*Global Perspectives*

# Nicotine and Carcinogen Exposure with Smoking of Progressively Reduced Nicotine Content Cigarette

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## Abstract

Background: **Reducing the nicotine content of cigarettes to make them non-addictive has been widely discussed as a potential strategy for tobacco regulation. A major concern with nicotine reduction is that smokers will compensate for reduced nicotine by smoking more cigarettes and/or smoking more intensively, thereby increasing their exposure to tobacco smoke toxins. This study examined whether gradual reduction in nicotine exposure increases exposure to tobacco smoke toxins.**
Methods: **This 10-week longitudinal study of 20 healthy smokers involved smoking their usual brand followed by different types of research cigarettes with progressively lower nicotine content, each smoked for 1 week. Subjects were followed for 4 weeks after returning to smoking their usual brand (or quitting). Smoking behaviors, chemical biomarkers of tobacco smoke exposure, and cardiovascular effect biomarkers were measured.**
Findings: **Intake of nicotine declined progressively as the nicotine content of cigarettes was reduced, with little evidence of compensation. 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 excretion decreased. Twenty-five percent of participants had spontaneously quit smoking 4 weeks after completing the research cigarette taper.**
Implications: **Our findings with reduced nicotine content cigarettes differ from those of commercial low yields for which compensatory smoking for lower nicotine delivery is substantial. Our data suggest that the degree of nicotine dependence of smokers can be lowered without increasing their exposure to tobacco smoke toxins. Gradual reduction of nicotine content of cigarettes seems to be feasible and should be further evaluated as a national tobacco regulatory strategy.** (Cancer Epidemiol Biomarkers Prev 2007; 16(11):2479–85)

## Introduction

That nicotine addiction sustains tobacco use for most smokers is well established (1). Once a person is addicted to nicotine, quitting smoking is difficult, and more than 90% of smokers who try to quit each year fail. Young people do not start to smoke because they are addicted. Rather, they start smoking because of psychosocial and environmental influences, particularly peer influences, psychological factors, and advertising, and to some extent genetic factors (2). Young people generally underestimate the addictiveness of nicotine, and most of them at first intend to smoke for only a few years (3). However, once they begin to smoke, many become addicted to nicotine, and this addiction sustains the self-injurious behavior into adulthood.

It is difficult to prevent the young from experimenting with cigarettes. However, federal regulation of the availability of nicotine in tobacco products might make it possible to avoid the transition from experimental or occasional smoking to addiction. A strategy for tobacco regulation that has been widely discussed is the Benowitz-Henningfield 1994 proposal to reduce the nicotine content of cigarettes to make cigarettes non-addictive (4-6). This proposal argued that if the nicotine content of cigarettes were lowered gradually, smokers would decrease their intake of nicotine (essentially weaning them from the nicotine addiction). This would reduce the level of addiction in smokers, making it easier for them to quit, and would prevent adolescents from becoming addicted. Tengs et al. (7) did a computer simulation of a nationally mandated nicotine reduction policy. This simulation predicted that a progressive decrease in the nicotine content of cigarettes over 6 years would result in a decline in smoking prevalence from 23% to

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5% of the U.S. population, with a cumulative gain of 157 million quality adjusted life-years.

A major concern with a nicotine reduction strategy has been that smokers would compensate for reduced nicotine levels by smoking more cigarettes and/or smoking cigarettes more intensely, therefore increasing their exposure to tobacco smoke toxins. Reduction of nicotine exposure might also result in undesirable withdrawal symptoms and/or mood disturbances; but might, if nicotine intake was to decline, result in a lower degree of dependence and more confidence in the ability to quit smoking. The present research examines these questions among adult, generally heavy smokers.

It is important to understand how reduced nicotine content (RNC) cigarettes studied in this research differ from commercial low-yield cigarettes. The research cigarettes used in the present study contain different amounts of nicotine, although they have similar tar yields (by machine testing) compared with popular normal yield cigarettes. In contrast, commercial low-yield cigarettes contain just as much nicotine per cigarette as do higher yield cigarettes (8, 9). Commercial low-yield cigarettes are low yield as a consequence of engineering characteristics, such as faster rate of burn, more porous paper, the use of reconstituted or expanded tobacco, and the placement of ventilation holes in or above the filter. Because there is plenty of nicotine available in the tobacco of commercial low-yield cigarettes, it is easy for the smoker to alter puff rate and/or smoking intensity and/or to block ventilation holes to increase nicotine intake per cigarette to the desired level (10).

## Materials and Methods

**Overview of Study Design.** This was a 10-week, unblinded study in which smokers smoked their usual brand of cigarette and then five types of research cigarettes. Progressively lower nicotine content cigarettes were smoked, each for 1 week. Smokers were then followed for an additional 4 weeks 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.

**Subjects.** Twenty-one healthy smokers were recruited by newspaper advertisements and were paid for participation in the study. Subjects were determined not to be interested in quitting smoking in the next 6 months. One subject withdrew before completion of the study due to an unanticipated need to travel. Subjects who completed the study included 11 men and 9 women with average age of 29 (range, 18-57). Before the study, subjects smoked an average of 20.1 cigarettes per day [range, 8-40; 95% confidence interval (95% CI), 16.4-23.8]; had smoked for an average of 12.4 years (95% CI, 7.9-16.8); had a Fagerstrom Test for Nicotine Dependence (FTND) score averaging 4.3 (95% CI, 3.3-5.2); and had an average baseline plasma cotinine concentration of 198 ng/mL (95% CI, 157-238). Written informed consent was obtained from each subject. The study was approved by the Institutional Review Board at the University of California, San Francisco.

**Study Protocol.** Subjects were studied in a community clinic. Subjects were asked to come to the clinic weekly, at which time cigarettes were dispensed, blood and urine samples were collected, and a battery of questionnaires was 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 provided with two more packs per week than they usually smoked and were asked to contact the research staff for additional cigarettes if they thought they would not have enough to last the week. Subjects typically attended the clinic in the late afternoon and early evening. In addition, the plasma nicotine concentration boost from smoking one cigarette was measured. This cigarette was smoked under observation, and plasma nicotine concentrations were measured before and 2 min after smoking the cigarette.

Plasma samples were assayed for concentrations of nicotine and cotinine (the proximate metabolite of nicotine), and blood was assayed for carboxyhemoglobin and for selected cardiovascular biomarkers. The following biomarkers were selected as predictors of coronary heart disease risk and/or markers of inflammation, endothelial function, and platelet activation: white blood cell count, C-reactive protein, fibrinogen, interleukin-6, sICAM, and P-selectin. Urine samples were assayed for concentrations of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a carcinogen itself and metabolite of the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK),as well as metabolites of four polycyclic aromatic hydrocarbons (PAH) found in tobacco smoke. NNAL and the PAH metabolites are biomarkers of exposure to common tobacco smoke carcinogens (11).

Questionnaires included smoking behavior over the previous week, Profile of Mood Scale (12), Minnesota Nicotine Withdrawal Scale (13), CESD Depression Scale (14), and a cigarette acceptance questionnaire (15). The cigarette acceptance questionnaire uses items with 7-point ratings that cluster into seven scales: satisfaction, similarity to usual brand, psychological reward, aversion, respiratory sensations, craving, and perceived strength. On entry into the study, at the end of the nicotine reduction phase and at the end of the study, subjects were also administered the FTND (16) and a self-efficacy questionnaire (17). 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 (17). Higher self-efficacy is associated with a higher probability of quitting smoking and lower risk of relapse after quitting.

**Cigarettes.** The RNC cigarettes were manufactured by Philip Morris Tobacco Company by blending nicotine-free tobacco with tobacco containing the usual amounts of nicotine. 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 five levels were selected so that at the end of tapering (week 6), the maximum nicotine intake could be expected to be 0.2 mg per cigarette or less, based on bioavailability calculations that have been described

previously (4). This level of nicotine availability represents an estimate of the threshold level of nicotine to maintain nicotine addiction. The characteristics of the research nicotine cigarettes, as well as the subjects' usual brand of cigarettes, are presented in Table 1. Machine testing of cigarettes using standard U.S. Federal Trade Commission procedures were done by the U.S. Centers for Disease Control and Prevention.

**Analytical Chemistry.** Plasma nicotine and cotinine were measured by gas chromatography with nitrogen-phosphorous detection modified for simultaneous determination of nicotine and cotinine using a capillary column (18, 19). Urine concentrations of NNAL (free plus conjugated) were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described previously (20), with the following modifications. A liquid-liquid extraction procedure was used instead of solid-phase extraction, and the HPLC separation was carried on a Phenomenex Synergi Polar-RP column, 2 mm ID × 250 mm length. Polycyclic aromatic hydrocarbon metabolites were measured in urine by LC-MS/MS (21). Cardiovascular biomarkers were assayed by enzyme immunoassay using commercial kits.

**Statistical Analysis.** Because measurements for each individual were correlated over time, a repeated measures model was constructed for each of the major variables. A mixed model regression analysis was done using PROC MIXED in SAS (version 9.1). The primary outcomes were changes from baseline to the end of tapering and to the end of follow-up, so data from weeks 1, 6, and 10 were included in the analyses. Means and 95% CIs were computed at each of the three time points. Percent differences in mean values were computed for each pair of time points, with $P$ values and 95% CIs for the differences constructed using the Tukey-Kramer adjustment for multiple comparisons. Variable values for total NNAL, polycyclic aromatic hydrocarbon metabolites, and several of the cardiovascular biomarkers were log-transformed to achieve approximate normality, and the analyses were done on the natural logarithm of the values. Geometric means and corresponding percent differences are reported for log-transformed variables. All data for the 20 participants who completed the study were included in the primary analysis. Because several subjects had stopped smoking at week 6 ($n$ = 4) and week 10 ($n$ = 5), the analyses were repeated omitting those subjects. Having stopped smoking was defined biochemically as having a plasma cotinine concentration of <10 ng/mL.

## Results

**Cigarette Consumption.** Average cigarette consumption increased slightly in weeks 2 to 5 and decreased slightly in week 6 compared with baseline smoking of the usual brand, but at the end of tapering, the change was not statistically significant (Fig. 1, Table 2). In a model that included all 10 weeks of data with the Tukey-Kramer adjustment for multiple comparisons, there were no significant differences in weeks 1 to 5, but cigarette consumption was significantly higher on week 5 compared with week 6. Cigarettes smoked per day were significantly lower at the end of the 4 weeks follow-up period compared with baseline or the end of tapering.

**Biochemical Exposures.** Plasma cotinine concentrations were similar while smoking usual brand and 12 mg RNC cigarettes, and then cotinine levels progressively decreased with progressive nicotine content reduction (Fig. 2, Table 2). During follow-up, cotinine levels increased significantly compared with week 6, but still remained significantly below baseline at week 10. Plasma nicotine followed similar trajectories over time. The boost in plasma nicotine after smoking a single cigarette decreased over the weeks of tapering (not measured at week 10). Blood carboxyhemoglobin did not significantly change when smoking RNCs, but decreased significantly between weeks 6 and 10 (Fig. 3). Urine NNAL was significantly reduced at week 6 compared with baseline and reduced at week 10 compared with both baseline and week 6. No significant temporal changes between baseline and the end of tapering were observed in urinary excretion of various polycyclic aromatic hydrocarbon metabolites. However, at week 10, urinary excretion of 2-naphthol and 2-hydroxyfluorene were significantly lower compared with week 6.

**Cardiovascular Measurements and Biomarkers.** Body weight increased significantly by an average of 0.9 kg comparing baseline and week 6, but these changes lessened and became nonsignificant by week 10 (Table 3).

**Table 1. Characteristics of research cigarettes**

| | Usual brand | Research cigarettes nominal nicotine content | | | | |
|---|---|---|---|---|---|---|
| | | 12 mg | 8 mg | 4 mg | 2 mg | 1 mg |
| Measured nicotine content (mg) | NM | 10.1 | 7.4 | 3.5 | 1.5 | 0.6 |
| Tobacco weight (mg) | NM | 624 | 619 | 620 | 618 | 614 |
| FTC method | | | | | | |
| Nicotine (mg) | 1.0 (0.9-1.2)* | 0.8 | 0.6 | 0.3 | 0.2 | 0.1 |
| Tar (mg) | 12.2 (10.8-13.7)* | 10.9 | 10.9 | 7.8 | 9.2 | 10.2 |
| Carbon monoxide (mg) | 12.6 (11.7-13.5) | 11.3 | 12.0 | 10.8 | 12.0 | 10.7 |
| NNK (ng) | NM | 63 | 67 | 64 | 57 | 56 |
| Pyrene (ng) | NM | 41 | 38 | 51 | 43 | 34 |
| Naphthalene (ng) | NM | 662 | 560 | 470 | 466 | 553 |
| Phenanthrene (ng) | NM | 120 | 120 | 106 | 113 | 132 |
| Fluorene (ng) | NM | 145 | 143 | 149 | 153 | 129 |

Abbreviation: NM, not measured.
*Mean (95% CI).

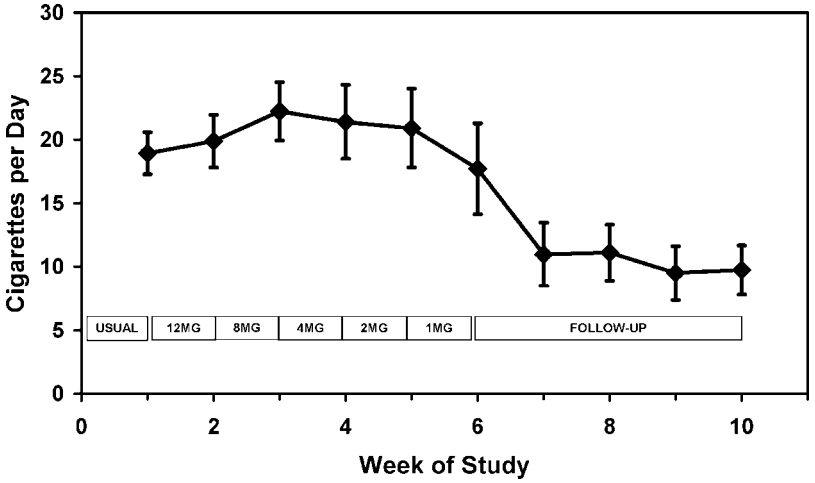


**Figure 1.** Cigarette consumption over weeks of the study during progressive reduction of nicotine content of cigarettes (weeks 1-6) and after return to usual cigarettes or quitting (weeks 7-10). *Points,* mean values for 20 subjects; *bars,* SE.

No significant changes between baseline and week 6 were observed in blood pressure, heart rate, white blood cell count, hemoglobin, HDL cholesterol, C-reactive protein, fibrinogen, sICAM, IL-6, or P-selectin.

**Subjective Responses.** No significant changes were observed in the Profile of Mood Scale scores or the CESD depression rating. The withdrawal scores for irritability and increased eating were significantly higher at week 6 compared with baseline [week 6 to week 1, 1.7 (95% CI, 0.4-3.0) and 2.3 (95% CI, 0.6-4.0)]. Self-reported eating remained higher at week 10 [2.2 (0.7-3.7)] compared with baseline. The cigarette acceptance questionnaire indicated that subjects found the reduced nicotine cigarettes to be less strong, less flavorful, of generally lower quality and less satisfying compared with the usual brand. There was, however, no significant increase in cigarette craving while smoking RNC cigarettes.

**Quitting/Self-Efficacy during Follow-up.** Although subjects did not intend to quit smoking on entry into the study, five subjects did quit smoking (confirmed by plasma cotinine levels of <10 ng/mL) after completing the RNC taper. The self-efficacy rating (inquiring as to how confident one is that he or she can quit) was significantly higher at weeks 6 and 10 compared with baseline [week 6 to week 1, 1.3 (95% CI, 0.3-2.3); week 10 to week 1, 2.3 (95% CI, 0.8-3.8)]. The FTND decreased from 4.3 (3.3-5.2) at baseline to 3.6 (2.4-4.7) at week 6 ($P = 0.09$) and 2.5 (1.3-3.6) at week 10 ($P < 0.001$). Analysis of the cigarette consumption, biochemical exposure, and cardiovascular data in only those subjects who continued to smoke at weeks 6 and 10 (that is, excluding data from subjects with cotinine levels <10 ng/mL) resulted in small effects on mean values and had effects on statistical significance of a few of the various comparisons. These included the comparison of cigarette consumption between weeks 6 and 10; weight gain between weeks 1 and 6; decrease in NNAL between weeks 1 and 6; and decreases in PAH metabolite excretion, all of which were no longer significant.

**Table 2. Smoking behavior and chemical exposures while smoking reduced nicotine cigarettes**

| | Week 1, mean (95% CI) | Week 6, mean (95% CI) | Week 10, mean (95% CI) | % difference week 6 versus week 1, mean (95% CI) | % difference week 10 versus week 1, mean (95% CI) | % difference week 10 versus week 6, mean (95% CI) |
|---|---|---|---|---|---|---|
| Cigarettes per day | 18.9 (15.5-22.3) | 17.7 (10.4-25.0) | 10.1 (6.2-14.0) | −6 (−37-24) | **−47 (−63 to −30)** | **−43 (−80 to −6)** |
| Pre-smoking plasma nicotine (ng/mL) | 13.0 (10.2-15.7) | 3.8 (1.6-6.1) | 8.3 (4.1-12.4) | **−70 (−101 to −40)** | −36 (−76-4) | **115 (28-202)** |
| Nicotine boost (ng/mL) | 8.2 (5.4-11.1) | 1.0 (0.6-1.4) | NM | **−88 (−122 to −54)** | NM | NM |
| Blood COHB (%) | 3.2 (2.6-3.9) | 3.6 (2.3-4.9) | 2.1 (1.2-3.0) | 11 (−22-45) | **−35 (−64 to −7)** | **−42 (−66 to −18)** |
| Plasma cotinine (ng/mL) | 194 (152-235) | 62 (28-96) | 109 (64-153) | **−68 (−93 to −43)** | **−44 (−63 to −25)** | 75 (9-142) |
| Total NNAL* (pmol/mg creat) | 1.17 (0.79-1.73) | 0.92 (0.58-1.44) | 0.53 (0.29-0.95) | **−22 (−38-0)** | **−55 (−71 to −32)** | **−43 (−60 to −17)** |
| 1-OH-pyrene* (pmol/mg creat) | 0.97 (0.62-1.33) | 1.06 (0.80-1.50) | 0.89 (0.62-1.33) | 18 (−12-57) | −6 (−44-56) | −20 (−46-16) |
| 2-Naphthol* (pmol/mg creat) | 77.9 (62.0-97.4) | 80.5 (62.0-104.4) | 57.5 (43.4-77.0) | 3 (−23-37) | **−26 (−43 to −5)** | **−28 (−48 to −1)** |
| Sum of hydroxyphenanthrene isomers* (pmol/mg creat) | 2.4 (1.8-3.4) | 2.6 (1.9-3.4) | 2.6 (1.7-3.8) | 6 (−23-45) | 5 (−25-47) | −1 (−24-30) |
| 2-Hydroxyfluorene* (pmol/mg creat) | 6.9 (5.1-9.3) | 7.8 (5.8-10.6) | 4.7 (2.9-7.7) | 13 (−15-50) | −32 (−58-11) | **−39 (−60 to −9)** |

NOTE: Week 1 is while smoking usual brand. Week 6 is while smoking the lowest RNC cigarette (1 mg). Week 10 is 4 weeks after the end of RNC smoking. Values in bold indicate significant differences ($P < 0.05$).
*Geometric means; NM = not measured; creat = creatinine.

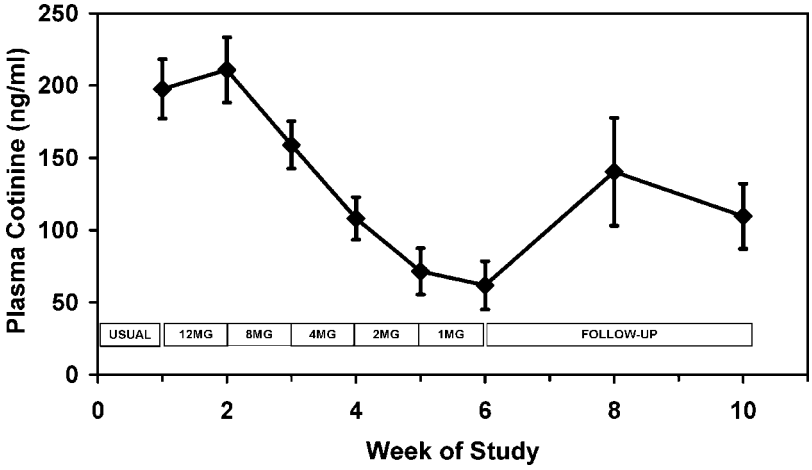


**Figure 2.** Plasma cotinine concentration over weeks of the study during progressive reduction of nicotine content of cigarettes (weeks 1-6) and after return to usual cigarettes or quitting (weeks 7-10).

Excluding quitters, the FTND decreased from 4.9 (4.1-5.7) at baseline to 4.4 (3.1-5.6) at week 6 (not significant) and 3.4 (2.1-4.6) at week 10 ($P < 0.01$).

## Discussion

We present novel findings on the smoking behavioral response, biochemical exposures, cardiovascular risk biomarkers and acceptability during a progressive reduction of the nicotine content of cigarettes. We found that progressive reduction of the nicotine content of cigarettes resulted in a progressive reduction in nicotine intake as measured by nicotine and cotinine levels. We found little evidence of compensation, as shown by stable levels of cigarette consumption and stable levels of the tobacco smoke biomarkers carbon monoxide and PAH metabolites.

Urine NNAL excretion was significantly decreased (about 20%) after nicotine reduction. NNAL is a metabolite of the tobacco-specific nitrosamine NNK, which is formed from nicotine in the presence of nitrates in tobacco, primarily during the curing process (22). As the nicotine content of cigarettes declines, one would expect that levels of NNK would decline as well. Comparing the 12- and 1-mg RNC machine deliveries, there was an 11% decrease in NNK yield. We did not have data on NNK yields for the usual brands of cigarettes, so we could not compare the machine yields of NNK for cigarettes smoked at weeks 1 and 6 to see if the change in yield corresponded to the actual change in NNAL excretion over the same period of time. However, it is most likely that lower NNK yields explain the observed decrease in NNAL excretion in our subjects while smoking RNC cigarettes.

Cardiovascular biomarkers showed no evidence of a more adverse risk profile when subjects smoked RNC. After stopping smoking of low nicotine content cigarettes, consumption of the subject's usual brand of cigarette dropped below baseline levels, and plasma cotinine remained lower than baseline for at least 4 weeks, suggesting that the level of nicotine dependence had been reduced. Nicotine withdrawal scores for irritability and eating increased over the course of tapering, consistent with the reduction in nicotine intake. The relatively mild intensity of these symptoms is consistent with the gradual reduction in nicotine intake. Also supporting a reduced level of nicotine dependence was the significant decline in the FTND score, observed both in the analysis of all subjects and after excluding subjects who had quit smoking.

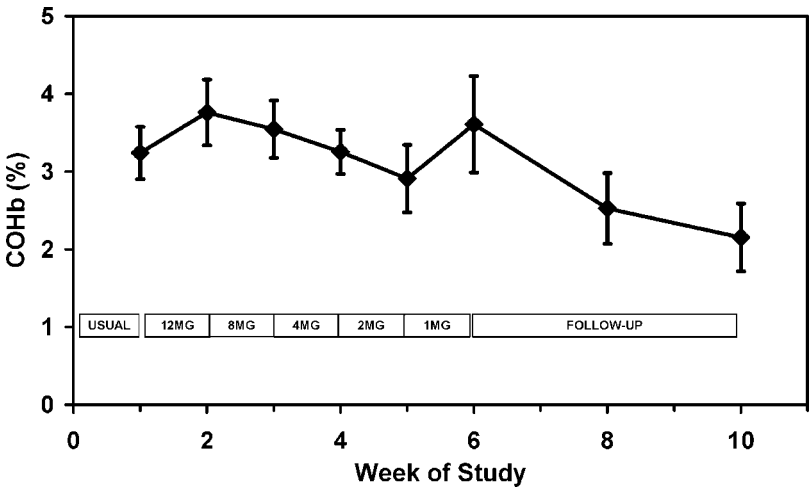


**Figure 3.** Blood carboxyhemoglobin (COHB) concentration over weeks of the study during progressive reduction of nicotine content of cigarettes (weeks 1-6) and after return to usual cigarettes or quitting (weeks 7-10).

**Table 3. Cardiovascular biomarkers while smoking reduced nicotine cigarettes**

| | Week 1, mean (95% CI) | Week 6, mean (95% CI) | Week 10, mean (95% CI) | % difference week 6 versus week 1, mean (95% CI) | % difference week 10 versus week 1, mean (95% CI) | % difference week 10 versus week 6, mean (95% CI) |
|---|---|---|---|---|---|---|
| Body weight (kg) | 71.4 (65.8-77.1) | 72.3 (66.7-78.0) | 72.0 (66.4-77.7) | **1 (0-2)** | 1 (0-2) | 0 (−1-1) |
| Systolic blood pressure (mm Hg) | 122 (116-129) | 124 (116-132) | 123 (117-130) | 1 (−4-7) | 1 (−5-7) | −1 (−8-7) |
| Diastolic blood pressure (mm Hg) | 79.0 (73.4-84.6) | 76.6 (71.9-81.2) | 78.8 (74.9-82.8) | −3 (−10-4) | 0 (−9-8) | 3 (−3-9) |
| Heart rate | 76.0 (71.2-80.7) | 72.9 (67.2-78.5) | 79.8 (73.7-86.0) | −4 (−12-3) | 5 (−6-16) | 10 (−3-22) |
| WBC count (1,000) | 7.3 (6.5-8.2) | 7.7 (6.9-8.4) | 7.6 (6.5-8.8) | 4 (−6-15) | 4 (−11-20) | 0 (−15-15) |
| Hemoglobin (%) | 14.7 (14.1-15.2) | 14.4 (13.8-14.9) | 14.4 (13.9-14.9) | −2 (−4-0) | −2 (−4-0) | 0 (−2-2) |
| HDL cholesterol (ng/dL) | 49.9 (40.9-58.8) | 51.2 (43.3-59.0) | 51.5 (42.3-60.7) | 3 (−7-12) | 3 (−6-13) | 1 (−9-10) |
| C-reactive protein* (mcg/mL) | 1.00 (0.59-1.68) | 1.32 (0.72-2.42) | 1.25 (0.67-2.35) | 33 (−26-136) | 26 (−36-148) | −5 (−57-107) |
| sICAM* (ng/mL) | 241 (219-265) | 253 (219-293) | 229 (207-253) | 5 (−6-18) | −5 (−12-2) | −10 (−18-0) |
| Fibrinogen *,† (mg/dL) | 247 (223−273) | 263 (232-298) | 259 (243-275) | 7 (−4-18) | 5 (−9-21) | −2 (−16-16) |
| IL-6* (pg/mL) | 1.02 (0.76-1.37) | 0.97 (0.71-1.31) | 1.16 (0.77-1.74) | −5 (−26-22) | 14 (−28-80) | 20 (−19-77) |
| P-selectin* (ng/mL) | 40 (35-45) | 41 (35-48) | 40 (35-46) | 3 (−6-13) | 1 (−5-7) | −3 (−14-10) |

NOTE: Week 1 is while smoking usual brand. Week 6 is while smoking the lowest RNC cigarette (1 mg). Week 10 is 4 weeks after the end of RNC smoking. Values in bold indicate significant differences ($P < 0.05$).
*Geometric means.
†$n = 11$.

The results of our study are quite different from those reported for commercial low-yield cigarette-switching studies. Smokers who switch from higher to lower yield commercial cigarettes exhibit a high degree of compensation, with relatively little or no reduction in nicotine intake or exposure to other tobacco smoke toxins (10, 20). The key difference between commercial low-yield cigarettes and the RNC cigarettes described in our study is that in the RNC cigarettes, the absolute content of nicotine in the tobacco is reduced. In contrast, commercial low-yield cigarette tobacco contains just as much nicotine as does higher yield cigarette tobacco, and compensation can easily be achieved by taking bigger and faster puffs and/or by blocking ventilation holes (8-10). These behaviors markedly reduce the extent of ventilation so that nicotine can easily be extracted from the cigarettes. In contrast, it is virtually impossible to fully compensate for RNC in cigarettes because nicotine is just not present in the tobacco in adequate amounts.

That most smokers compensate little or not at all when the nicotine content of cigarette tobacco is reduced in the absence of changes in tar and other characteristics of the cigarette was observed in another study of smoking single cigarettes with variable nicotine content conducted in our laboratory (23), as well in a study by Rose et al. (24). If the smoker finds it is very difficult to extract nicotine from a cigarette, he or she may give up trying and accept lower doses of nicotine, gradually reducing their level of dependence. Tar and other combustion products in cigarette smoke also contribute to the sensory characteristics of inhaled smoke. Tar-related sensory characteristics of the cigarette smoke do provide some reinforcement and may lessen withdrawal symptoms compared with the combined reduction of tar and nicotine deliveries (25). Regardless of the mechanism, our study suggests that smokers can be safely switched to RNC cigarettes without increasing their exposure to toxic tobacco smoke chemicals and without any apparent adverse cardiovascular effects.

A reduction in nicotine intake while smoking reduced content cigarettes might be expected to be associated with the emergence of nicotine withdrawal symptoms, including related mood disturbances. Our subjects did report significantly more irritability and increased eating at week 6 compared with baseline, consistent with nicotine withdrawal. Body weight increased an average of 0.9 kg at week 6, which is also a feature of nicotine withdrawal. There was no increase in cigarette craving, and no significant changes in mood or depression scores were recorded. The relatively mild nicotine withdrawal symptoms reported most likely are due to the gradual reduction of nicotine exposure over several weeks. Although subjects did not find the research cigarettes to be as strong, flavorful, or as satisfying as the usual brand, in general subjects found the cigarettes to be acceptable. Although compliance with smoking only the research cigarette and not other brands during the tapering phase could not be verified, the observed decline in nicotine exposure indicated that compliance was substantial.

Our study had some limitations. The number of subjects was relatively small, and there was a relatively rapid lowering of the nicotine content of their cigarettes. It is possible that a longer period of smoking at each nicotine reduction stage would have resulted in a different degree of compensation for lower nicotine availability. The study was not blinded, although this would also be the case if low nicotine content cigarettes were mandated as part of a national strategy to reduce the addictiveness of cigarettes. Compliance with smoking only the research nicotine cigarettes could not be tested, but the observation of a steady reduction of nicotine exposure, as evidenced by the decline in blood cotinine levels, argues for compliance—a lack of compliance would be expected to have diminished such a treatment effect. Finally, our subjects were relatively young, generally middle class and well educated and may not be typical of highly addicted smokers in developed countries.

The implications of our findings are twofold. First, our data suggest that gradual nicotine reduction of cigarettes is safe and is a potentially feasible regulatory strategy. As the number of participants in our study is small and the

tapering rapid, further research on more gradual reduction and longer term exposure to reduce nicotine cigarettes is certainly warranted. Teng et al. who modeled the effects of a reduced nicotine policy on public health as mentioned previously, concluded that ''Policy makers would be hard-pressed to identify another domestic public health intervention short of historical sanitation efforts, that has offered this magnitude of benefit to the population''(7).

Although not a primary purpose of this research, our study provides evidence that reduction of the nicotine content of cigarettes reduces the level of nicotine dependence and makes it easier for smokers to quit smoking. We observed that after gradual reduction of nicotine intake and upon returning to smoking their usual brands, smokers smoked fewer cigarettes per day and took in less nicotine per day compared with their usual level before the reduced nicotine cigarette intervention. Furthermore, their FTND score decreased significantly from baseline to when subjects had returned to smoking their usual brand. In support of this trend, both at the end of tapering and also at week 10 after resuming their usual cigarettes, self-efficacy (measured by a questionnaire assessing confidence in being able to quit smoking) was significantly greater compared with baseline. Several of our subjects quit smoking spontaneously, although they had not intended to do so when entering the study. It is likely that this occurred because the level of physical dependence was reduced. We view this as an intriguing finding, but because the number of subjects in the study was small and the study was not controlled, no definitive conclusion about quitting can be made. However, if the level of dependence can be reduced as suggested, one might expect that smoking cessation would be easier. Thus, gradual reduction of nicotine intake as a regulatory strategy might make it easier for smokers to quit smoking. Our study did not address the question of whether reduced nicotine cigarettes results in reduced addiction potential among adolescent experimental smokers, an issue that must be addressed in future research.

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