Effects of Timing and Extent of Smoking, Type of Cigarettes, and Concomitant Risk Factors on the Association Between Smoking and Subclinical Atherosclerosis

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Background and Purpose—The purpose of this study was to evaluate the effects of timing and extent of smoking, type of cigarettes, and concomitant vascular risk factors (VRFs) on the association between smoking and carotid intima-media thickness (C-IMT) in a lipid clinic population.

Methods—1804 patients (869 men, age 21 to 85 year) participated in the study. Smoking habits were recorded and C-IMTs were measured by B-mode ultrasound. The associations of C-IMT with smoking status (never, former, and current) and with the cigarettes’ content of tar, nicotine, and carbon monoxide (alone or combined to define “light” or “regular” cigarettes) as well as the interactions between smoking status, gender, and VRFs were evaluated before and after adjustment for confounders.

Results—C-IMT was highest in current smokers, lower in former, and lowest in never smokers. C-IMT of former and current smokers differed only after data adjustment for variables describing the extent and timing of smoking exposure. C-IMT was positively related to the number of pack-years (number of cigarettes smoked per day [cigarettes/d] multiplied by number of years smoked/20) in both former and current smokers. There were no differences in C-IMT between smokers of cigarettes with high or low nicotine, tar, or carbon monoxide content. Both diabetes and hypertension interacted positively with smoking in determining C-IMTs.

Conclusions—In the present cross-sectional observational investigation, carried out in a cohort of patients attending a lipid clinic, consumption of light cigarettes does not reduce the atherogenic effect of smoking on C-IMT. The number of pack-years, cigarettes/d, and years of smoking are relevant covariates in evaluating the effects of smoking on vascular health. The presence of diabetes or hypertension strengthens the association between smoking and cardiovascular risk.

Key Words: atherosclerosis ■ carotid intima-media thickness ■ smoking ■ type of cigarettes ■ imaging

The harmful effect of smoking on atherosclerosis and cardiovascular health is well established; nevertheless, many people continue or even start to smoke.

Carotid intima-media thickness (C-IMT), a marker of subclinical atherosclerosis, has been used as a surrogate end point to investigate the effects of cigarette smoking. Some studies have failed to report a difference in C-IMT between former and current smokers, which suggests that the effect of smoking on vascular walls is irreversible; yet, categorizations that do not take into account the extent and timing of smoking may yield misleading conclusions. For example, an individual with a 40-year history of cigarette smoking who stopped smoking 1 year ago is classified as a former smoker, but his/her C-IMT may well not differ from that of a current smoker. Conversely, a current smoker is included in this category even if he/she started smoking only a few months ago with an effect of smoking still negligible.

Other factors potentially modifying the effect of smoking on the arterial walls are the cigarette contents of tar, nicotine, and carbon monoxide (CO) as well as the possible interactions with other common vascular risk factors (VRFs). To the best of our knowledge, these issues have not been fully investigated until now.

We aimed to investigate: (1) the effects of chronic use of “light” or “regular” cigarettes (as defined by the tar/nicotine/CO content declared on the pack) on C-IMT; (2) to what extent variables such as the number of years of smoking and the number of cigarettes smoked per day (cigarettes/d) modify the effect of smoking on C-IMT; and (3) whether there is a synergy between smoking, gender, and conventional VRFs in patients at high risk of cardiovascular disease.

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Materials and Methods

Patients
Consecutive patients (n=1804, 869 men, age-range 21 to 85 years), attending for the first time the University Centre for Dyslipidemias - E. Grossi Paolotti (Niguarda Hospital, Milan, Italy) had their C-IMT measured by B-mode ultrasound. Patients attend this Lipid Clinic either spontaneously or referred by general practitioners.

Data from medical history, physical examination, and laboratory determinations were collected. Subjects were carefully questioned face-to-face about smoking habits, including the year when smoking began (and ended, for former smokers), number of cigarettes/d, and the unique or predominant cigarette brand used. Data about cigarettes’ content of tar, nicotine, and CO were collected from the information reported on the pack. For former smokers, years elapsed since smoking cessation (YESSC) was calculated. The extent of cigarette exposure, referred as “pack-years,” was calculated as: number of cigarettes smoked per day multiplied by number of years smoked/20.

Patients were classified according to their smoking status as never, former, and current smokers. Never smokers (n=1113) were defined as those who had never smoked any cigarette in their lifetime. Current smokers (n=315) were defined as those who were smokers at enrollment and had a pack-years ≥0.6. Former smokers (n=376) were defined as those who had a pack-years ≥0.6 but had not smoked for at least 1 year before their interview. Smokers of cigars and other tobacco products, cigarette consumers with a pack-years <0.6, or those who had stopped smoking throughout the year preceding the interview were excluded because equivocally classifiable.

Patients were considered hypercholesterolemics or hypertriglyceridemics if plasma concentrations of LDL-cholesterol or triglycerides were >4.14 and 1.71 mmol/L, respectively, or when they were being treated with lipid-lowering drugs; hypoalphalipoproteineemic if HDL-C levels were <0.104 mmol/L (in males) or <1.33 mmol/L (in females); hypertensive if systolic or diastolic blood pressure were >140 and 95 mm Hg, respectively, or when they were on treatment with antihypertensive drugs; and diabetics if blood glucose concentrations were >7.01 mmol/L or they were being treated with insulin or oral hypoglycemic drugs.

The study complies with the Declaration of Helsinki and was approved by the Hospital Institutional Review Board. Informed consent was obtained from all patients.

B-Mode Ultrasound Examinations
C-IMT was measured in real-time using the electronic caliper of the ultrasonic device. The ultrasonic standardized protocol, the intra- and interobserver repeatability, and the rationale for using this clinically applicable approach rather than an automated edge-detection system were described previously. Scanning was performed by trained sonographers unaware of the data on smoking.

Statistical Analysis
Continuous and categorical data are expressed as mean±SD and number (percentage), respectively. Variables were tested for normal distribution using Kolmogorow-Smirnov test and those with a skewed distribution (ie, triglycerides and C-IMT) were log transformed. Group comparisons for continuous variables were performed by ANOVA and χ² test, respectively. Correlations were assessed by Pearson analysis. Multiple regression analysis was used to confirm the independence of the relationships between variables related to timing/extent of smoking and C-IMT.

Covariance analysis (General Linear Models) was used to adjust for confounding factors and to evaluate interactions between smoking habits, gender, and VRFs.

To compare C-IMTs of high/low-tar, high/low-CO, and high/low-nicotine cigarette consumers, 4 models were run using IMTmean or IMTmax as dependent variables and possible confounders as independent variables. The first model was run without any adjustment; the second by adjusting for age and gender (the variables most consistently associated with C-IMT); the third by adding, among covariates, variables related to the amount of cigarettes smoked (years of smoking, cigarettes/d); and the fourth by adding all possible confounders.

Statistical significance was assumed if 2-tailed P was ≤0.05. Data were analyzed using SPSS version 13.0.

Results
Table 1 shows the characteristics of subjects stratified according to smoking habits. Age- and gender-adjusted C-IMTs in both current and former smokers were significantly larger than in never-smokers, whereas the difference between former and current smokers was not significant (Table 1).

Effect of Cigarette Smoking According to Extent and Timing of Exposure
To determine whether the atherogenic effect of smoking is dose-dependent, C-IMT was plotted against pack-years (Figure 2). Carotid IMTmean increased with pack-years in both former and current smokers; no interaction was found between pack-years and whether the smoking status was “former” or “current.” Similar findings were obtained when C-IMTmax (r=0.34 and r=0.37 for former and current smokers, respectively; both P<0.0001) or single-segment ultrasonic variables (CC-IMTmean, Bif-IMTmean and ICA-IMTmean) were considered (lowest r=0.32; all P<0.0001).

Effect of “Light” and “Regular” Cigarettes

(Light and Regular Cigarettes)

(Individual Effects of Tar, Nicotine, and CO)
To evaluate whether the atherogenic effect of smoking depends on the tar, nicotine, or CO content of the cigarettes smoked, current smokers were stratified into consumers of high/low-tar, high/low-nicotine, and high/low-CO cigarettes. Cigarettes were classified as low-tar when the tar content reported on the pack was <7 mg, as low-nicotine when the nicotine content was <0.7 mg, and as low-CO when the CO content was <7 mg.

Table 2 shows the results of covariance analyses of the use of high/low-tar, high/low-nicotine, and high/low-CO cigarettes on C-IMT. For each of these stratifications, 4 models were calculated using IMTmean or IMTmax as dependent variables and possible confounding factors as independent variables. No differences in IMTmean were detected between high/low-tar or high/low-CO consumers. Differences in IMTmax between users of high/low-tar cigarettes became statistically significant after adjustment for age and gender, years of smoking, and cigarettes/d (Table 2, lines 2 and 3), but...
differences were again not significant after adjusting for other possible confounders (line 4).

Significant differences in IMT$_{\text{mean}}$ and IMT$_{\text{max}}$ were observed when high- and low-nicotine cigarette users were compared (Table 2, line 5); however, after adjustment for confounders, the differences in IMT$_{\text{mean}}$ lost statistical significance, whereas those in IMT$_{\text{max}}$ remained close to statistical significance in each model considered (Table 2, lines 6 to 8). Similar results were obtained when analyses were performed for pooled current and former smokers, and also when YESSC was added to covariates (data not shown).

The last 3 lines in Table 2 show the analyses of C-IMT differences between smokers of low-tar or low-nicotine and low-CO cigarettes and never smokers. In these models, C-IMTs of never smokers were always significantly smaller than those of smokers, even of the supposedly less toxic cigarette brands. Statistical significances were much greater
Effect of “Light” and “Regular” Cigarettes
(Combined Effects of Tar, Nicotine, and CO)
Cigarettes were defined as “light” or “regular” on the basis of the simultaneous presence of the 3 components (tar, nicotine, and CO) below or above the selected respective thresholds (7, 0.7, and 7 mg). No difference in C-IMTs between smokers of light or regular cigarettes was detected (all $P_{\text{H0.05}}$). Similar results were obtained when the data were analyzed for moderate (pack-years <30) or heavy (pack-years ≥30) smokers separately (all $P_{\text{H0.05}}$).

To ensure that between-group differences in the extent of smoking exposure had not introduced a bias in these results, a further analysis was performed by comparing C-IMT between 71 smokers of light cigarettes and 71 smokers of regular cigarettes matched for age, gender, and pack-years (Figure 3). Again, no differences between groups were found either before or after adjustment of the analysis for all possible confounders considered (listed in the figure legend). Being these differences are not significant, a power analysis was performed to quantify type II error. In this analysis, our sample size of 71 patients per group allowed a 70% power of detecting as significant (with an alpha error of 0.05) a difference in IMT_{mean} of 0.095 mm, assuming a standard deviation of 0.27 mm.

Multiple Regression Analyses
In 5 multivariate models performed by entering each one of the 5 ultrasonic variables considered as dependent variable, and the variables listed in Table 1 as independent (excluding pack-years because of collinearity with cigarettes/d and years of smoking), cigarettes/d was the only variable retaining statistical significance ($P_{\text{H0.0001}}$ in all the models) after the stepwise selection of the multivariate model, whereas all the others, including tar, nicotine, and CO, did not.

Interaction Between Smoking Habits, Gender, and Vascular Risk Factors
To investigate whether smoking habits affect C-IMT by interacting with gender or other VRFs, we stratified never and current smokers according to gender or the presence of hypertension, diabetes, hypertriglyceridemia, and hypo-
phalipoproteinemia (frequencies in supplemental Table I, available online at http://stroke.ahajournals.org). The interaction with hypercholesterolemia was not investigated because most patients were hypercholesterolemic. Covariance analyses using C-IMT as the dependent variable and hypertension and smoking as independent variables showed that smoking habit and hypertension were both independent determinants of C-IMT, with a significant interaction between hypertension and smoking habit (Figure 4, top panel). Similar results were obtained when subjects were stratified according to presence or absence of diabetes (Figure 4, bottom panel). No interaction with smoking habit was observed when patients were stratified according to gender, hypertriglyceridemia, or hypoalphalipoproteinemia (all P > 0.05).

**Discussion**

The major finding of the present study is that no relevant difference in C-IMT is detectable between consumers of “light” and “regular” cigarettes. In some analyses, C-IMT seems to be slightly higher in regular cigarette consumers, but differences were not significant and negligible com-
pared with those observed between smokers and never smokers.

A posteriori estimates of statistical power are meaningful only when based on a specific alternative hypothesis, such as an effect size thought to be biologically significant. We have assumed as biologically significant a C-IMT difference between light and regular cigarettes consumers equal to at least 50% of the difference observed between regular cigarette consumers and never smokers. The sample size of 71 patients per group allowed a 70% power to detect as significant a difference in IMTmean of 0.095 mm, a value equivalent to the 53% of the difference observed between regular cigarettes consumers and never smokers. Consequently, our results do not support the hypothesis that light cigarettes have a less unfavorable effect than regular cigarettes. As far as we know, the present study is the first to provide detailed findings on this issue. Although previous reports showed that switching from regular to light cigarettes does not reduce tobacco-related cardiovascular morbidity, mistaken beliefs about the possible benefits of light cigarettes are still widespread even in countries where considerable efforts have been made to educate people about the misconception of “light.” For example, one study showed that many smokers use light cigarettes in the belief that this may reduce the risks of smoking or as a first step toward stopping smoking; in the same study, however, most participants declared that they would much more probably have stopped smoking if they had known that light cigarettes confer the same risk as regular ones. Information herein reported comparing the atherogenic effect of light and regular cigarettes is thus not only of scientific interest but provides strong support for health-promoting programs.

Another important finding of the present study is that the inclusion in the analyses of covariates related to lifelong smoking exposure (pack-years, cigarettes/d, years of smoking, and YESSC) unmask differences between former and current smokers, thus explaining, at least in part, the lack of differences in C-IMT between current and former smokers reported by others.

The present report also indicates that diabetes or hypertension, but not hypertriglyceridemia or hypoalphalipoproteinemia, interact with smoking in determining C-IMT. The interaction of smoking with diabetes is apparently in contrast to the study of Kong et al., who showed no differences in C-IMTs between smoking and nonsmoking type 2 diabetics. It must be emphasized, however, that in Kong’s study former smokers were classified as nonsmokers, irrespective of YESSC or smoking duration, and this may have considerably influenced results. Our findings, by contrast, are in line with those reported in the ARIC study, which showed that the effect of cigarette smoking on C-IMT progression rate in diabetic patients was almost twice that observed in nondia-
betic patients. Regarding the interaction between cigarette smoking and hypertension, the present data agree with those of Liang and coworkers.7

Thus, the identification of atherogenic interactions warrants intensified efforts to promote smoking cessation in patients with diabetes or hypertension.

Finally, we observed that age- and sex-adjusted C-IMTs increase with the number of pack-years, in both former and current smokers, thus confirming a direct dose-dependent relationship between smoking and C-IMT.7,10,23–26 It has also been suggested that the relation between smoking and C-IMT may be different for each carotid segment,8 but in our study pack-years correlated well with C-IMT in each carotid segment considered.

With regard to possible gender-specific effects, 2 studies suggested that pack-years are predictive for C-IMT only in men,27–29 but in these studies men had a higher lifetime exposure to smoking than women and data were not adjusted for other smoking variables. In the present study, after data stratification for pack-years, the atherogenic effect of smoking was equally strong in both sexes (P trend <0.0001 for both men and women after adjustment for all variables included in Table 1) without any interaction between tertiles of pack-years and gender (P =0.12).

Study Limitations

The present study included patients attending a Lipid Clinic mostly exposed to dyslipidemia and a variety of other risk factors and risk-reducing interventions. Hence, despite the low prevalence of patients treated with lipid lowering drugs (an issue probably related to the fact that they attended the clinic for the first time), no conclusions can be drawn from this study about the effect of light or regular cigarettes smoking on C-IMT among normolipidemics or subjects from the general population. Other potential limitations are the cross-sectional nature of the study (which implies that the results are based on indirect evidences; ie, self-reported data) and the inclusion of drug therapies in the statistical analyses as binary variables (yes/no at the time of assessment) without taking into account the duration, doses, and efficacy of therapies. In addition, because the study is focused on carotid arteries, it does not provide any information about the effect of light or regular cigarettes consumption on the extent of atherosclerosis in other vascular districts. Finally, lack of data about individual socioeconomic status, which was reported to be associated with both smoking habits30 and C-IMT,31 does not allow to exclude a potential confounder effect of this variable on the results reported.

Summary

Having established that smoking is dose-dependently associated with subclinical carotid atherosclerosis, this study also shows that the consumption of light cigarettes does not reduce the atherogenic effect of smoking on C-IMT. Pack-years, cigarettes/d, years of smoking, and YESSC are important covariates that should be taken into account to properly evaluate in clinical studies the effects of smoking on health. Finally, both diabetes and hypertension strengthen the association between smoking and atherosclerosis, so that particular efforts to stop smoking should be made for patients with these conditions.

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Disclosures

None.

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