Smoking Behavior and Exposure to Tobacco Toxicants during 6 Months of Smoking Progressively Reduced Nicotine Content Cigarettes

Neal L. Benowitz, Katherine M. Dains, Sharon M. Hall, Susan Stewart, Margaret Wilson, Delia Dempsey, and Peyton Jacob III

Abstract

Background: Recent federal legislation gives the U.S. Food and Drug Administration authority to regulate the nicotine content of cigarettes. A nationwide strategy for progressive reduction of the nicotine content of cigarettes is a potential way to reduce the addictiveness of cigarettes, to prevent new smokers from becoming addicted, and to facilitate quitting in established smokers. We conducted a trial of progressive nicotine content tapering over 6 months to determine the effects on smoking behaviors and biomarkers of tobacco smoke exposure and cardiovascular effects.

Methods: One hundred and thirty-five healthy smokers were randomly assigned to one of two groups. A research group smoked their usual brand of cigarettes followed by five types of research cigarettes with progressively lower nicotine content, each smoked for one month. A control group smoked their own brand of cigarettes for the same period of time.

Results: Nicotine intake, as indicated by plasma cotinine concentration, declined progressively as the nicotine content of cigarettes was reduced. Cigarette consumption and markers of exposure to carbon monoxide and polycyclic aromatic hydrocarbons, as well as cardiovascular biomarkers remained stable, whereas urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) excretion decreased. No significant changes in biomarkers of exposure or cardiovascular effects were observed in controls.

Conclusions: Our data support the proposition that the intake of nicotine from cigarettes of smokers can be substantially lowered without increasing exposure to other tobacco smoke toxins.

Impact: These findings support the feasibility and safety of gradual reduction of the nicotine content in cigarettes.

Introduction

In June 2009, the U.S. government passed HR 1256, the Family Smoking Prevention and Tobacco Control Act that grants the U.S. Food and Drug Administration (FDA) the power to regulate tobacco products (1). This legislation gives the FDA the authority to control the nicotine content of cigarettes. A nationwide strategy for the progressive reduction of the nicotine content in cigarettes has been widely discussed as a potential way that would result in a cigarette that does not sustain or result in addiction and/or aid smoking cessation (2–6).

We have shown in prior research that when smokers smoke single cigarettes with differing nicotine content the nicotine intake per cigarette is proportional to the nicotine content of the cigarettes, without evidence of compensation (7). Furthermore, we have previously reported on a small uncontrolled clinical trial of 20 smokers who smoked cigarettes of their usual brand, then cigarettes of progressively lower nicotine content, each for one week (8). That trial confirmed that the nicotine intake declined progressively as the nicotine content of cigarettes was lowered. Measurement of CO and tobacco smoke carcinogens indicated minimal or no compensation, suggesting that gradual reduction of the nicotine content of cigarettes is no more hazardous than smoking regular nicotine cigarettes. We also observed in that study that 25% of smokers quit smoking after the taper, despite having expressed no desire to quit on entry into the study. These data suggested that the degree of nicotine dependence can be lowered without increasing exposure to tobacco smoke toxins using reduced nicotine contents (RNC).

Limitations of our prior RNC clinical trial included a relatively small number of subjects and a brief duration of the tapering at each yield level. There is concern among...
some tobacco researchers that over the long-term smokers will attempt to obtain the nicotine that they crave by increasing the frequency and depth of inhalation. We now present data from a longer duration study, with nicotine yield tapering at monthly intervals, and which included a larger number of subjects as well as a control group of smokers smoking their own cigarettes. The full study is a 2-year study with an initial 6-month nicotine tapering phase followed by 6 months of smoking the lowest nicotine content cigarettes and then a 1 year follow-up without research cigarettes. In this article, we present data on the 6 months of progressive tapering.

**Methods**

**Overview of study design**

This was a 2-year, 2-arm, randomized, unblinded study in which smokers smoked their usual brand of cigarette for a baseline period of 2 weeks and then were randomly divided into a control arm and a research arm. The control group smoked their usual brand of cigarettes throughout the study. The research (RNC) group smoked 5 types of progressively lower nicotine content cigarettes. The first 4 levels of RNC were smoked for 4 weeks each. The lowest nicotine content cigarette was smoked for 6 months. Thereafter, all subjects were followed for an additional year after returning to smoking cigarettes of their choosing (or quitting). The study was not blinded because we wanted to simulate a real world regulatory situation in which the nicotine content of cigarettes is progressively decreased with the knowledge of the smoker. The present analysis focuses on the first 6 months of the study during which the nicotine content of cigarettes was tapered.

**Subjects**

Smokers were recruited by newspaper advertisements looking for smokers interested in a reduced nicotine cigarette study. Subjects were determined not to be interested in quitting smoking in the next 6 months. Inclusion criteria included being between the ages of 18 and 70, being healthy based on medical history and screening blood tests, smoking 10 or more cigarettes per day for the past year, and having an expired CO levels of 25 ppm or a saliva cotinine level of 100 ng/mL or more at the screening visit. Exclusion criteria included pregnancy or lactation, current use of smokeless tobacco, pipes or cigars, and alcohol or drug dependence.

Two hundred and thirty-eight smokers were screened for participation. One hundred and thirty-nine subjects met entry criteria and completed the baseline assessment. The reasons for subject exclusion included cotinine levels <100 ng/mL (45%), drug or alcohol abuse (35%), history of fainting, poor veins, or health issues (20%). Four subjects who completed the baseline screening declined to participate.

One hundred and thirty-five subjects were randomized to RNC or control groups in blocks of 10 subjects. The number of subjects studied was limited by the supply of research cigarettes Twenty-one subjects randomized to the RNC group withdraw between weeks 2 and 6 of study initiation, during which time they were smoking the highest level nicotine research cigarette. Subjects withdrew primarily because they did not like the taste of the research cigarettes. Because the subjects did not experience any nicotine tapering, these 21 subjects were replaced. Another 11 subjects withdrew during the tapering phase (5 in the control group and 6 in the RNC group) and were not replaced. A total of 53 subjects in the RNC and 50 subjects in the control group completed the tapering phase of the study. Of the 26 subjects who quit in the research group, 17 quit due to not liking the cigarettes, 7 relocated, 2 became ill, and 1 was a no show. Of the 5 who quit in the control group 1 subject died unexpectedly, 2 relocated, and 2 were no shows.

**Study protocol**

Subjects were studied in a community-based clinic. Visits were scheduled biweekly, at which time cigarettes were dispensed; expired CO, height, weight, and blood pressure were measured; blood and urine samples were collected; and questionnaires were administered. Subjects were instructed to smoke their cigarettes as desired, but not to smoke any other type of cigarette and not to use other forms of tobacco or nicotine medications. Subjects were also told that if they did smoke cigarettes other than study cigarettes, that they should report such lapses to the research staff, and that there would be no penalty with respect to remaining in the study.

Plasma samples were assayed for concentrations of nicotine and cotinine (the proximate metabolite of nicotine) and for selected cardiovascular biomarkers. The following biomarkers were selected as predictors of coronary heart disease risk: white blood cell count, hemoglobin, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and serum fibrinogen. Urine samples were assayed for concentrations of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of the carcinogenic tobacco-specific nitrosamine, 4-methylnitrosamino-1-(3-pyridyl)-1-butanolone (NNK), and metabolites of 4 polycyclic aromatic hydrocarbons (PAH) found in tobacco smoke. NNAL and the PAH metabolites are biomarkers of exposure to common tobacco smoke carcinogens (9).

Questionnaires were administered at the end of each of the 4-week tapering intervals and included a report of smoking behavior over the previous 4-week period, Profile of Mood States (POMS; 10), the Minnesota Nicotine Withdrawal Scale (11), the Fagerström Test for Nicotine Dependence (FTND; ref. 12), and a cigarette acceptance questionnaire (13). The cigarette acceptance questionnaire uses items with 7-point ratings that cluster into 7 scales: satisfaction, similarity to usual brand, psychologic reward, aversion, respiratory sensations, craving, and perceived strength. A self-efficacy questionnaire...
(14), the Prochaska Stages of Change questionnaire (15), and the CESD Depression Scale (16) were administered on the milestone visits—baseline, 3 months, 6 months, 1 year, and 2 years. The self-efficacy questionnaire is a 14 item instrument that asks about the confidence of smokers in their ability to resist smoking in various high-risk situations. The Stages of Change questionnaire assesses the early stages of movement toward quitting smoking, including precontemplation (no intention to quit within the next 6 months), contemplation (seriously considering quitting in the next 6 months), and preparation. Subjects were paid for participation. Written, informed consent was obtained from each subject. The study was approved by the Institutional Review Board at the University of California, San Francisco, CA.

Cigarettes

The RNC cigarettes were manufactured by Philip Morris Tobacco Company by blending very low nicotine tobacco with tobacco containing higher amounts of nicotine. Very low nicotine tobacco was produced by a supercritical extraction method. The paper and filters and weight of tobacco in the research cigarettes were similar to that of a Marlboro cigarette. The target nicotine content per cigarette were 12, 8, 4, 2, and 1 mg, to allow for a 50% reduction in nicotine dose at each step between 8 and 1 mg. These 5 levels were selected so that by the end of tapering, the highest systemic nicotine intake could be expected to be 0.2 mg per cigarette or less, based on bioavailability calculations that have been described previously (2). The lowest level of nicotine availability was based on an estimate of the threshold level of nicotine to maintain nicotine addiction. The characteristics of the research nicotine cigarettes are presented in Table 1. Data on the extent of ventilation of the cigarettes were not available. The cigarette filters were perforated with 2 rows of perforations, similar to those found in the filter of a Marlboro Light cigarette. Cigarettes were stored at 55°F until shortly before they were dispensed to the subjects.

Analytical chemistry

Plasma nicotine and cotinine were measured by gas chromatography with nitrogen-phosphorous detection (17, 18). Urine concentrations of NNAL (free plus conjugated) and PAH metabolites, including 2-naphthol, 1, 2 and 3+4 hydroxyphenanthrenes, 1-hydroxypyrene, and 2-hydroxyfluorene, were measured by liquid chromatography/tandem mass spectrometry (LC/MS-MS; refs. 19, 20). Cardiovascular biomarkers were assayed by enzyme immunoassay using commercial kits.

Analysis of compensation

Compensation was defined as the degree to which proportional changes in a subject’s intake of a smoke constituent make up for the proportional change in the machine-determined yield of cigarette content of that constituent. As we have described previously, compensation can be expressed mathematically as follows: 

$$ C = 1 - \frac{\log (\text{marker} 2) - \log (\text{marker} 1)}{\log (\text{yield} 2) - \log (\text{yield} 1)} $$

In the present study, we computed compensation using plasma cotinine concentrations as the marker of nicotine intake and the machine determined nicotine yields of usual cigarettes and RNC cigarettes. For example, assume that a smoker smokes a cigarette at baseline with a nicotine yield of 1.0 mg and compensation is assessed when smoking an RNC cigarette with a yield of 0.4 mg. Assume the plasma cotinine concentrations at baseline and while smoking the RNC cigarette are 256 and 131 ng/mL, respectively. Using the equation above, $C = 1 - \frac{\log 131 - \log 256}{\log 0.4 - \log 1.0} = 0.27$. Thus compensation is estimated to be 27%.

Statistical analysis

Because measurements for each individual were correlated over time, a repeated measures model was

<table>
<thead>
<tr>
<th>Table 1. Characteristics of research cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research cigarettes nominal nicotine content</td>
</tr>
<tr>
<td>12 mg</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Measured nicotine content, mg</td>
</tr>
<tr>
<td>Tobacco weight, mg</td>
</tr>
<tr>
<td>FTC method</td>
</tr>
<tr>
<td>Nicotine, mg</td>
</tr>
<tr>
<td>Tar, mg</td>
</tr>
<tr>
<td>Carbon monoxide, mg</td>
</tr>
<tr>
<td>NNK, ng</td>
</tr>
<tr>
<td>NNN, ng</td>
</tr>
</tbody>
</table>

NOTE: Machine testing of research cigarettes using standard U.S. Federal Trade Commission procedures were conducted by the U.S. Centers for Disease Control and Prevention. Abbreviations: FTC, Federal Trade Commission; NNN, N’-nitrosornicotine.
constructed for each of the major variables. A mixed effects regression analysis was conducted with PROC MIXED in SAS (version 9.2). Measurements at baseline, 3 months, and 6 months were modeled as a function of time and study arm, using time by study arm interactions to assess intervention effects. Models were examined with and without adjustment for age, gender, race/ethnicity, and use of menthol cigarettes. Because results were unchanged, unadjusted data are presented. Least square means and 95% confidence intervals (CI) were computed within each study arm at each of the 3 time points. Differences in mean values were computed for each pair of time points within each study arm, as well as the difference between the study arms with respect to each time point comparison; \( P \) values and 95% CIs for the differences were constructed using the Bonferroni adjustment to account for 3 time point comparisons. Variable values for total NNAL, PAH metabolites, and several of the cardiovascular biomarkers were log transformed to achieve approximate normality, and the analyses were conducted on the natural logarithm of the values. Geometric means and corresponding ratios are reported for log-transformed variables.

All data for the 103 participants who completed the first 6-month period of the study were included in the primary analysis. Dropouts were excluded from the analysis because they had missing data for many or most of the visits. Because several subjects had stopped smoking at various time points the analyses were repeated omitting observations on nonsmoking visits (\( n = 6 \)). For individuals who reported not smoking for the previous 24 hours, having stopped smoking was defined biochemically as having a plasma cotinine concentration of less than 10 ng/mL. Analyses that excluded observations when subjects were not smoking did not alter the results so all analyses that are presented include all observations.

At various times 11 subjects in the RNC group reported noncompliance with the research cigarettes—that is, they had smoked some commercial cigarettes in the previous 4 weeks. The analyses were conducted both including and excluding these subjects.

Another sensitivity analysis was conducted in which data from those subjects who dropped out during the RNC taper phase (5 in the control group and 6 in the RNC group) were included, carrying forward their measurements from the last visit before they dropped out. This analysis examined cigarettes per day, plasma cotinine, and expired CO. Urine samples from dropouts for measurement of NNAL or PAHs were not retained, so these measures were not part of the sensitivity analysis.

**Results**

**Demographic and baseline smoking data**

Demographic data and baseline smoking data for subjects in the 2 treatment groups as well as for dropouts are shown in Table 2. The FTND score was significantly higher for dropouts than for those who completed the study; they did not differ significantly with respect to cigarettes per day. Among retained subjects, the research and control groups did not differ significantly with respect to either FTND or cigarettes per day. Other characteristics were similar across groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (N = 50)</th>
<th>Research group (N = 53)</th>
<th>Drop outs (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>37.4 (34.4–41.0)</td>
<td>36.6 (33.4–39.2)</td>
<td>36.6 (32–41)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>70</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>African American</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>10</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Other/mixed</td>
<td>12</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>BMI</td>
<td>24.8 (24.5–25.0)</td>
<td>26.3 (26.1–26.6)</td>
<td>25.8 (23.4–28.2)</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.7 (14.9–16.1)</td>
<td>15.1 (14.6–15.8)</td>
<td>14.5 (9–17)</td>
</tr>
<tr>
<td>CPD</td>
<td>19.9 (17.9–22.0)</td>
<td>23.4 (21.5–25.4)</td>
<td>24.3 (20.9–27.8)</td>
</tr>
<tr>
<td>Years smoked</td>
<td>21.4 (17.9–24.8)</td>
<td>20.5 (17.5–23.5)</td>
<td>19.9 (15.4–24.5)</td>
</tr>
<tr>
<td>Menthol, n (%)</td>
<td>5 (10)</td>
<td>6 (11)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>FTC nicotine, mg</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.1)</td>
</tr>
<tr>
<td>FTC tar, mg</td>
<td>11.6 (10.8–12.3)</td>
<td>11.4 (10.6–12.1)</td>
<td>11.8 (10.7–13.0)</td>
</tr>
<tr>
<td>FTND score</td>
<td>5.5 (4.9–6.2)</td>
<td>5.6 (5.2–6.1)</td>
<td>6.5 (5.7–7.4)*</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CPD, cigarettes per day; FTC, Federal Trade Commission.

*Significant difference at \( P < 0.05 \).
Cigarette consumption
Average cigarette consumption increased by an average of 3 cigarettes per day in the control group comparing week 26 versus baseline (Fig. 1A, Table 3). Cigarette consumption was unchanged in the RNC group between baseline and week 14 but decreased significantly by 4 cigarettes per day at 26 weeks to baseline and to 14 weeks. The findings were similar for RNC smokers who were or were not compliant and when dropouts with data carried forward were included (data not shown for the latter).

Biochemical exposures
Plasma nicotine and cotinine concentrations declined slightly over 26 weeks in the control smokers, but these changes were not significant (Fig. 1B, Table 3). In RNC subjects average plasma nicotine and cotinine concentrations remained stable for the first 6 weeks but then declined significantly at 14 and 26 weeks compared with baseline. For plasma cotinine, which is the most stable indicator of daily intake of nicotine, the levels at week 26 were 44% of baseline for all RNC subjects and 30% of baseline in those who complied. Significant interactions were observed in the change in plasma nicotine and cotinine comparing the control and RNC groups. Including dropouts with data carried forward, plasma cotinine was 51% of baseline at 26 weeks ($P < 0.001$).

Expired CO increased by an average of 4 ppm comparing baseline to week 14 for all groups, although the change was significant only for the RNC group (Fig. 1C). Changes were not significant when dropouts were included. Urine NNAL remained unchanged during the 26 weeks in the

Figure 1. A, mean cigarette consumption over 26 weeks of the study in smokers smoking their usual brand of cigarettes (C, N = 50) or during progressive reduction of nicotine content of cigarettes (R, N = 53). R(excNC) indicates subjects in the RNC group excluding those who did not comply with smoking RNC cigarettes only (N = 42). The bars represent SEM. B, mean plasma cotinine concentration over 26 weeks of the study in smokers smoking their usual brand of cigarettes (C, N = 50) or during progressive reduction of nicotine content of cigarettes (R, N = 53). R(excNC) indicates subjects in the RNC group excluding those who did not comply with smoking RNC cigarettes only (N = 42). The bars represent SEM. C, mean expired CO concentration over 26 weeks of the study in smokers smoking their usual brand of cigarettes (C, N = 50) or during progressive reduction of nicotine content of cigarettes (R, N = 53). R(excNC) indicates subjects in the RNC group excluding those who did not comply with smoking RNC cigarettes only (N = 42). The bars represent SEM.
compensation at the lowest nicotine levels was greater in those who did not fully comply with smoking RNC than those who did comply.

**Cardiovascular measurements and biomarkers**

Body weight did not change significantly in control and among all RNC subjects. Body weight did significantly increase among compliant RNC smokers, from 81 kg (95% CI, 71–81) at baseline to 83 kg (95% CI, 75–80) at 26 weeks ($P < 0.0166$). Of note there was no change in body weight in this group comparing baseline to 14 weeks. No significant changes were observed in any group for blood pressure, heart rate, white blood cell count, hemoglobin, HDL cholesterol, or fibrinogen.

**Table 3.** Smoking behavior and biomarkers of exposure while smoking reduced nicotine cigarettes means

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline–week 2 (usual) Control (N = 50) Research (N = 53)</th>
<th>Week 14 (4 mg) Control (N = 50) Research (N = 53)</th>
<th>Week 26 (1 mg) Control (N = 50) Research (N = 53)</th>
<th>Significant effects $P &lt; 0.0166$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine,$^a$ pmol/mg creatinine</td>
<td>1.0 (0.7–1.3) 1.4 (1.1–1.7) 1.3 (1.0–1.6)</td>
<td>0.9 (0.7–1.2) 1.2 (1.0–1.5) 1.2 (1.0–1.4)</td>
<td>0.9 (0.6–1.2) 0.8 (0.5–1.1) 0.7 (0.5–0.9)</td>
<td>W26 vs. W2: R W26 vs. W14: R W26 vs. W2: R vs. C W26 vs. W14: vs. C</td>
</tr>
<tr>
<td>Total NNAL</td>
<td>3.5 (2.8–4.4) 4.0 (3.3–4.7) 3.7 (3.1–4.5)</td>
<td>3.5 (2.9–4.4) 3.8 (3.3–4.3) 3.5 (3.0–4.0)</td>
<td>4.0 (3.3–4.7) 3.9 (3.1–4.8) 4.0 (3.1–5.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Sum of fluors</td>
<td>13 (10–17) 17 (14–22) 17 (14–22)</td>
<td>12 (9–17) 18 (15–22) 18 (14–22)</td>
<td>15 (12–18) 17 (13–23) 20 (15–26)</td>
<td>NS</td>
</tr>
<tr>
<td>1-Hydroxypyrene</td>
<td>1.1 (0.9–1.5) 1.4 (1.1–1.7) 1.3 (1.1–1.7)</td>
<td>1.2 (0.9–1.6) 1.4 (1.2–1.6) 1.3 (1.1–1.5)</td>
<td>1.4 (1.1–1.6) 1.5 (1.2–1.9) 1.6 (1.2–2.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: C, Control; R, RNC.  
$^a$Arithmetic mean (95% CI).  
$^b$Geometric means.
Quitting and dependence-related questionnaires

Overall, the RNC were rated as not quite as good as their usual cigarette brand. Cigarettes. Overall, the RNC were rated as not quite as good as their usual cigarette brand.

Figure 2. Mean percentage of compensation for smokers during nicotine reduction at different levels of nicotine content. Compensation is calculated on the basis of plasma cotinine levels and machine-determined nicotine yields comparing RNCs to the usual brand.

Subjective responses

There were no significant time- or group-related changes in the total Minnesota Nicotine Withdrawal Score, the total POMS score, or the CESD score. There was a significant decrease in the POMS vigor score comparing baseline to weeks 14 and 26 in the full RNC group and between baseline and week 14 in compliant RNC subjects ($P < 0.0166$). There was a significant increase in the POMS confusion score in the full RNC group comparing baseline to weeks 14 and 26 ($P < 0.0166$). Responses to the cigarette acceptance questionnaire indicated that on average the RNC were milder, less satisfying, had lower nicotine effect, and were of lesser quality than their usual cigarettes. Overall, the RNC were rated as not quite as good as their usual cigarette brand.

Quitting and dependence-related questionnaires

Although subjects did not intend to quit smoking on entry into the study, 3 subjects did quit smoking after completing the RNC taper. Two were in the RNC and one in the control group. All subjects were in the precontemplation stage on study entry. At 6 months 49% of RNC subjects compared with 86% of control subjects were still in the precontemplation stage, indicating that many more RNC subjects were thinking about quitting ($P < 0.001$). Comparing baseline and week 26 there were no significant changes in the FTND score, time to first cigarette, or in the self-efficacy score in any of the groups. Comparing baseline and week 26 in the full RNC group (mean, 5.70–5.13, $P < 0.05$). This change was significant in the middle nicotine content cigarettes and relatively low compensation (20%–40%) when smoking cigarettes with the lowest nicotine contents.

Discussion

The present study replicates the main findings of our previous research with some important differences. The present trial includes a larger number of subjects; nicotine tapering was conducted over a much longer period of time; and a control group of smokers smoking their own brand of cigarettes was added. Consistent with our prior work, we find that progressively reducing the nicotine content of cigarettes is associated with a progressive reduction in nicotine intake by the smokers. Thus, whereas smoking the lowest RNC cigarette plasma nicotine concentration was 22% and cotinine concentration 30% of the baseline value. These reductions are similar to what we observed with a 6-week taper and what was reported by Hatsukami and colleagues with a sudden reduction from usual cigarettes to 0.05 mg nicotine delivery cigarettes (8, 22). Reducing the nicotine content of cigarettes does not seem to be harmful to smokers as evidenced by no increase in cigarettes smoked per day and no increase in exposure to tobacco smoke combustion products (CO or PAHs). Furthermore, there was no adverse effect of RNC tapering on selected cardiovascular biomarkers that are associated with future risk of adverse cardiovascular events. As expected, smokers of their usual brand had consistent levels of intake of nicotine and other smoke constituents over the course of the 6 months.

An analysis of percentage of compensation of various RNCs compared with the usual brand shows that smokers compensated nearly completely when smoking a research cigarette with nicotine delivery similar to the usual brand. Partial compensation (40%–60%) was seen whereas smoking the middle nicotine content cigarettes and relatively low compensation (20%–40%) when smoking cigarettes with the lowest nicotine contents.

The reason for incomplete compensation for reduced nicotine delivery from the RNC cigarettes mostly likely relates to the design of the cigarettes, such that the nicotine content is lowered without altering the remainder of the tobacco or altering ventilation. Commercial low yield cigarettes in contrast are low yield primarily because they are highly ventilated; they contain as much nicotine as regular cigarettes (23). The smoke from such cigarettes is diluted with air and is perceived as less strong than higher yield cigarettes. This signals the smoker to take a larger puff. Another consequence of ventilation is less resistance to draw. In response to a highly ventilated cigarette the smoker inhales smoke more quickly, increases the volume of smoke inhaled, and reduces the efficiency of ventilation. Compensation for nicotine is easily accomplished. In contrast, the RNC cigarettes used in the present study present the smoker with smoke of a similar strength and resistance to draw independent of the nicotine content, thereby making compensation more difficult.

As was noted in our prior study, switching to RNCs is associated with a significant reduction in urine NNAL, meaning less exposure to the tobacco-specific nitrosamine and lung carcinogen NNK (8). NNK is formed from nicotine in the presence of nitriles in tobacco, so reducing the nicotine content of cigarettes reduces exposure to
Another third of smokers dropped out. The cigarettes were several years old and no cigarette, indicating that the cigarette quality rather from the control group (9%). Most of the dropouts from the RNC group, a greater number than dropouts from the control group comparing weeks 14 and 26.

Our study had some limitations that may limit the generalizability of the findings. The number of subjects might have been due to the design of the present study, which offered an additional 6 months of low nicotine cigarettes after the end of tapering. Analysis of Stages of Change did indicate that many more RNC smokers were thinking about quitting in the near future compared with controls. There were no significant changes in the FTND, time to first cigarette, or in their ratings of self-efficacy in the ability to quit over the course of the study, although FTND did decrease significantly in RNC subjects comparing weeks 14 and 26.

Change did indicate that many more RNC smokers might have been due to the design of the present study, although FTND did decrease significantly in RNC subjects comparing weeks 14 and 26.

Progressive reduction of the nicotine content of cigarettes as a national regulatory policy might have important potential benefits for the population. One is that reduced intake of nicotine is expected to result in a lower level of dependence and a greater likelihood of smoking cessation. Adolescents initiate smoking for social reasons, with friends, and later begin to smoke for pharmacologic reasons related to dependence. Presumably a cigarette with very low nicotine content would be less likely to support the transition from social to dependence smoking, although the threshold level of nicotine to prevent this transition is not yet known.

Disclosure of Potential Conflicts of Interest

N.L. Benowitz is a consultant to several pharmaceutical companies that market medications to aid smoking cessation and has served as a paid expert witness in litigation against tobacco companies. S. Hall has received material support for an ongoing clinical trial from Pfizer. No potential conflicts of interest were disclosed by the other authors.

Acknowledgments

The authors thank Dr. Faith Allen for data management, Lita Ramos for conducting the nicotine and cotinine analyses, the U.S. Centers for Disease Control and Prevention for cigarette smoke analyses, and Marc Olmsted for editorial assistance and Philip Morris for providing research cigarettes. Philip Morris has no involvement in any aspect of the design of the study or analysis or interpretation of the data.
Grant Support
The study was supported by U.S. Public Health Service grants CA78603 from the National Cancer Institute, DA02277, DA12393, and DA016752 from the National Institute on Drug Abuse, NIH.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked

References

Received July 13, 2011; revised January 25, 2012; accepted February 13, 2012; published OnlineFirst February 21, 2012.
Smoking Behavior and Exposure to Tobacco Toxicants during 6 Months of Smoking Progressively Reduced Nicotine Content Cigarettes

Neal L. Benowitz, Katherine M. Dains, Sharon M. Hall, et al.

*Cancer Epidemiol Biomarkers Prev* 2012;21:761-769. Published OnlineFirst February 21, 2012.

Updated version  
Access the most recent version of this article at:  
doi:10.1158/1055-9965.EPI-11-0644

Cited articles  
This article cites 22 articles, 7 of which you can access for free at:  
http://cebp.aacrjournals.org/content/21/5/761.full.html#ref-list-1

Citing articles  
This article has been cited by 48 HighWire-hosted articles. Access the articles at:  
/content/21/5/761.full.html#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, contact the AACR Publications Department at permissions@aacr.org.