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Smokeless Tobacco Use and Salivary Cotinine Concentration

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Abstract

The objective of the current study was to examine demographic, tobacco-related, and psychosocial factors associated with cotinine concentration in a group of 256 male smokeless tobacco (ST) users living in the Ohio Appalachian region. Participants completed a survey that included questions on: 1) current and past tobacco use behaviors; 2) demographics; 3) tobacco dependence; 4) decisional balance; 5) health behaviors; and 6) perceived stress and depressive symptoms. Saliva samples were obtained for measurement of cotinine. The variables related to salivary cotinine concentration in the multiple regression model were age, marital status, occupation, quit attempts, years of ST use, and tobacco dependence score (adjusted $R^2 = 0.24$). Among the 199 snuff only users, cotinine concentration was positively related to age, being divorced/widowed/separated, no quit attempts in the previous year, dependence score, and brand of snuff (adjusted $R^2 = 0.29$). This is one of the largest studies to examine influences beyond topography on cotinine concentration in a group of rural ST users. These findings suggest that smokeless tobacco users and smokers share some similarities with respect to tobacco dependence.

Keywords

Cotinine; smokeless tobacco; dependence

Introduction

Cotinine is the major metabolite of nicotine and has become the standard marker of nicotine exposure (Jarvis et al., 1987). However, data also indicate that it is a marker of nicotine dependence. The Society for Research on Nicotine and Tobacco (SRNT) Subcommittee on Biochemical Verification published guidelines for use of biomarkers in tobacco control studies (SRNT, 2002), and one of the recommendations is to use cotinine as an indicator of addiction severity. However, it should be noted that the basis for this recommendation are results obtained from the literature on smoking, not smokeless tobacco use. Limited information exists on the correlates of cotinine among rural male smokeless tobacco (ST) users, a group with a high prevalence of use. Among ST users, cotinine concentration has been positively associated with age, years of ST use, dips per day, duration of a dip, and total dipping time (Lemmonds et al., 2005; Hatsukami et al., 1988). In general, most of the studies that have examined factors

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associated with cotinine concentration among ST users have been small and primarily focused on characterizing topography using diaries (Lemmonds et al., 2005; Hatsukami et al., 1988). As a logical extension of these studies, a cross-sectional field study that allows for an estimation of the usual concentration of cotinine and examination of additional factors is warranted. Demographic and psychosocial factors associated with cotinine concentration among ST users have not been reported in the literature. Knowledge of such relationships is important when developing effective cessation interventions (Fiore et al., 2000).

The objectives of the analyses presented in this paper were to describe demographic, tobacco-related, and psychosocial factors associated with baseline cotinine concentration in a group of 256 men enrolled in a ST cessation study. This study adds to the literature on the correlates of cotinine and dependence among ST users by reporting data that were collected from a large group of rural Appalachian residents using field study methodology.

Methods

Setting

This study was conducted in two Ohio Appalachia counties: Ross County and Muskingum County. The Ohio Appalachian population is medically underserved and experiences high rates of unemployment, poverty, educational disparities, and poor health (Friedell et al., 1998). Poverty is estimated at 13.5% (10.6% in Ohio) and 22% of the residents have not attained a high school diploma (17% in Ohio). With respect to health insurance, 14.6% of Appalachian residents are estimated as uninsured (11.7% in Ohio) and, among those insured, 65.5% do not have adequate coverage (59.7% in Ohio) (Dorsky et al., 2002). Cancer mortality rates are high, particularly for tobacco-related cancers (MMWR, 2002). Smokeless tobacco use is estimated at 9.5% in Ohio Appalachia (3.6% in Ohio) (Renaud et al., 2006) and there is a long history of tobacco farming in the entire Appalachian region. Approximately 97% of all burley tobacco is grown in Appalachia (Wood, 1998) and in Ohio tobacco farming occurs in 16 of the Appalachian counties. Consequently, the social norms surrounding tobacco use are influenced by the reliance on tobacco for economic well-being (Denham and Rathbun, 2005).

Subjects

The study protocol and research procedures were approved by The Ohio State University Institutional Review Board. The subjects included in this analysis were enrolled in a smokeless tobacco cessation study that involved an appointment with a dentist at a rural health department clinic. After receiving a brief oral examination and strong advice from the dentist to quit using ST, the participant was assigned to either lay-led counseling with nicotine replacement therapy or usual-care control. All men were recruited through ad placement at community agencies in the two Appalachian Ohio counties. Eligible participants were male county residents, aged 18 and older, who were daily users of ST with no contraindications for nicotine replacement therapy (NRT) use.

Measures

The baseline questionnaire consisted of the following sections: 1) current and past tobacco use behaviors; 2) demographics; 3) dental health; 4) tobacco dependence; 5) decisional balance; 6) health behaviors; and 7) perceived stress and depressive symptoms. The tobacco use section captured data about use of various forms of tobacco, including snuff, chewing tobacco, and cigarettes. Ever use was measured, as well as details about current use such as dips per day, duration of each dip, time between dips, and type of ST used most often. Tobacco dependence was measured with a modification of the Fagerström Test of Nicotine Dependence (FTND) developed by Severson & Gordon (1997), called the Smokeless Tobacco Dependence Scale. The range of this scale is 2–9, with a higher number implying greater tobacco dependence. The

psychometric properties of the ST dependence scale have been examined and reported (Ferketich et al., 2007). Briefly, the correlation between the total score and salivary cotinine concentration was moderate among the ST only users (r = 0.34), whereas it was lower (r = 0.19) among the ST + cigarette users. Among ST only users, the coefficient alpha for the scale was 0.40; however, it was higher among the ST + cigarettes group (alpha = 0.61). Decisional balance was measured using a modification of the smoking decisional balance scale (Velicer et al., 1985). Briefly, this scale consists of two 10-item subscales: a pro subscale evaluating positive aspects of tobacco use and a con subscale evaluating negative aspects. Decisional balance is calculated as the pro score minus the con score; thus higher scores indicate more favorable views of tobacco use. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression (CES-D) scale, a 20-item questionnaire (Radlor, 1977). Stress was assessed with the 14-item Perceived Stress Scale (Cohen et al., 1982). For both of these scales, higher scores indicate more symptoms (i.e. more symptoms of depression and higher levels of perceived stress, respectively).

A saliva sample was also obtained from each man at baseline. Saliva was collected and was processed in the county health department, refrigerated at 4° C, and brought weekly to our laboratory for storage at −85°C until analyses were conducted. Cotinine was extracted from saliva using a gas chromatography/mass spectrometry (GC-MS) technique (Hariharan and VanNoord, 1991).

Statistical analysis

The objective of the analysis was to describe the factors associated with cotinine concentration in ST users. The first part of the analysis involved calculating descriptive statistics, including the mean, standard deviation, median, and range of cotinine concentration, by participant characteristics. For continuous measures, such as scores on the scales, scatterplots were examined and a correlation coefficient was estimated to determine the linear relationship between the score and cotinine concentration. If a linear relation was not apparent, then the variable was categorized. Additionally, if a variable was not truly continuous in nature in the sense that a one-unit increase has the same meaning over the range of possible values (e.g. quit attempts), then an ordinal variable was created. A linear regression model was fit to the data to determine which factors were significantly related to salivary cotinine among all ST users. A similar analysis was performed after limiting the data set to snuff only users. The method of forward selection was used for inclusion of variables and the significance level was set to 0.05; variables were not removed if the p-value increased following inclusion of other covariates. The two model assumptions, normality and equal variances of the residuals, were examined. Transformations, such as the natural log or square root transformation, were applied to the cotinine data when necessary to meet the assumptions.

Results

A total of 256 men completed the baseline survey. The average age of the sample was 34 years and the median cotinine concentration was 460 ng/mL (range 17–2469 ng/mL). Table 1 contains the frequency distributions for the demographic characteristics of the sample. Overall, it was a group with a low socioeconomic status: 14.5% had not received a high school diploma, 28.1% were unemployed, 28.9% had an income under $25,000, and only 63.7% had private health insurance. The majority of participants (86.7%) spent the first 18 years of their life in the Appalachian region. Simple linear regression models were fit to the data to estimate the association between each demographic variable and cotinine concentration. The model assumptions were not met; therefore the results are presented for the square-root transformed cotinine data, since this transformation resulted in residuals that more closely met the model

assumptions. Being divorced or widowed or separated, working full time, and being a skilled laborer were associated with significantly higher salivary cotinine concentration.

With respect to tobacco use characteristics (Table 2), 24.2% of the men were under age 10 when they started using ST regularly, 31% reported using ST for more than 20 years, 15.6% smoked in addition to daily ST, 87.9% used snuff only, and 57.1% had made at least one quit attempt in the past year. A small percentage of men reported leaving ST in over night (8.4%) and almost half (45.3%) reported that the time between consecutive dips was 30 minutes or less. Among the snuff users, the three most popular brands were Copenhagen (40%), Skoal (28.4%), and Timberwolf (15.8%). On average, snuff users consumed 4.6 cans per week and each dip remained in the mouth for 70 minutes. Cotinine concentration was positively related to years of ST use, no quit attempts in the past year, a shorter time between dips, and the tobacco dependence score. Additionally, among snuff only users, mean cotinine concentration was higher among men who used Red Seal and Copenhagen.

Results concerning the continuous variables (age, psychosocial scale variables, and tobacco dependence score) are listed in Table 3. Age and the tobacco dependence score were significantly and positively correlated with cotinine concentration. Additionally, all three psychosocial variables were significantly associated with cotinine concentration; however, the correlation coefficients were small in magnitude. The large sample size likely contributed to the significant result.

The multiple regression model results are presented in Table 4. The variables that were included in the overall final model were age, marital status, occupation, quit attempts, tobacco dependence score, and CES-D score. Cotinine concentration was positively related to being divorced/widowed/separated (compared to being single or married), having a skilled labor occupation (compared to professionals), having no quit attempts in the previous year, having a higher tobacco dependence score, and having a lower CES-D score. The adjusted R^2 from the model was 0.27 and the diagnostics performed did not suggest problems with outliers or influential observations. Among the 199 snuff only users, cotinine concentration was positively related to age, no quit attempts, and tobacco dependence score, and negatively related to CES-D score (Table 5). Brand of snuff was also related to cotinine concentration in this model. The adjusted R^2 was 0.36 and diagnostics indicated a good fit.

Discussion

To our knowledge, this is one of the largest studies to examine influences beyond tobacco use characteristics on cotinine concentration in a group of ST users. Another unique feature of this study is the focus on rural ST users. While several demographic, social, and psychosocial variables were related to cotinine concentration in the univariate analyses, only age, occupation, marital status, and CES-D score were retained in the final model that included all ST users. With respect to occupation, men who worked as skilled laborers had a significantly higher cotinine concentration compared to men in professional occupations. Occupation has not been previously associated with smokeless tobacco use; however, it has been related to smoking in several studies, with laborers or blue-collar occupations smoking at higher rates compared to professionals (Shavers et al., 2005). While employment status was not retained in the final model, it was significant in the univariate model with a higher cotinine concentration among employed men. It is possible that men who work full-time are using more ST because smoking is prohibited at the worksite. Recent data from the Ohio Adult Tobacco Survey suggest that 69% of Appalachian residents report having official policies that ban smoking in public/common areas at their worksite and 75% report having policies that completely ban smoking in work areas (Renaud et al., 2006). Marital status was also retained in the final model and the results indicated that men who were single or married had a significantly lower cotinine

concentration compared to men who were divorced, widowed, or separated. From studies reported in the smoking literature it appears as though marital disruption is related to tobacco consumption and an inability to quit (Nystedt, 2006), and being married is associated with greater success at cessation among men (Broms et al., 2004).

Years of tobacco use, quit attempts in the previous year, and time between dips were significantly related to cotinine concentration in the univariate models; however, only quit attempts remained in the final model. Hatsukami and colleagues reported that the number of dips per day, the average duration of a dip, the total duration of ST use in a day, and the mean inter-dip interval were significantly related to cotinine concentration in a group of 56 male Copenhagen users (Hatsukami et al., 1988). In a later study, only average total daily dip duration was related to cotinine in a group of 54 male ST users (Lemmonds et al., 2005).

Similar associations were found among snuff only users, although occupation and marital status were not retained in the final model and snuff brand was significantly associated with cotinine concentration. Red Seal® and Copenhagen® users had the highest concentration of cotinine, followed by the other brands. The men who used these two brands were longer-term ST users in general, compared to the men who used the other brands (81.3% versus 66.7% had used ST for more than 10 years). This result supports the work of Tomar and colleagues on brand switching (Tomar et al., 1995). They found that over time youth in their study switched from low nicotine snuff to high nicotine brands, specifically Copenhagen. In the current study, the association between snuff brand and cotinine concentration remained significant even after controlling for years of ST use.

In both models, the tobacco dependence scale score was associated with cotinine, which indicates that these two measures of dependency are significantly related among ST users. These results are consistent with the findings reported in the smoking literature (Heatherton et al., 1991). Decisional balance, however, was not strongly associated with cotinine concentration in the univariate model. While the direction of the correlation coefficient suggested that men who associated ST use with more cons than pros had lower cotinine concentrations, the magnitude of the coefficient was very small and it did not remain significant during model building.

Interestingly, the associations between cotinine and both depressive symptoms and stress were not strong in the univariate models; moreover, the correlation coefficients were negative. The CES-D score was significantly related to cotinine concentration in the final model; however, as before, the parameter estimate was negative which suggests higher cotinine concentrations among men with lower CES-D scores (i.e. fewer symptoms of depression). These findings for depressive symptoms and perceived stress are contrary to those from the smoking literature, where both variables are associated with higher levels of tobacco dependence (John et al., 2006; Hu et al., 2006). Thus, in this cohort of male ST users, it does not appear as though more tobacco is used among men who report higher levels of perceived stress and/or depressive symptoms. A possible explanation for our finding of no relation between cotinine concentration and both perceived stress and depressive symptoms is that the rewards are different for ST users compared to cigarette smokers. One reward, relaxation, is reported by approximately 75% of smokers; however, only 50% of ST users state that feeling calm or relaxed is a reason for using ST (CDC, 1994; Hatsukami and Severson, 1999).

The main limitation of this study relates to the sample of smokeless tobacco users. All of the users were male volunteers who were interested in joining a dental clinic tobacco cessation study and they were all from the Appalachian region in one state, which could limit the generalizability of the findings. A second limitation arises because there is a question of whether cotinine is a valid marker of dependence among ST users. The behavior of swallowing

tobacco juice, which was reported by approximately 34% of the men in this study, may artificially raise the concentration of cotinine among individuals who swallow the tobacco juices. Ebbert and colleagues reported that tobacco juice swallowing was related to a higher concentration of serum cotinine, but not to a higher concentration of serum nicotine (Ebbert et al., 2004). Thus, there may be some men who had a high cotinine concentration because of engaging in this behavior and not because they are more dependent on ST. The tobacco dependence questionnaire includes a question on swallowing tobacco juice; therefore this behavior was controlled for in the analysis as part of the total tobacco dependence score.

In conclusion, we noted several factors related to cotinine concentration among ST users. Some factors are similar to those reported in the cigarette smoking literature, including occupation, marital status, and tobacco dependence scale score. Depression and perceived stress were negatively associated with cotinine, and only the former was retained in the final model. This association deserves further examination as it is not consistent with studies published in the smoking literature. It is possible that ST use may operate differently with regard to affective states.

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Table 1

Demographic Characteristics of 256 Males in a Smokeless Tobacco Cessation Study

Variable	Number (%) in Sample	Mean ± SD Cotinine (ng/mL)	Median Cotinine (ng/mL)	Cotinine Range (ng/mL)
Educational Attainment				
< HS diploma	37 (14.5%)	483 ± 293	428	33–1264
HS diploma	96 (37.5%)	584 ± 414	485	17–2469
> HS diploma	123 (48.0%)	532 ± 341	440	29–2077
Marital Status***				
Divorced/Widow/Separated	46 (18.0%)	682 ± 520	544	17–1596
Married/Living with partner	161 (62.9%)	562 ± 319	479	73–2469
Never Married	49 (19.1%)	364 ± 254	277	33–1028
Employment Status*				
Full-time worker	173 (67.5%)	581 ± 364	478	17–2097
Part-time worker	11 (4.3%)	389 ± 264	284	118–937
Unemployed	72 (28.1%)	482 ± 368	387	33–2469
Occupation**				
Professional	40 (15.6%)	505 ± 322	434	29–1179
Skilled labor	128 (50.0%)	615 ± 361	524	53–2097
Unskilled labor	88 (34.4%)	460 ± 371	392	17–2469
Income				
≤ $25,000	72 (28.9%)	501 ± 403	443	38–2469
$25,001–50,000	95 (38.2%)	550 ± 344	460	21–2077
> $50,000	82 (32.9%)	590 ± 357	504	17–1596
Insurance Type				
Medicare	10 (3.9%)	632 ± 342	577	213–1264
Medicaid	34 (13.3%)	444 ± 296	409	33–1037
Private insurance	163 (63.7%)	566 ± 351	476	17–2077
Self-pay	49 (19.1%)	529 ± 446	394	92–2469
County Residence thru age 18				
Appalachian	222 (86.7%)	540 ± 371	460	17–2469
Non-Appalachian	34 (13.3%)	578 ± 327	461	38–1193

* $p < 0.05$ obtained from the nonparametric Wilcoxon Rank Sum test

** $p < 0.01$ obtained from the nonparametric Wilcoxon Rank Sum test

*** $p < 0.0001$ obtained from the nonparametric Wilcoxon Rank Sum test

Table 2

Tobacco Use Characteristics of 256 Males in a Smokeless Tobacco Cessation Study

Variable	Number (%) in Sample	Mean ± SD Cotinine (ng/mL)	Median Cotinine (ng/mL)	Cotinine Range (ng/mL)
Age at initiation				
≤ 10 years	62 (24.2%)	610 ± 387	491	33–2077
11–17 years	142 (55.5%)	516 ± 336	445	17–2097
18 or older	52 (20.3%)	546 ± 409	454	29–2469
Years of ST use***				
< 10	74 (29.0%)	409 ± 323	331	29–2097
10–19	102 (40.0%)	524 ± 232	466	17–1484
≥ 20	79 (31.0%)	697 ± 438	587	39–2469
Other tobacco use				
ST only	216 (84.4%)	560 ± 370	463	33–2097
ST + cigarettes	40 (15.6%)	460 ± 332	438	17–2469
Type of ST				
Snuff only	225 (87.9%)	542 ± 353	463	21–2469
Chew only	23 (9.0%)	578 ± 478	449	17–2077
Snuff + chew	8 (3.1%)	520 ± 362	397	211–1352
Quit attempts in past year***				
0	105 (42.9%)	672 ± 368	622	29–2077
≥ 1	140 (57.1%)	457 ± 345	395	17–2469
Time between dips**				
≤ 30 minutes	116 (45.3%)	620 ± 400	501	21–2077
> 30 minutes	140 (54.7%)	483 ± 321	417	17–2469
Leave dip in over night				
Yes	20 (8.4)	663 ± 530	627	38–2469
No	217 (91.6)	530 ± 328	459	21–2097
Snuff Only Users (n=190) **				
Type of snuff				
Copenhagen	76 (40.0%)	644 ± 381	618	78–2469
Skoal	54 (28.4%)	464 ± 339	343	21–1205
Timberwolf	30 (15.8%)	435 ± 241	422	76–937
Red Seal	15 (7.9%)	675 ± 273	676	262–1082
Other	15 (7.9%)	570 ± 377	443	154–1484

** $p < 0.01$ obtained from the nonparametric Wilcoxon Rank Sum test

*** $p < 0.0001$ obtained from the nonparametric Wilcoxon Rank Sum test

Table 3

Descriptive Statistics for Continuous Variables among 256 Males in a Smokeless Tobacco Cessation Study

Variable	Mean ± SD	Correlation with Cotinine
Age***	34.1 ± 11.1	0.36
Center for Epidemiologic Studies Depression Scale*	9.9 ± 7.8	−0.14
Perceived Stress Scale*	20.6 ± 8.3	−0.15
Decisional Balance (Cons of tobacco – Pros of tobacco)*	0.3 ± 8.7	−0.13
Tobacco Dependence Score***	5.3 ± 1.5	0.31
Snuff Only Users (n=190)		
Snuff consumption	4.6 ± 3.3 cans per week	0.10
Time each dip is in mouth	70 ± 67 minutes	0.12

* $p < 0.05$ from the Spearman Rank Correlation coefficient test

*** $p < 0.001$ from the Spearman Rank Correlation coefficient test

Table 4

Final Multiple Regression Model for Square-Root Transformed Cotinine in 256 Male Smokeless Tobacco Users

Variable	Parameter Estimate	S.E.	t-statistic	p-value
Demographic Characteristics				
Age	0.17	0.04	3.91	0.0001
Marital Status				
Divorced/Widowed/Separated	--			
Married	−2.36	1.19	−1.98	0.049
Single	−3.42	1.54	−2.22	0.028
Occupation				
Professional	--			
Skilled labor	2.92	1.24	2.35	0.020
Unskilled labor	1.63	1.38	1.19	0.236
Tobacco Use Characteristics				
Quit attempts in the past year				
0	--			
≥ 1	−3.27	0.91	−3.59	0.0004
Tobacco Dependence Score	1.27	0.29	4.41	<0.0001
Psychosocial Characteristic				
Center for Epidemiologic Studies Depression Scale	−0.14	0.06	−2.42	0.016

Adjusted $R^2 = 0.27$

Table 5

Final Multiple Regression Model for Square-Root Transformed Cotinine in 199 Male Snuff Tobacco Users

Variable	Parameter Estimate	S.E.	t-statistic	p-value
Demographic Characteristic				
Age	0.32	0.05	6.16	<0.0001
Tobacco Use Characteristics				
Quit attempts in the past year				
0	--			
≥ 1	−2.13	0.95	−2.23	0.027
Tobacco Dependence Score	1.44	0.32	4.46	<0.0001
Type of Snuff				
Red Seal	--			
Copenhagen	−2.04	1.73	−1.18	0.24
Skoal	−4.60	1.77	−2.60	0.010
Timberwolf	−4.21	1.91	−2.20	0.029
Other	−4.64	2.23	−2.07	0.039
Psychosocial Characteristic				
Center for Epidemiologic Studies Depression Scale	−0.17	0.06	−2.85	0.005

Adjusted $R^2 = 0.36$