Effects of Cigarette Reduction on Cardiovascular Risk Factors and Subjective Measures*

Dorothy K. Hatsukami, PhD; Michael Kotlyar, PharmD; Sharon Allen, PhD, MD; Joni Jensen, MS; Shelby Li, PhD; Chap Le, PhD; and Sharon Murphy, PhD

Study objectives: **To assess the effect of continued smoking and smoking reduction on cardiovascular biomarkers (*eg*, WBC count, cholesterol concentrations, BP, heart rate).**
Design, setting, and participants: **This study, conducted at the University of Minnesota, randomized smokers interested in significantly reducing cigarette use but not quitting to either start 12 weeks of smoking reduction immediately (n = 102), assisted by nicotine replacement therapy, or to a 6-week wait list (n = 49). Those starting smoking reduction were required to reduce smoking by 25% for 2 weeks, 50% for 2 weeks, and 75% during the final 2 weeks. After 6 weeks, the subjects were asked to maintain a 50% reduction or quit. Nicotine gum and, if necessary, nicotine patch were used to achieve reduction goals. The wait list group (n = 49) smoked *ad libitum* for 6 weeks and then reduced smoking as previously described.**
Measurements and results: **Cardiovascular biomarkers (*eg*, WBC count, cholesterol concentrations, BP, heart rate) were assessed at several time points after enrollment. During *ad libitum* smoking, cardiovascular biomarkers remained relatively stable with correlation coefficients across the various time measurements, ranging from 0.44 to 1.00 ($p < 0.01$ for all measures). Among successful nonabstinent reducers (64 of 151 subjects), significant improvements were found in many biomarkers (*eg*, hemoglobin, hematocrit, RBC and WBC counts, lipids, BP, heart rate, respiratory symptoms, all $p < 0.0167$).**
Conclusions: **These results show the availability of reliable and dose-sensitive biomarkers and that reduction in smoking can lead to significant but only modest changes in cardiovascular risk factors in healthy smokers. It is not known whether the reductions in cardiovascular risk factors observed after smoking reduction are also associated with reduced disease risk. Additional research is necessary to address this issue.** ***(CHEST 2005; 128:2528–2537)***

Key words: biomarkers; cardiovascular risk factors; cigarette reduction; harm reduction

Abbreviations: ApoA1 = apolipoproteins A1; ApoB = apolipoproteins B; CPD = cigarettes per day; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume

Although the idea of reducing tobacco toxin exposure among continuing smokers is not a new concept, recent efforts by the tobacco industry to develop and market potential reduced-exposure products have resulted in an increased interest in examining this approach. The escalating introduction of potential reduced-exposure products has prompted the US Food and Drug Administration to sponsor a report from the Institute of Medicine and for the National Cancer Institute to convene an expert panel to consider the feasibility of this approach, the necessary science and systems that need to be in place in order to ensure public health, and the specific research areas that will need to be pursued.[1,2] The identification of reliable and valid

*From the Transdisciplinary Tobacco Use Research Center (Drs. Hatsukami, Li, Le, and Murphy, and Ms. Jensen), University of Minnesota; Department of Experimental and Clinical Pharmacology (Dr. Kotlyar), College of Pharmacy, University of Minnesota; and Department of Family Practice (Dr. Allen), University of Minnesota, Minneapolis, MN.
This study was performed at the University of Minnesota, Minneapolis, MN.
This study was supported by National Institutes of Health grant P50DA 13333.

Manuscript received January 27, 2005; revision accepted April 4, 2005.

Correspondence to: Dorothy K. Hatsukami, PhD, University of Minnesota, Tobacco Use Research Center, 2701 University Ave SE, Minneapolis, MN 55414; e-mail: hatsu001@umn.edu

biomarkers for tobacco toxin exposure was determined to be a particularly important area of research.

Biomarkers can be considered as measures of the following: (1) toxins specifically related to exposure of tobacco constituents, such as nicotine or tobacco-specific nitrosamines; (2) risk contributors to disease, such as lipoproteins, C-reactive protein, WBC count; (3) disease markers such as pulmonary function; or (4) clinical outcome measures, such as hospitalizations, occurrence of disease, or death. Smokers compared to nonsmokers have significantly elevated risk factors for cardiovascular disease (CVD),[3] and these risk factors improve among smokers after cessation of cigarettes.[1,4] To date, few studies have examined the effects of changes in cigarette dose on cardiovascular risk factors. Of the studies that currently exist, the results show significant improvement on these measures; however, the sample sizes have tended to be small,[5] and no control groups have been used.[5,6]

In this study, the reliability and validity of measures of risk contributors to CVD were examined. The reliability of these measures was determined by examining the consistency of these measures over time during *ad libitum* tobacco use. The potential validity and sensitivity of these measures were determined by examining the dose-response relationship of these measures as the number of cigarettes smoked is reduced. We hypothesized that smoking reduction leads to a dose-related improvement on cardiovascular risk factors.

As a secondary aim, this study examined the feasibility of reducing the number of cigarettes smoked among smokers unwilling or unable to quit smoking. Prior studies[1,7] have shown that smokers are able to reduce the number of cigarettes smoked with or without the use of pharmacologic agents; however, whether a significant proportion of the population is able to sustain this reduction[4,7,8] or whether this reduction leads to significant reduction in biomarkers for disease[9] has been called to question. Data were analyzed to determine the extent to which subjects were able to reduce smoking and the proportion of subjects able to sustain this reduction. We hypothesized that the majority of subjects can reduce smoking; however, sustaining significant reductions in smoking that leads to beneficial effects from smoking may be difficult to achieve.

Materials and Methods

Study Design

Details of the study design have been described previously.[10] In brief, cigarette smokers from 18 to 70 years of age and interested in significantly reducing cigarette use were recruited. Inclusion criteria included the following: (1) smoking from 15 to 45 cigarettes per day (CPD) for the past year (in order to reduce heterogeneity); (2) uninterested in and no plans for quitting in the next 30 days; (3) good physical health (no unstable medical condition); (4) no contraindications for nicotine replacement use; (5) good mental health (*eg*, not meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[11] criteria for any psychiatric diagnosis, including substance abuse, within the past 6 months); (6) not using other tobacco or nicotine products or medications that might affect tobacco use or be affected by reduction of tobacco use; and (7) for female subjects, not pregnant or nursing. The University of Minnesota Institutional Review Board approved this study and the informed consent procedures.

Subjects who met inclusion criteria monitored their use of cigarettes (and other tobacco products) on a daily basis for a period of 2 weeks to assess baseline tobacco use. The following week, subjects returned for the baseline visit (visit – 1), when they were randomly assigned to the experimental cigarette reduction group or to the wait list control group for 6 weeks. Subjects monitored their smoking for another week, after which baseline measures were repeated at a second baseline visit (visit 0). Subjects assigned to the wait list control were the basis for the analysis that examined the consistency or intrasubject reliability across the various biomarkers for health risks or tobacco toxin exposure. This group was required to maintain and monitor smoking for a total period of 8 weeks. Subjects were assessed on all dependent measures during the first two baseline visits and then at weeks 4 and 6 after the second baseline visit. After the 8 weeks of *ad libitum* smoking, subjects entered the treatment reduction phase as described below.

Subjects assigned to the cigarette reduction group were expected to reduce their cigarette intake by 25% in the first 2 weeks, 50% in the subsequent 2 weeks, and 75% in the final 2 weeks. Subjects were given 4-mg nicotine gum to assist in their reduction of cigarette smoking and were instructed on several possible methods to use nicotine gum to achieve reduction goals, including substitution of nicotine gum for cigarettes, timed interval for nicotine gum use, and situational use of nicotine gum. The amount of gum recommended was based on the number of cigarettes smoked (*eg*, 10 pieces of nicotine gum for a 20-CPD smoker for a 50% reduction in cigarettes; 15 pieces of nicotine gum for a 20-CPD smoker for a 75% reduction in cigarettes). If a subject was unable to approach the 50% goal (more than two cigarettes from 50% reduction goal), he or she was offered the option of using a 14-mg patch (Nicoderm CQ; SmithKlineBeecham; Research Triangle Park, NC) in conjunction with the nicotine gum for a 2-week period until the 75% reduction period. Similarly, if a subject was unable to approach the 75% reduction goal or expressed concern about that level of reduction, an option of using a 21-mg Nicoderm CQ patch in conjunction with the nicotine gum was offered. After the 6-week treatment period, subjects who demonstrated some reduction in smoking were given nicotine replacements (nicotine gum or patch) for another 6 weeks, with the goal of gradually reducing their use of nicotine gum over this latter 6-week period.

In addition to the pharmacologic therapies, subjects met with a trained counselor during the clinic visits for brief individual sessions lasting approximately 10 min. During these sessions, a specific, structured format was followed. Topics included the following: (1) current tobacco use status; (2) motivations for tobacco reduction; (3) problems encountered; (4) problem solving in these difficult situations; and (5) providing support. If at any time after (or during) the 6-week treatment sessions the subject reported wanting to quit, a target quit date was established and self-help treatment manuals were dispensed. Brief