were drawn roughly represent the middle ground for all of the graphs.

Table 3 shows statistical comparisons of model-adjusted serum cotinine levels between white and black smokers. Comparisons in predicted cotinine levels were made at each combination of the following covariates: FTC 0.8 mg and FTC 1.1 mg of cigarette nicotine, menthol, and non-menthol cigarettes; body weights of 150 lbs and 200 lbs; and cigarettes smoked per day categories of 5, 10, 15, 20, and 25. Model 1 in Table 3 fits nicotine, sex, and body weight as a function of cpd before any effects of menthol are considered. For most combinations of the covariates, blacks' predicted cotinine levels exceeded whites' predicted cotinine levels, more so for females than males. Model 2 adds menthol main effects and menthol × nicotine interaction terms to model 1. Blacks' predicted cotinine levels were still greater than whites' predicted cotinine levels, although there were somewhat fewer combinations where these differences were statistically significant.

We also used models 1 and 2 to test whether the addition of the menthol variables significantly improved the fit of the model. The addition of the menthol variables, after controlling for nicotine, sex, and body weight, was not a significant predictor of serum cotinine within either white ($F = 0.5$, $P = 0.79$) or black smokers ($F = 1.9$, $P = 0.10$). Also, we did not find that smoking a menthol brand has an effect on serum cotinine concentration among white or black adult smokers even when we did not control for FTC machine–determined deliveries of nicotine levels ($P > 0.05$).

Discussion

Using an exponential model that takes into account individual smoker characteristics (age, sex, body weight) and smoking behavior (cpd), we found no differences in serum cotinine concentration for white or black smokers

Table 2. Geometric mean serum cotinine levels (ng/mL) among 1,943 smokers aged 20 years or older by race/ethnicity and cigarettes smoked per day, NHANES 2001–2006

Cigarettes per day	Non-Hispanic white				Non-Hispanic black				*N*
	N	Geometric mean	Lower CL	Upper CL	*N*	Geometric mean	Lower CL	Upper CL	
1–3	74	32.7	23.2	46.1	64	94.4	72.2	123.6	104
4–9	191	100.9	86.9	117.2	200	194.6	177.9	212.9	135
10–16	408	195.3	184.2	206.9	160	263.9	243.6	285.9	83
17+	706	239.7	228.4	251.5	140	292.2	265.6	321.4	54

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Table 3. Comparisons of non-Hispanic white versus non-Hispanic black model–predicted serum cotinine levels, by sex, FTC nicotine, cigarette menthol, body weight, and cigarettes smoked per day: NHANES 2001–2006

Model[a]	Sex[b]	FTC nicotine, mg[c]	Menthol[b]	Body weight, lbs[b,d]	Cigarettes per day	Non-Hispanic white–predicted cotinine (N = 1,145)	Non-Hispanic black–predicted cotinine (N = 486)	Difference (non-Hispanic white–black)	Significance[e]
1	F	0.8	x	150	5	105.4	202.1	–96.7	*
			x	150	10	178.1	275.7	–97.7	*
			x	150	15	203.9	288.8	–85.0	*
			x	150	20	211.1	290.9	–79.7	*
			x	150	25	213.0	291.2	–78.1	*
			x	200	5	94.7	197.8	–103.2	*
			x	200	10	148.0	266.7	–118.7	*
			x	200	15	175.0	276.0	–100.9	*
			x	200	20	186.5	277.0	–90.6	*
			x	200	25	191.0	277.2	–86.2	*
		1.1	x	150	5	114.5	189.8	–75.3	*
			x	150	10	186.3	279.5	–93.2	*
			x	150	15	210.6	311.3	–100.7	*
			x	150	20	217.3	320.8	–103.6	*
			x	150	25	219.0	323.5	–104.5	*
			x	200	5	104.7	184.0	–79.2	*
			x	200	10	157.2	276.6	–119.4	*
			x	200	15	182.5	301.7	–119.3	*
			x	200	20	192.8	307.4	–114.6	*
			x	200	25	196.7	308.6	–111.9	*
	M	0.8	x	150	5	162.3	198.0	–35.8	
			x	150	10	239.4	261.5	–22.1	
			x	150	15	246.9	275.4	–28.5	
			x	150	20	247.5	278.0	–30.5	
			x	150	25	247.6	278.5	–31.0	
			x	200	5	133.5	190.1	–56.6	*
			x	200	10	211.4	253.0	–41.6	*
			x	200	15	222.9	263.4	–40.5	*
			x	200	20	224.3	265.0	–40.7	*
			x	200	25	224.5	265.2	–40.7	*
		1.1	x	150	5	170.4	196.5	–26.1	
			x	150	10	246.5	265.1	–18.5	
			x	150	15	253.7	294.0	–40.3	*
			x	150	20	254.3	304.7	–50.5	*
			x	150	25	254.3	308.5	–54.2	*
			x	200	5	141.3	182.2	–40.9	*
			x	200	10	218.2	260.1	–41.9	*
			x	200	15	229.2	285.7	–56.6	*
			x	200	20	230.4	293.0	–62.5	*
			x	200	25	230.6	294.9	–64.3	*
2	F	0.8	N	150	5	109.3	201.8	–92.6	*
			N	150	10	180.9	304.0	–123.1	*
			N	150	15	204.1	322.4	–118.2	*
			N	150	20	210.1	325.1	–115.0	*
			N	150	25	211.5	325.5	–113.9	*
			N	200	5	97.4	211.8	–114.4	*
			N	200	10	151.5	297.5	–146.0	*

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Table 3. Comparisons of non-Hispanic white versus non-Hispanic black model–predicted serum cotinine levels, by sex, FTC nicotine, cigarette menthol, body weight, and cigarettes smoked per day: NHANES 2001–2006 (Cont'd)

Model[a]	Sex[b]	FTC nicotine, mg[c]	Menthol[b]	Body weight, lbs[b,d]	Cigarettes per day	Non-Hispanic white–predicted cotinine (*N* = 1,145)	Non-Hispanic black–predicted cotinine (*N* = 486)	Difference (non-Hispanic white–black)	Significance[e]
			N	200	15	177.1	306.7	–129.5	*
			N	200	20	187.2	307.5	–120.3	*
			N	200	25	190.9	307.6	–116.7	*
			Y	150	5	93.5	196.9	–103.4	*
			Y	150	10	170.3	252.5	–82.2	*
			Y	150	15	203.4	276.7	–73.3	*
			Y	150	20	214.4	286.2	–71.8	*
			Y	150	25	217.8	289.8	–72.0	*
			Y	200	5	81.9	177.4	–95.6	*
			Y	200	10	134.9	249.3	–114.5	*
			Y	200	15	168.0	269.5	–101.6	*
			Y	200	20	185.0	274.4	–89.4	*
			Y	200	25	193.0	275.5	–82.5	*
		1.1	N	150	5	117.9	162.1	–44.3	
			N	150	10	188.2	280.6	–92.4	*
			N	150	15	209.5	326.2	–116.7	*
			N	150	20	214.7	340.0	–125.3	*
			N	150	25	215.9	343.9	–128.0	*
			N	200	5	106.6	176.2	–69.6	*
			N	200	10	159.9	293.8	–133.9	*
			N	200	15	183.4	320.5	–137.1	*
			N	200	20	192.2	325.3	–133.2	*
			N	200	25	195.3	326.2	–130.9	*
			Y	150	5	107.1	185.8	–78.8	*
			Y	150	10	182.7	254.3	–71.6	*
			Y	150	15	214.3	285.1	–70.7	*
			Y	150	20	224.8	297.1	–72.3	*
			Y	150	25	228.1	301.7	–73.6	*
			Y	200	5	98.1	174.3	–76.2	*
			Y	200	10	149.5	256.8	–107.3	*
			Y	200	15	180.1	280.3	–100.2	*
			Y	200	20	195.6	285.8	–90.3	*
			Y	200	25	202.9	287.1	–84.3	*
	M	0.8	N	150	5	163.9	182.1	–18.2	
			N	150	10	238.5	274.7	–36.2	
			N	150	15	245.4	303.2	–57.8	
			N	150	20	245.9	310.5	–64.5	
			N	150	25	246.0	312.2	–66.2	
			N	200	5	134.9	185.9	–51.0	
			N	200	10	211.5	275.8	–64.3	*
			N	200	15	222.5	292.5	–70.0	*
			N	200	20	223.8	295.1	–71.3	*
			N	200	25	223.9	295.5	–71.6	*
			Y	150	5	152.2	283.3	–131.1	*
			Y	150	10	242.4	282.3	–39.9	
			Y	150	15	253.3	281.6	–28.3	
			Y	150	20	254.3	281.2	–26.9	

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Table 3. Comparisons of non-Hispanic white versus non-Hispanic black model–predicted serum cotinine levels, by sex, FTC nicotine, cigarette menthol, body weight, and cigarettes smoked per day: NHANES 2001–2006 (Cont'd)

Model[a]	Sex[b]	FTC nicotine, mg[c]	Menthol[b]	Body weight, lbs[b,d]	Cigarettes per day	Non-Hispanic white–predicted cotinine (N = 1,145)	Non-Hispanic black–predicted cotinine (N = 486)	Difference (non-Hispanic white–black)	Significance[e]
			Y	150	25	254.4	280.9	–26.5	
			Y	200	5	121.7	191.9	–70.1	*
			Y	200	10	211.7	234.1	–22.5	
			Y	200	15	228.7	252.7	–24.0	
			Y	200	20	231.2	260.2	–29.1	
			Y	200	25	231.5	263.2	–31.7	
		1.1	N	150	5	171.6	154.0	17.6	
			N	150	10	244.1	233.1	11.0	
			N	150	15	250.4	282.0	–31.6	
			N	150	20	250.9	307.9	–57.0	
			N	150	25	250.9	320.6	–69.7	*
			N	200	5	142.4	152.3	–9.9	
			N	200	10	217.1	255.1	–38.0	
			N	200	15	227.2	295.6	–68.4	*
			N	200	20	228.3	308.3	–80.0	*
			N	200	25	228.4	312.1	–83.6	*
			Y	150	5	163.6	248.0	–84.3	*
			Y	150	10	254.2	264.4	–10.2	
			Y	150	15	265.1	275.0	–9.9	
			Y	150	20	266.1	281.6	–15.5	
			Y	150	25	266.2	285.8	–19.6	
			Y	200	5	132.6	180.2	–47.5	*
			Y	200	10	222.6	235.0	–12.3	
			Y	200	15	239.5	259.8	–20.3	
			Y	200	20	242.0	269.9	–28.0	
			Y	200	25	242.3	273.8	–31.5	

[a]Model 1: cpd + continuous nicotine + sex + continuous weight. Model 2: Model 1 terms + menthol + (nicotine × menthol) potential effect modification terms. (Both models were stratified by race/ethnicity.)
[b]"x" means the factor was not considered in the model.
[c]Nicotine comparisons at 0.8 and 1.1 were chosen according to common-overlap considerations (Fig. 1).
[d]Weight comparisons at 150 and 200 were chosen to roughly cover the middle half of all race × sex distributions (data not shown).
[e]Asterisks (*) indicate $P < 0.05$ for H0: non-Hispanic white = non-Hispanic black–predicted cotinine geometric means; the standard errors of prediction were manually combined to create a comparison standard error (not adjusted for design effects and treated as if independent across race/ethnicity, which may err on the side of too many falsely significant results for each test run at the 5% level of significance).

when using UPC-assessed menthol versus nonmenthol brands. The potential health risks associated with menthol flavoring of cigarettes is a topic of considerable interest, in part because menthol cigarettes are disproportionately preferred by black smokers. It has been proposed that the anesthetic and cooling sensation properties of menthol allow smokers of menthol cigarettes to inhale more smoke from each cigarette than smokers of nonmenthol cigarettes (17, 18). It has been hypothesized that the resulting higher smoke exposure over time results in higher smoking-related diseases among smokers of menthol cigarettes (19). As previously stated, our results showed that a higher percent of black smokers smoked a menthol cigarette brand and cigarettes with a higher FTC nicotine level than white smokers. Also, on an average, the specific menthol brand and subbrands black smokers smoked had a higher FTC nicotine levels than the nonmenthol brands (the preferred type of cigarette smoked by whites) smoked by white smokers.

At least 2 previous studies have found higher cotinine concentrations among smokers of mentholated cigarettes (20, 21), whereas others did not (22–27). In a recent study

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of nicotine and nitrosamine metabolites in smokers, Muscat and colleagues findings suggested that "menthol does not affect biological exposure to tobacco smoke constituents," although it may inhibit detoxification of the lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL; ref. 25). In our study, we found no evidence of higher serum cotinine concentrations among smokers (white or black) of menthol cigarettes compared to smokers of nonmentholated cigarettes when smoking the same number of cigarettes smoked per day. Among black smokers specifically, we found no differences in serum cotinine concentration between smokers of menthol and nonmenthol cigarettes, nor in the number of cigarettes smoked per day even after adjustment for the FTC nicotine yield (9.1 vs. 9.3, respectively; results not shown); likewise, we found no differences in the number of cigarettes smoked per day by whites who smoked mentholated or nonmentholated cigarettes (results not shown). In contrast, in a cross-sectional study of 19,545 smokers hospitalized for non–tobacco-related diseases, Muscat and colleagues noted that among both whites and blacks, menthol brands were more often listed by smokers of 1 pack per day or less, compared with heavier smokers (28). In particular, black and white smokers of menthol cigarettes did not have higher mean serum cotinine concentrations than smokers of nonmenthol cigarettes. If serum cotinine concentration is, in fact, a proxy for overall smoke exposure, our findings provide no evidence of higher exposure to overall smoke among smokers of menthol brands. This conclusion would be strengthened by data showing no effect of cigarette mentholation status on smoking topography and by patterns of cigarette consumption by mainstream smoke menthol levels.

A key question that remains to be answered is what accounts for racial differences in serum cotinine concentrations between black and white smokers if smoking a menthol or nonmenthol brand does not explain the difference? (7) When looking at racial differences by FTC-measured nicotine levels, levels that in fact are highly correlated with menthol cigarette brands, we found that black smokers consistently had higher serum cotinine concentrations at a cpd of 5 of less than white smokers regardless of the FTC-measured nicotine level (0.8 or 1.1 mg). In a study conducted by Pérez-Stable and colleagues in a clinical investigation of smokers who smoked half to one pack per day, they concluded that the higher levels of serum cotinine concentrations in black smokers compared with white smokers was explained by higher nicotine intake (30% more) per cigarette and slower cotinine clearance in the black subjects (29). The NHANES data we used for our study showed a much higher intake of nicotine per cigarette in black smokers, especially at the lower levels of cigarettes smoked per day. We found that at lower levels of cigarette smoking (1–3 and 4–9 cpd), black smokers had serum cotinine levels almost 200% to 300% higher than that of white smokers, and at higher smoking levels ($\geq$10 cpd), they were 22% to 35% higher in black smokers than white smokers. It is important to note that serum cotinine concentration increased rapidly up to 10 to 15 cpd, more so among black smokers than white smokers, before leveling off at approximately 15 to 20 cpd. Muscat and colleagues (30) pointed out that this plateau effect partly explains why the frequency of daily smoking is only moderately correlated with cotinine levels. Because the smokers studied by Pérez-Stable and colleagues all smoked one half pack or more per day, it is unknown whether there are even greater racial differences in intake or clearance at low levels of smoking that would account for our findings. It is possible that other factors such as extreme inhalation at the lowest levels of cigarette smoking (<10 cpd) and time to first cigarette after waking may explain some of these differences. The higher percent of blacks in NHANES who were at the poverty level might explain the much higher intake smoke, where persons of low income need to maximize their nicotine intake per cigarette. Finally, more research needs to be conducted to assess why black females appear to be different from white females in serum cotinine concentration.

Our study has limitations. As mentioned, we were not able to measure the actual concentration of menthol on each cigarette brand smoked by smokers in this study, although the difference in mainstream smoke menthol concentration between menthol and nonmenthol brands is an order of magnitude greater than the between-brand difference for any 2 menthol brands (13). Still, our study assessed the relation between smoking a menthol brand and serum cotinine levels and not the relation of the amount of menthol in each cigarette brand and serum cotinine levels. Second, cigarette brands, including menthol brands, may have changed over time in the amount of menthol flavoring or nicotine they have in it; thus, our study is specific to brands used by smokers in the United States between 2001 and 2006.

Our study also has some methodologic advantages over previous population-or laboratory-based studies. First, our study sample represents the U.S. noninstitutionalized population, including smokers, and thus we were able to assess serum cotinine concentrations among smokers in the United States who smoked their cigarettes under natural smoking conditions. Second, the information we collected on cigarette brand was collected first by the interviewer looking at the pack used by the smoker and then verified using the specific UPC bar code information on the side of the cigarette pack, allowing accurate ascertainment of whether the brand was menthol or nonmenthol. In contrast, self-reports of types of cigarettes smoked are subject to bias (31).

The dangers of smoking have been known for decades (32, 33), and during that period, many policy options for reducing those dangers have been developed (34, 35). The focus on tar, nicotine, and carbon monoxide testing after the 1964 report on smoking and health (32) led to multiple product changes (36), but these product changes did not promote public health.

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(37) The FDA now has the authority to regulate cigarette additives and labels, smokeless tobacco, and roll your own tobacco and the potential to change the landscape of accessibility to cigarettes and other tobacco products. FDA can also require changes in the composition of tobacco products, reduce the amount of nicotine in cigarettes, and require changes in other potentially harmful ingredients to reduce exposure to toxic and carcinogenic emissions in people who continue to use the products and nonusers exposed to the smoke of some of these products. The FDA is now examining options for regulating menthol cigarettes; although, there is no statutory requirement for FDA to make a decision or take action on menthol cigarettes. Formulation and implementation of product-based policies require further studies like ours as part of an effort to improve our ability to predict metabolic, behavioral, and health consequences of changes in tobacco product design.

Disclosure of Potential Conflicts of Interest

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Received December 22, 2010; revised March 10, 2011; accepted March 13, 2011; published OnlineFirst March 23, 2011.

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