

Research Article

Effect of Oral Snus and Medicinal Nicotine in Smokers on Toxicant Exposure and Withdrawal Symptoms: A Feasibility Study

Michael Kotlyar^{1,2}, Louise A. Hertsgaard¹, Bruce R. Lindgren³, Joni A. Jensen¹, Steven G. Carmella^{1,3}, Irina Stepanov³, Sharon E. Murphy^{1,3}, Stephen S. Hecht^{1,3}, and Dorothy K. Hatsukami^{1,3}

Abstract

Background: Smokeless, spitless tobacco products are being introduced and marketed as cigarette substitutes. Data are needed regarding how smokers interested in cessation would use these products, the levels of resultant toxicant exposure, and the feasibility of using these products as aids for tobacco cessation.

Methods: Smokers were randomized to receive Camel Snus ($n = 51$), Taboka ($n = 52$), or medicinal nicotine ($n = 27$) and required to quit smoking for 4 weeks. Measures of toxicant exposure and symptoms of craving and withdrawal were assessed prior to and during product use.

Results: Concentrations of exhaled carbon monoxide, urinary cotinine, urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), and urinary *N*'-nitrosonornicotine and its glucuronide (total NNN) were significantly (P values < 0.05) lower at the end of treatment in each group except for total NNN in those receiving Camel Snus ($P = 0.066$). A significant group \times time effect was observed for total NNAL concentrations ($P = 0.002$) with the decrease greatest in the medicinal nicotine group and smallest decrease in the Camel Snus group. No significant differences between groups were found in craving and withdrawal symptoms.

Conclusions: Enrolling smokers into a cessation study utilizing newer smokeless tobacco products is feasible. Camel Snus and Taboka use was not found to be superior to medicinal nicotine in reducing withdrawal symptoms but decreases in NNAL were smaller in users of Camel Snus.

Impact: This study demonstrates the feasibility of conducting a smoking cessation study utilizing these newer tobacco products. An appropriately powered study is needed to assess smoking cessation rates using these newer products compared with established, safer products such as medicinal nicotine. *Cancer Epidemiol Biomarkers Prev*; 20(1); 91–100. ©2011 AACR.

Introduction

The use of smokeless tobacco as a substitute for cigarette smoking has been suggested by some because it is considered to be a less harmful tobacco product (1–4). Smokeless tobacco lacks the toxicants associated with combustion, and data suggest that for an individual, there is less risk of disease (e.g., cardiovascular disease, lung disease) compared with continued smoking (5). In

addition, secondhand smoke risks are eliminated when smokeless tobacco is used. Smokeless tobacco products however are not harmless. Swedish moist snuff (i.e., snus) contains lower levels of carcinogens than most other brands of moist snuff contain, but even these products have been found to contain nitrosamines (5, 6) and the use of these products has been associated with increased risk of pancreatic cancer (7, 8). Some studies have suggested that use of Swedish snus also may be associated with a higher risk of oral or gastroesophageal cancer and cardiovascular disease (9–11).

In recent years, a number of spitless, smokeless tobacco products have been introduced in the United States. These products are among those broadly referred to as "potential reduced exposure tobacco products" (PREPs) or modified risk tobacco products (a term used in the U.S. Family Smoking Prevention and Tobacco Control Act) and are often marketed to be used when smoking bans prevent cigarette use or as a substitute for cigarettes. Although dual use of oral tobacco and cigarettes may

Authors' Affiliations: ¹University of Minnesota Tobacco Use Research Center, ²Department of Experimental and Clinical Pharmacology, College of Pharmacy, and ³University of Minnesota Masonic Comprehensive Cancer Center, University of Minnesota, Minneapolis, Minnesota

Clinical Trials.gov #: NCT00469079.

Corresponding Author: Dorothy K. Hatsukami, 717 Delaware St. SE, Minneapolis, MN 55414. Phone: 612-627-1808; Fax: 612-624-4610. E-mail: hatsu001@umn.edu.

doi: 10.1158/1055-9965.EPI-10-0349

©2011 American Association for Cancer Research.

not significantly reduce exposure to toxicants, a complete switch to oral tobacco products may have promise for reducing individual risk for disease. Furthermore, some researchers have indicated that smokeless tobacco may be more effective for smoking cessation than the currently available products, particularly among smokers who have been unsuccessful in the past (12, 13). A cross-sectional survey of Norwegian men found that smoking cessation rates were higher for those who used snus compared with those who used nicotine gum, but a larger proportion of snus users (relative to medicinal nicotine users) reporting continued long-term use (14). Large-scale prospective studies are needed to determine if these products may be useful as aids to smoking cessation, particularly because there is the concern that these products may in fact undermine the smoking cessation attempt.

The goal of the current study is to determine if smokers interested in cessation would be willing to enroll in and complete a study in which they are required to switch to these newer products. This would determine the feasibility of conducting a larger study assessing smoking cessation. Because there is relatively little published data regarding these newer products, additional goals of this study were to evaluate extent of exposure to selected toxicants and severity of craving and withdrawal symptoms following the use of the smokeless tobacco products Camel Snus (produced by RJ Reynolds) and Taboka (produced by Phillip Morris, no longer on the market). These products are pasteurized rather than fermented, leading to lower tobacco specific nitrosamine levels, and they contain less moisture to eliminate spitting (15). These 2 products were selected because they have substantially different amounts of free nicotine and therefore may be used in different ways by smokers, with Camel Snus having higher amounts of nicotine than Taboka (15). Nicotine replacement therapy was included in this study as a comparison condition because it has proven efficacy in assisting smoking cessation and has few adverse health effects.

Methods

Subjects

Cigarette smokers in generally good health between the ages of 18 and 70 who were interested in quitting smoking were recruited via advertisement. To be eligible, potential study participants must have reported smoking an average of at least 10 cigarettes per day for at least 1 year. Subjects were excluded if they (a) had uncontrolled or unstable medical or psychiatric conditions, or conditions that would require medical attention during the course of the study; (b) reported current or recent (within 6 months) alcohol or drug abuse; (c) had any contraindications for nicotine replacement therapy; (d) were using any medication that could interact with the products being tested or could affect the outcomes of interest in this study; or (e) regularly used tobacco products other than cigarettes.

Study design

Subjects were first screened via telephone to determine interest in participation and initial eligibility. Those interested and determined likely to qualify were invited to attend an orientation meeting where the study was explained in greater detail, informed consent was obtained, and full screening evaluation occurred to ensure subject eligibility. Eligible subjects who were interested in continuing with the study were then asked to continue smoking at their normal rate for a 2-week period during which baseline measurements were obtained.

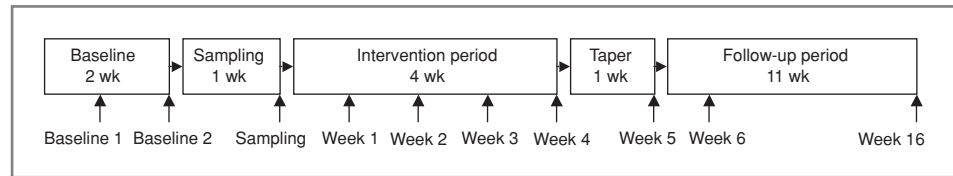
At the end of the 2 weeks of baseline data collection, smokers were randomly assigned to one of 3 conditions: (a) quit smoking by using either the 4-mg nicotine gum or 4-mg lozenge (subjects were given a choice of these products prior to assignment); (b) switch to Camel Snus; or (c) switch to Taboka. During a 1-week sampling period, smokers were given their assigned product and asked to use it as a substitute for smoking at times of their choosing but to use the product at least 1 to 2 times per day. Those assigned to nicotine replacement were given the choice of receiving the mint flavor of either nicotine gum or nicotine lozenge; those assigned to Taboka were given the choice of either Green (mint) or Regular flavor; and those assigned to Camel Snus were given the choice of either Original, Frost or Spice flavor. Subjects were free to choose either 1 flavor or a combination of flavored versions of each product at each study visit.

Taboka supplies for the study were purchased on 3 occasions (October 2006, August 2007, and October 2007) in Indianapolis, IN. Camel Snus was purchased as needed every 1 to 2 months between October 2006 and October 2008 from Austin, TX. Camel Snus was modified in June 2008 at which time the amount of nicotine and tobacco in each pouch increased, therefore subjects who received supplies after that point received the new formulation. Seventeen of the subjects receiving Camel Snus had completed the study by this point and therefore used the older formulation exclusively.

After the 1-week sampling period, smokers quit smoking cigarettes and used only their assigned product. During the 4-week intervention period, subjects were told to use their assigned product at least every 2 hours (i.e., a minimum of 6 to 8 doses per day) and to use additional doses when necessary. Starting in the fifth week following smoking cessation, subjects gradually reduced the amount of product used such that by the end of that week they would completely discontinue use of all nicotine and tobacco products.

Subjects were seen at weekly clinic visits during the study starting with the first baseline visit until the 1-week post cessation visit that occurred after subjects quit all nicotine and tobacco products (i.e., week 6 in Figure 1). An additional visit occurred 11 weeks after tobacco and nicotine cessation to determine smoking status. At each visit, subjects received standardized brief behavioral-supportive counseling of 10 minutes duration, first to

Figure 1. Diagram of the study design.



prepare for smoking cessation and then to support use of the study products and finally to stop the use of all tobacco and nicotine products. Counseling was performed by an individual trained in tobacco cessation counseling and was based on topics suggested in the National Cancer Institute's "Clearing the Air" manual that includes identifying high-risk situations for smoking and developing tools to deal with these situations. The counselor was not blind to the treatment assigned to the subject.

Outcome measures

Use of study products and cigarettes was determined by subject daily diaries that were reviewed at each of the weekly study visits. Subjects were encouraged to use only the study products after the sampling week but were told that it is crucial for the study that they report use of any non-study products. They were not penalized for use of such products.

Exhaled carbon monoxide (CO) was measured at every visit using a Bedfont Micro Smokerlyzer (Bedfont Scientific Limited). Urinary cotinine (a metabolite of nicotine) was measured at baseline, during product use (i.e., weeks 2 and 4) and during follow-up. For purposes of analysis, baseline cotinine concentration was calculated using the measure obtained at the first visit (i.e., baseline 1 in Figure 1) because a subject's smoking behavior is likely to start changing during the week prior to cessation (i.e., in anticipation of cessation). Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), which are metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were measured at baseline and during product use at weeks 2 and 4 (Figure 1, ref. 16). Urinary *N'*-nitrosornicotine and its glucuronide (total NNN), which are metabolites of the tobacco-specific carcinogen *N'*-nitrosornicotine were measured at baseline and during product use at week 4 (Figure 1; ref. 17).

Tobacco craving and withdrawal symptoms were measured at each visit using the Minnesota Nicotine Withdrawal Scale, which asked subjects to rate several withdrawal symptoms (i.e., craving, irritability / anger, anxiety / tension, difficulty concentrating, restlessness, impatience, problems with sleep, increased appetite, drowsiness, and depressed mood) on a scale from 0 (i.e., not present) to 4 (i.e., severe; refs. 18, 19). This scale has been used in other studies examining withdrawal signs and symptoms from cigarettes, nicotine gum, and smokeless tobacco (19–24).

Statistical analysis

Baseline characteristics, including demographics and smoking history, were summarized by treatment groups. The 3 groups were compared by Fisher's exact test for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. The baseline value of the outcome variables was measured on 2 consecutive weeks. The value from the first baseline week was used in the analysis, if available; otherwise the second baseline value was used. For biomarker concentrations below the lower limit of detection, a value of one-half of the lower level of detection was used (this occurred for 9% of the NNAL samples and 14% of NNN samples). A generalized linear mixed model was used for outcomes that had been repeatedly measured from baseline through the end of the treatment period. This model includes cases with missing data points due to dropouts or missed visits. As a result, all available data from each subject is included in the analysis. Each repeated-measures model included the treatment effect, a visit effect, the interaction between treatment and visit, the interaction between subject error and within-subject error terms. The variance/covariance structure for the data was estimated using restricted maximum likelihood (REML). The *P* values reported for multiple comparisons were unadjusted. Because of a very skewed distribution to high values, the biomarkers total NNAL, total NNN, and cotinine were analyzed in the natural logarithmic scale. The geometric means in the original units were used for constructing the graphs for these biomarkers. In addition to the dropout rates, the 7-day point prevalence abstinence at the end of treatment and at follow-up visits and the continuous abstinence rate (no smoking during the 4-week treatment period) were compared between groups using Fisher's exact test. SAS version 9.1 (SAS institute Inc.) was used for all analyses. A value of *P* < 0.05 indicated statistical significance.

Results

Subjects

A total of 1,159 smokers responded to advertisements placed to solicit interest in the study. The advertisements specifically stated that the study was assessing use of oral tobacco products and the study was described to subjects during that first phone call. Of the 801 subjects who were able to be reached and were screened over the telephone, 372 either did not qualify for the study or were not interested in participating. Of the 429 scheduled for orientation, 212 did not show up to the orientation meeting. Only 2 subjects volunteered that they were not

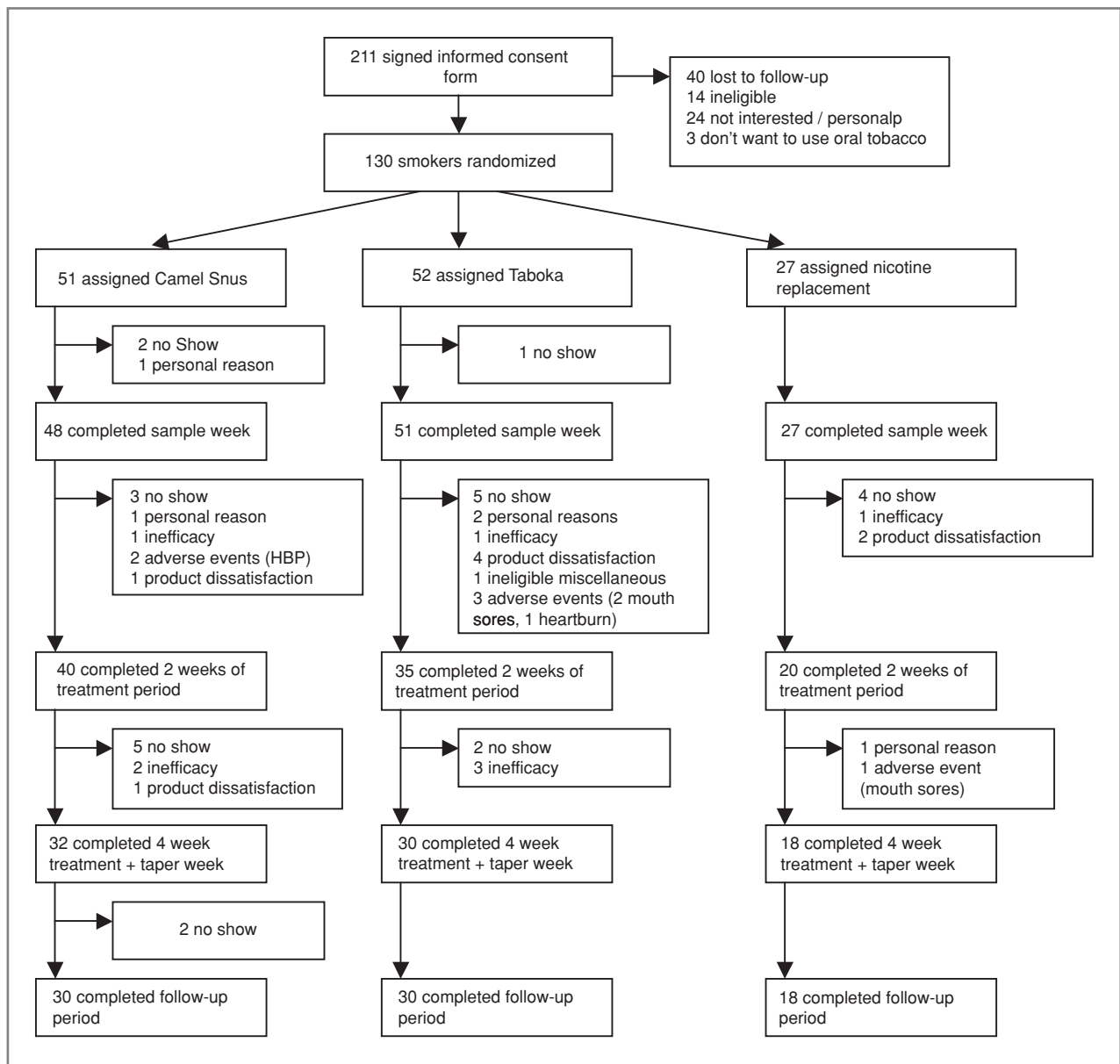


Figure 2. Flow of subjects through the study.

interested in the study because they were not interested in using oral tobacco products, however this information was not systematically solicited from subjects.

A total of 217 subjects attended the orientation session of which 211 subjects were enrolled in the study and 130 were randomized to treatment (51 to Camel Snus; 52 to Taboka; and 27 to nicotine replacement). One hundred twenty-six subjects completed the 1-week sampling period and 80 subjects completed the 4 weeks of product use and 1-week taper period. Seventy-eight subjects completed the follow-up period. The number of subjects dropping out of the study at various time-points and the reasons given are illustrated in Figure 2. No significant

differences in dropout rates were observed among the groups. The baseline demographics of the subjects are summarized in Table 1. There were no significant differences found among the groups except for score on the Fagerstrom test for nicotine dependence (FTND; $P < 0.01$). Mean baseline FTND score in those receiving medicinal nicotine was 5.2 compared to 3.8 in those randomized to Taboka and 4.4 in those randomized to Camel Snus. There were no significant differences in demographics between subjects who dropped out of the study after randomization and those who completed the entire study except in the number of previous quit attempts reported. The median number of quit attempts for completers was 5 and, for

Table 1. Baseline demographics of subjects

	Camel Snus (n = 51)		NRT (n = 27)		Taboka (n = 52)		P
Demographics							
Age (mean ± SD)	51	43.6 ± 11.5	27	42.4 ± 12.8	52	42.4 ± 11.2	0.84
Female	20	39.20%	12	44.40%	21	40.40%	0.92
Caucasian	44	86.30%	24	88.90%	40	76.90%	0.45
Education							
Some high school	0	0%	1	3.70%	0	0%	0.85
High school graduate	15	29.40%	7	25.90%	13	25.00%	
Some college/2-year degree	24	47.10%	15	55.60%	25	48.10%	
College graduate/4-year degree	10	19.60%	3	11.10%	11	21.20%	
Graduate/professional	2	3.90%	1	3.7%	3	5.80%	
Cigarettes per day (mean ± SD)	51	19.7 ± 5.3	27	23.6 ± 8.5	52	19.8 ± 6.1	0.1
Age becoming a regular smoker, y (mean ± SD)	50	17.0 ± 2.9	27	17.4 ± 3.2	21	17.1 ± 3.3	0.85
Number of quite attempts (mean ± SD)	51	6.9 ± 6.1	27	6.4 ± 6.7	52	7.3 ± 14.2	0.33
Motivation to quit (0–10 scale; mean ± SD)	51	9.3 ± 1.0	27	9.2 ± 1.0	52	8.6 ± 1.8	0.1
FTND Score (mean ± SD)	50	4.4 ± 1.6	25	5.2 ± 1.2	52	3.8 ± 1.1	<0.01

those who dropped out, it was 3 ($P = 0.013$). In addition, within each of the 3 groups, FTND score and number of cigarettes smoked were similar between those who completed the study and those who did not. FTND scores in those who completed the study were 4.4 ± 1.6 for those assigned to Camel Snus, 4.1 ± 1.3 for those assigned to Taboka, and 5.1 ± 1.1 for those assigned to medicinal nicotine. For those who did not complete the study, FTND scores were 4.3 ± 1.6 , 3.5 ± 0.8 , and 5.2 ± 1.6 , respectively. Cigarettes smoked per day for those who completed the study were 19.9 ± 6.4 for those assigned to Camel Snus, 19.1 ± 7.1 for those assigned to Taboka, and 22.8 ± 8.3 for those assigned to medicinal nicotine. For those who did not complete the study, cigarettes smoked per day were 19.3 ± 3.5 , 20.8 ± 4.4 , and 25.2 ± 9.0 , respectively.

Product use during treatment

For subjects receiving Taboka, 10% chose to use the Regular flavor exclusively, 33% chose the Mint flavor, and the rest used both flavors. For subjects receiving Camel Snus, 16% used 1 flavor exclusively (i.e., Frost or Regular), 38% used the same 2 flavors throughout, and 47% used multiple flavors. In those receiving medicinal nicotine, 44% chose to use the gum exclusively, 22% chose to use the lozenge exclusively, and the rest used both products.

The average amount of assigned product and regular cigarettes used at baseline and during the treatment period is illustrated in Figure 3A and B. There was a significant group effect found for amount of product used ($P = 0.012$) with smokers assigned to Taboka using fewer doses per day than those assigned to either Camel Snus or medicinal nicotine. At the week 4 treatment visit, those assigned to Taboka used significantly less product and

smoked significantly more of their usual brand cigarettes than those assigned to either of the other 2 conditions (all P values < 0.05). The percentage of subjects smoking on an average more than 3 cigarettes per day during the treatment weeks was 9.1% in the Camel Snus group, 13.6% in the medicinal nicotine group, but 26.8% in the Taboka group. Fewer doses of Taboka (than of the other 2 products) were also used among subjects who reported being abstinent from cigarettes during weeks 2, 3, and 4 of the treatment period, although this difference did not reach statistical significance (6.9 pouches of Camel Snus per day vs. 5.8 pouches of Taboka per day vs. 7.4 pieces of medicinal nicotine per day; $P = 0.052$).

Effects of products on biomarkers of exposure

Concentrations of exhaled CO, urinary cotinine, total NNAL, and total NNN at baseline and during treatment are illustrated in Figure 4A–D. Significant time effects were seen for all 4 biomarkers (all P values ≤ 0.001). Concentrations of each of the biomarkers were significantly (all P values < 0.05) lower at the end of treatment (i.e., week 4) compared with concentrations measured at baseline in each of the 3 treatment groups for all measures except for urinary NNN concentrations in those receiving Camel Snus ($P = 0.066$). There were no significant group effects for any of the biomarkers measured, however a significant group \times time effect was observed for urinary total NNAL concentrations ($P = 0.002$). Thus, the decrease in total NNAL during treatment was greatest for those receiving NRT and smallest for those receiving Camel Snus. Analyzing biomarkers only in subjects who were abstinent from cigarettes at weeks 2 to 4 resulted in similar results for most biomarkers, however for total NNAL

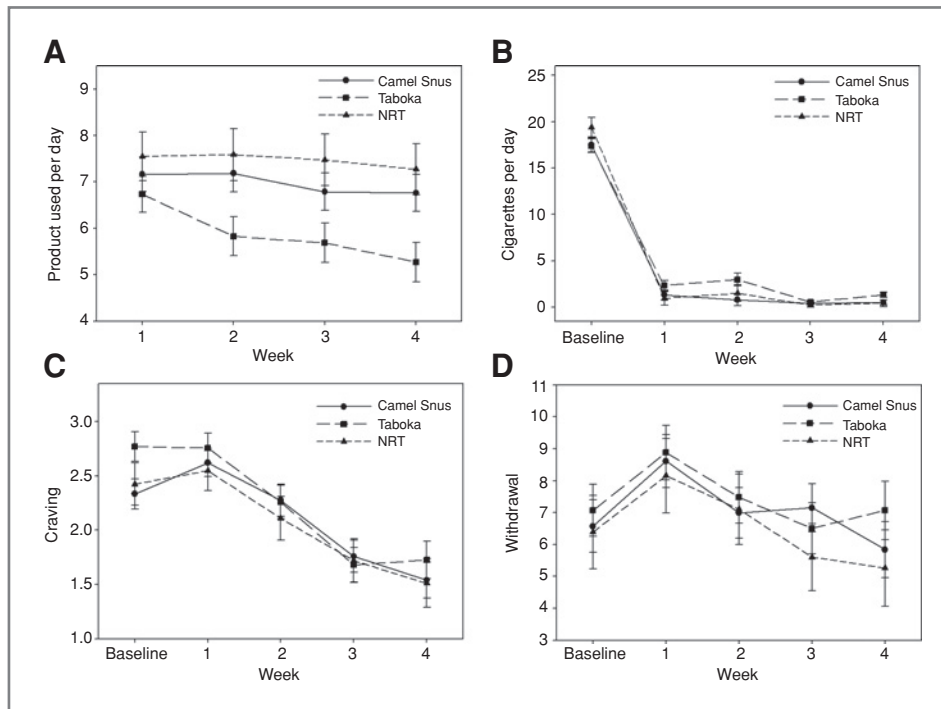


Figure 3. Least-squares (LS) mean (\pm SE) of amount of (A) study product used per day, (B) number of cigarettes smoked per day, (C) craving and (D) withdrawal symptoms

there was a significant group effect ($P = 0.05$) with a significant difference found between the Camel Snus and medicinal nicotine group (i.e., total NNAL concentrations were higher in the Camel Snus group; $P = 0.032$). The group \times time interaction continued to be significant for total NNAL ($P < 0.001$).

Effects of study products on craving and withdrawal symptoms

Nicotine craving and withdrawal symptom scores are illustrated in Figure 3C and D. Changes in craving and withdrawal symptoms were assessed at the time of discontinuation of usual brand cigarettes (i.e., baseline

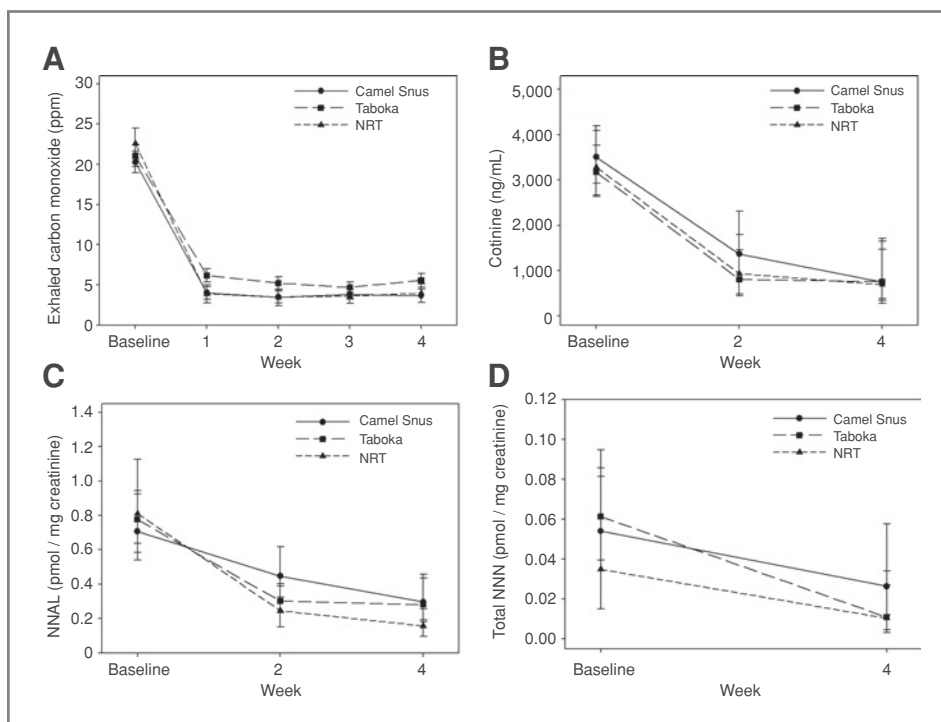


Figure 4. A, Least squares mean (\pm SE) of exhaled carbon monoxide concentrations, Geometric Mean (95% confidence interval) of (B) total cotinine (ng/mL), of (C) total NNAL (pmol/mg creatinine), and (D) of total NNN (pmol/mg creatinine)

compared to week 1) and overall craving and withdrawal symptoms scores during treatment were compared. Upon discontinuation of cigarette smoking, significant increases in withdrawal symptoms were observed in the Camel Snus and Taboka groups (Camel Snus, $P = 0.010$; Taboka, $P = 0.028$; NRT $P = 0.113$) whereas craving did not increase significantly in any of the groups ($P > 0.1$). No significant differences in magnitude of symptom change were found among the groups (craving, $P = 0.492$; withdrawal, $P = 0.971$). Overall craving and withdrawal scores decreased during the 4 weeks of treatment (significant time effect for both measures; $P < 0.001$), with no differences observed among the groups in either the overall levels of craving and withdrawal (no significant group effect for either measure) or in changes in craving or withdrawal symptoms during the treatment period (no significant group \times time effects for either measure). Similar results were found when craving and withdrawal symptoms were analyzed only in those subjects who were abstinent from cigarettes at weeks 2 to 4.

Abstinence

This study was not powered to detect differences in smoking cessation rates between groups; however, smoking status was collected at each visit to obtain preliminary data. Point prevalence (no smoking during the previous 7 days) cigarette abstinence rates were calculated at the week-4 visit and at each of the 2 follow-up visits. Continuous abstinence rates were calculated for the 4-week period between the week 1 and week 4 visits. Abstinence at all visits was assessed by self-report (i.e., no cigarettes smoked) and confirmed by an exhaled CO of less than 8 ppm. At the follow-up visits, abstinence was also confirmed by both exhaled CO concentrations and urinary cotinine concentration (<35 ng/mL). One subject in whom exhaled CO data were missing but urinary cotinine was less than 35 ng/mL was counted as abstinent. Because subjects used nicotine-containing products during the treatment period, cotinine-confirmed abstinence rates were not calculated for those visits. No significant differences in abstinence rates were seen between groups at any of time-points calculated (Table 2). Analyzing only subjects still remaining in the study after the sampling period (i.e., smokers interested in the products) resulted in similar results with no significant differences in quit rates found among groups. At the 1-week follow-up visit, NRT use was reported by 4 subjects in the Camel Snus group, 3 subjects in the Taboka group, and 13 subjects in the NRT group. At the week 11 follow-up visit, NRT use was reported by 3 subjects in the Camel Snus group, 4 subjects in the Taboka group, and 6 subjects in the NRT group. Five subjects reported oral tobacco use during the follow-up period (2 subjects in the Camel Snus group and 3 subjects in the Taboka group).

Discussion

This study found that enrolling smokers in a cessation study utilizing newer smokeless tobacco products is feasible. The proportion of subject dropping out in those assigned to 1 of 2 smokeless tobacco products (i.e., Camel Snus, Taboka) was similar to the proportion assigned to medicinal nicotine and the overall dropout rate during the treatment period was comparable to other smoking cessation studies (25, 26). Although many of those who initially responded to advertisements did not subsequently enroll in the study, many of the reasons for not enrolling were not reasons that suggest a resistance to using the study products (e.g., some could not be reached by telephone, others did not meet inclusion / exclusion criteria). Overall, this study therefore found smokers who were willing to enroll and complete a cessation study that used the newer tobacco products and did not find that smokeless tobacco was superior to nicotine replacement in decreasing craving or withdrawal symptoms; however, nicotine replacement use resulted in larger decreases in total NNAL than Camel Snus.

Differences in how the 3 products were used may be related to the amount of nicotine in each of the products. Subjects used significantly fewer doses of Taboka than either Camel Snus or the nicotine replacement product. A recent study found that Taboka had 0.844 to 1.26 mg free (unprotonated) nicotine per g dry weight and 19.9 to 21.1 mg total nicotine per g dry weight, whereas Camel Snus had 6.09 to 9.16 mg free nicotine per g dry weight and 23.7 to 28.2 mg total nicotine per g dry weight (15). Products with similar amount of nicotine as Taboka (e.g., Revel) have been found to result in lower plasma nicotine concentrations than the nicotine lozenge (5, 27). Therefore, the nicotine concentrations obtained from Taboka may not have been sufficient to maintain product use. Very low nicotine cigarettes, or nicotine-free cigarettes, have shown promise as potential aids for cessation but it is not clear that low nicotine smokeless products would be equally effective (28–30). Unlike the extra low nicotine or nicotine-free cigarettes, low nicotine smokeless products are likely not as effective at substituting for the sensory and behavioral aspects of smoking. This is consistent with the finding that during the last week of treatment those receiving Taboka smoked significantly more of their usual brand cigarettes than those assigned to either of the other 2 treatments. Our study therefore suggests that for smokeless products to be effective at substituting cigarettes, nicotine concentrations likely have to surpass a certain threshold. Quit rates for Camel Snus were comparable to those obtained with nicotine replacement therapy, therefore a properly powered study is needed to determine if the use of smokeless tobacco products with higher nicotine content can be an effective path to smoking cessation, perhaps, especially among smokers who are not interested in or previously were not successful with using approved pharmacotherapies.

Table 2. Abstinence rates at follow-up**Continuous Abstinence (weeks 1–4)**

	Treatments						
	Snus (n = 51)		Taboka (n = 52)		NRT (n = 27)		<i>P</i> -value
	abstinent	%	abstinent	%	abstinent	%	
¹ CO Verified	22	43.1	17	32.7	11	40.7	0.55

CO verified point prevalence abstinence

Visit	Treatments						
	Snus (n = 51)		Taboka (n = 52)		NRT (n = 27)		<i>P</i> -value
	abstinent	%	abstinent	%	abstinent	%	
Week 4	29	56.9	22	42.3	15	55.6	0.3
Week 6 (1 week follow-up)	24	47.1	20	38.5	15	55.6	0.35
Week 16 (11 weeks follow-up)	16	31.4	12	23.1	9	33.3	0.54

CO and cotinine verified point prevalence abstinence

Visit	Treatments						
	Snus (n = 51)		Taboka (n = 52)		NRT (n = 27)		<i>P</i> -value
	abstinent	%	abstinent	%	abstinent	%	
Week 6 (1 week follow-up)	14	27.5	12	23.1	8	29.6	0.76
Week 16 (11 weeks follow-up)	10	19.6	7	13.5	4	14.8	0.71

This study addressed the issue of whether switching smokers to smokeless tobacco offers any advantages relative to switching to medicinal nicotine. In the various outcomes assessed (i.e., craving, withdrawal symptoms, toxicant concentrations), no clear advantages were found for smokeless tobacco over medicinal nicotine. Previous studies similarly found few differences in subjective measures after use of a single dose or repeated doses of some of the newer smokeless tobacco products versus nicotine lozenge and have shown no significant increases in craving after switching from cigarettes to medicinal nicotine or other newer products (27, 28, 31). However, studies assessing these measures are relatively small and may not be able to detect small differences between groups. In measures of toxicant exposure, switching to medicinal nicotine resulted in lower levels of NNAL than switching to one of the smokeless tobacco products. This is consistent with other studies demonstrating that many of the newer smokeless tobacco products, although having lower levels of toxicants than cigarette smoke, are not toxicant free (6, 15, 31–33). The lack of significant differences among groups in total NNN exposure was perhaps due (at least in part) to endogenous NNN production (from nicotine) in those receiving medicinal nicotine (34, 35). Further research is needed to determine the extent to which this occurs. This study therefore suggests that for smokers interested in quitting, medicinal nicotine should be the first option recommended, and barriers to medicinal nicotine use should be identified and removed if possible.

Several limitations are present in the current study. Smokeless tobacco products commercially available in the United States have been introduced, withdrawn, or changed at a relatively rapid rate. As a result, one of the products tested in the current study (Taboka) is no longer commercially available and changes to the other product (Camel Snus) occurred during the time period that the study occurred. Nonetheless, the study provides important information regarding the feasibility of conducting studies with these products and information regarding toxicant exposure during their use. Lack of commercial availability of these products for most of the subjects during the follow-up period precludes evaluating if and how smokers introduced to these products would use them in a natural setting once these products were no longer provided by the study. An additional limitation is that in the measurement of toxicant exposure, it is not known how much of the exposure was contributed by the study products as compared with cigarettes that subjects were smoking during the study (i.e., as the amount of product used and the amount smoked differed significantly between groups). A strength of this approach, however is that it more closely resembles toxicant exposure when these smokers are given these products in the natural environment. Furthermore, when examining smokers who were verified to be abstinent, those assigned to Camel Snus continued to have higher toxicant exposure compared with those assigned to medicinal nicotine. It should be noted that the results of this study are limited in applicability only to smokers who are interested in quit-

ting smoking and willing to use nicotine replacement therapy. It is not known how these products would compare in smokers not interested in cessation or smokers interested in cessation but not interested in using nicotine replacement therapy. Future studies are needed to address these issues.

In summary, this study demonstrated that smokers interested in quitting smoking were willing to enroll in and complete a study evaluating the newer smokeless tobacco products. In addition, this study did not find that the "modified risk" smokeless tobacco products tested were superior to medicinal nicotine in decreasing subjective measures (i.e., craving, withdrawal) but resulted in greater exposure to one of the toxicants assessed. Further studies are needed to definitively determine if these products are effective at increasing cessation rates and to determine how smokeless tobacco products might be used in smokers not immediately interested in smoking cessation.

References

- Russell MA, Jarvis MJ, Feyerabend C. A new age for snuff? *Lancet* 1980;1:474-5.
- Rodu B. An alternative approach to smoking control. *Am J Med Sci* 1994;308:32-4.
- Russell MA, Jarvis MJ, Devitt G, Feyerabend C. Nicotine intake by snuff users. *BMJ (Clin Res Ed)* 1981;283:814-7.
- Rodu B, Godshall WT. Tobacco harm reduction: an alternative cessation strategy for inveterate smokers. *Harm Reduct J* 2006;3:37.
- Hatsukami DK, Ebbert JO, Feuer RM, Stepanov I, Hecht SS. Changing smokeless tobacco products new tobacco-delivery systems. *Am J Prev Med* 2007;33:S368-78.
- Hatsukami DK, Lemmonds C, Zhang Y, et al. Evaluation of carcinogen exposure in people who used "reduced exposure" tobacco products. *J Natl Cancer Inst* 2004;96:844-52.
- Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 2005;114:992-5.
- Luo J, Ye W, Zendehele K, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 2007;369:2015-20.
- Hergens MP, Alfredsson L, Bolinder G, Lambe M, Pershagen G, Ye W. Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men. *J Intern Med* 2007;262:351-9.
- Zendehele K, Nyren O, Luo J, et al. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *Int J Cancer* 2008;122:1095-9.
- Roosaar A, Johansson AL, Sandborgh-Englund G, Axell T, Nyren O. Cancer and mortality among users and nonusers of snus. *Int J Cancer* 2008;123:168-73.
- Tilashalski K, Rodu B, Cole P. A pilot study of smokeless tobacco in smoking cessation. *Am J Med* 1998;104:456-8.
- Rodu B, Phillips CV. Switching to smokeless tobacco as a smoking cessation method: evidence from the 2000 National Health Interview Survey. *Harm Reduct J* 2008;5:18.
- Lund KE, McNeill A, Scheffels J. The use of snus for quitting smoking compared with medicinal products. *Nicotine Tob Res* 2010;12:877-22.
- Stepanov I, Jensen J, Hatsukami D, Hecht SS. New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine Tob Res* 2008;10:1773-82.
- Carmella SG, Han S, Fristad A, Yang Y, Hecht SS. Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. *Cancer Epidemiol Biomarkers Prev* 2003;12:1257-61.
- Stepanov I, Hecht SS. Tobacco-specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. *Cancer Epidemiol Biomarkers Prev* 2005;14:885-91.
- Hughes J, Hatsukami DK. Errors in using tobacco withdrawal scale. *Tob Control* 1998;7:92-3.
- Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986;43:289-94.
- Hatsukami DK, Gust SW, Keenan RM. Physiologic and subjective changes from smokeless tobacco withdrawal. *Clin Pharmacol Ther* 1987;41:103-7.
- Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal. A replication and extension. *Arch Gen Psychiatry* 1991;48:52-9.
- Hatsukami D, McBride C, Pirie P, Hellerstedt W, Lando H. Effects of nicotine gum on prevalence and severity of withdrawal in female cigarette smokers. *J Subst Abuse* 1991;3:427-40.
- Hatsukami D, Huber M, Callies A, Skoog K. Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology (Berl)* 1993;111:449-56.
- Hatsukami D, Anton D, Keenan R, Callies A. Smokeless tobacco abstinence effects and nicotine gum dose. *Psychopharmacology (Berl)* 1992;106:60-6.
- Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685-91.
- Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47-55.
- Kotlyar M, Mendoza-Baumgart MI, Li ZZ, et al. Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge. *Tob Control* 2007;16:138-42.
- Hatsukami DK, Kotlyar M, Hertzgaard L, et al. Reduced Nicotine Content Cigarettes: Effects on Toxicant Exposure, Dependence and Cessation Addiction 2010;105:343-55.
- Walker N, Bullen C, McRobbie H. Reduced-nicotine content cigarettes: Is there potential to aid smoking cessation? *Nicotine Tob Res* 2009;11:1274-9.
- Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P III. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers Prev* 2007;16:2479-85.

Disclosure of Potential Conflicts of Interest

D. Hatsukami: commercial research grant, funding for a clinical trial from Nabi Biopharmaceuticals. S. Hecht: expert testimony, smokeless tobacco case.

Acknowledgments

We thank Aleksandar Knezevich for technical support.

Grant Support

This study was funded by P50 DA01333 and K23DA017307.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 2, 2010; revised October 8, 2010; accepted November 4, 2010; published OnlineFirst November 10, 2010.

31. Mendoza-Baumgart MI, Tulunay OE, Hecht SS, et al. Pilot study on lower nitrosamine smokeless tobacco products compared with medicinal nicotine. *Nicotine Tob Res* 2007;9:1309–23.
32. Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res* 2006;8:309–13.
33. Gray JN, Breland AB, Weaver M, Eissenberg T. Potential reduced exposure products (PREPs) for smokeless tobacco users: clinical evaluation methodology. *Nicotine Tob Res* 2008;10:1441–8.
34. Stepanov I, Carmella SG, Briggs A, et al. Presence of the carcinogen N'-nitrosornicotine in the urine of some users of oral nicotine replacement therapy products. *Cancer Res* 2009;69:8236–40.
35. Stepanov I, Carmella SG, Han S, et al. Evidence for endogenous formation of N'-nitrosornicotine in some long-term nicotine patch users. *Nicotine Tob Res* 2009;11:99–105.

Correction: Effect of Oral Snus and Medicinal Nicotine in Smokers on Toxicant Exposure and Withdrawal Symptoms: A Feasibility Study

In this article (1), which was published in the January 2011 issue of *Cancer Epidemiology, Biomarkers & Prevention*, the following modifications were requested by the authors. The corrected data include the following: (i) Table 1 and Subjects portion of results section: Baseline FTND score was 5.2 ± 1.8 for those receiving Camel Snus, 5.3 ± 1.9 for those receiving medicinal nicotine, and 5.5 ± 1.7 for those receiving Taboka ($P = 0.78$). For those who completed the study, FTND scores were 5.4 ± 1.9 for those receiving Camel Snus, 5.1 ± 2.0 for those receiving medicinal nicotine, and 5.2 ± 2.0 for those receiving Taboka. For those who did not complete the study, FTND scores were 5.0 ± 1.6 , 5.6 ± 1.8 , and 6.0 ± 1.1 , respectively; (ii) Outcome Measures portion of Methods section: The items in the withdrawal symptoms scale used were craving, irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, increased appetite/weight gain, depressed or sad mood, and insomnia/sleep problems; (iii) Table 1: The average age reported for becoming a regular smoker in the Taboka group was based on 51 subjects; and (iv) Statistical Analysis portion of the Methods section: Each repeated-measures model included the treatment effect, a visit effect, the interaction between treatment and visit, and the between-subject error and within-subject error terms.

Reference

1. Kotlyar M, Hertzgaard LA, Lindgren BR, Jensen JA, Carmella SG, Stepanov I, et al. Effect of oral Snus and medicinal nicotine in smokers on toxicant exposure and withdrawal symptoms: a feasibility study. *Cancer Epidemiol Biomarkers Prev* 2011;20:91–100.

©2011 American Association for Cancer Research.

doi: 10.1158/1055-9965.EPI-11-0050

Published online May 5, 2011.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

Effect of Oral Snus and Medicinal Nicotine in Smokers on Toxicant Exposure and Withdrawal Symptoms: A Feasibility Study

Michael Kotlyar, Louise A. Hertsgaard, Bruce R. Lindgren, et al.

Cancer Epidemiol Biomarkers Prev 2011;20:91-100. Published OnlineFirst November 10, 2010.

Updated version Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-10-0349](https://doi.org/10.1158/1055-9965.EPI-10-0349)

Cited articles This article cites 35 articles, 7 of which you can access for free at:
<http://cebp.aacrjournals.org/content/20/1/91.full#ref-list-1>

Citing articles This article has been cited by 8 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/20/1/91.full#related-urls>

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

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

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/20/1/91>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's
(CCC)
Rightslink site.