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Original Article

The effect of smoking on carotid intima–media thickness progression rate and rate of lumen diameter reduction

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ABSTRACT

Objective: The purpose of the study was to investigate the long-term associations between smoking habits, environmental tobacco smoke exposure (ETS), carotid intima–media thickness (IMT) progression rate, and rate of lumen diameter reduction in the carotid artery during a 16-year follow-up. Another objective was to investigate if an effect of smoking on progression rate could be explained by increased low grade inflammation.
Methods: The study population included 2992 middle-aged men and women in the 1991–1994 (baseline) and the 2007–2012 (re-examination) investigation of the Malmö Diet and Cancer Study cardiovascular cohort. Associations between smoking, progression of carotid IMT and lumen diameter reduction due to plaque protrusion were assessed by linear regression.
Results: IMT progression rates and rate of lumen diameter reduction increased from never smokers with no ETS through former, moderate and heavy smokers, even after adjustment for traditional risk factors (e.g., differences in yearly progression rates (mm/year) of maximal IMT in the carotid bifurcation compared to never smokers; former smokers 0.0074 (95% CI: 0.0018–0.0129), moderate smokers 0.0106 (95% CI: 0.0038–0.0175), and heavy smokers 0.0146 (95% CI: 0.0061–0.0230)). Former smokers showed distinct lowering of progression rates after more than five years since smoking cessation. Smoking and former smoking was associated with increased low grade inflammation, however, the effect of smoking on atherosclerotic progression rate remained fairly unchanged after such adjustment.
Conclusion: The effect of smoking and former smoking on carotid IMT progression rates and change in lumen reduction due to plaque protrusion could not be explained by differences in traditional risk factors or low grade inflammation.

1. Introduction

Active smoking is a major risk factor in the development of atherosclerosis and cardiovascular events [1–3]. Studies have found an excess risk up to ten years after smoking cessation, indicating the involvement of chronic processes besides acute effects in the mechanisms connecting smoking to cardiovascular disease [3]. The mediating mechanisms include vascular dysfunction, impaired endothelial and platelet function, and altered lipid profiles [2,4]. Furthermore, inflammatory mechanisms have been shown to be important in the development and progression of the atherosclerotic disease process, [5–7] even though there are also negative studies [8]. Since smoking has been shown to be associated with a variety of markers of low grade inflammation [9], low grade inflammation is one possible link between smoking and progression of atherosclerosis.

Earlier population-based longitudinal studies have shown associations between baseline smoking habits and carotid atherosclerotic progression rate [10–16]. Most studies have used progression of common carotid intima–media thickness (IMT), carotid IMT in the bifurcation or composite measures of IMT, as measures of carotid atherosclerosis. Intima–media thickness and the presence of carotid plaques are commonly used as indicators of carotid atherosclerosis strengthened by their associations with risk factors [17,18] and cardiovascular events [19]. Furthermore, progression of IMT and carotid plaques have been shown to be associated with baseline levels cardiovascular risk factors and an increased risk of cardiovascular events [20,21], even though

Abbreviations: CCA, Common carotid artery; CI, Confidence interval; CRP, C-reactive protein; ETS, Environmental tobacco smoke; HDL, High density lipoprotein-cholesterol; IMT, Intima–media thickness; LDL, Low density lipoprotein-cholesterol; MDCS, Malmö Diet and Cancer Study; OR, Odds ratio; TPA, Total plaque area; WBC, White blood cells count.

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there are also inconclusive studies [22]. Recent studies, however, have questioned the value of IMT common carotid artery (CCA) as a marker of carotid atherosclerosis [23,24]. None of the abovementioned studies investigated the potential mediating effect of low grade inflammation of smoking on the progression of carotid IMT or rate of lumen diameter reduction.

The objective of the present population-based study was to investigate the long-term associations between smoking habits, environmental tobacco smoke (ETS) and progression of carotid intima–media thickening and change in lumen diameter reduction (due to plaque protrusion) in various segments of the carotid artery. We also wanted to investigate whether smoking cessation reduced such progression rates. Furthermore, we investigated if any effect of smoking on the progression of IMT or lumen diameter reduction could be explained by increased low grade inflammation.

2. Methods

2.1. Study population

The study population constituted a sub-cohort of the men and women, born during 1926–1945, who participated in the 1991–1994 (baseline) and the 2007–2012 (re-examination) investigation of the cardiovascular cohort of Malmö Diet and Cancer Study (MDCS) [25,26]. All participants in the baseline study ($n = 6103$) who were alive and who had not emigrated from Sweden at the time for re-investigation ($n = 4924$) were invited to the re-examination including ultrasound during 2007–2012, using an identical investigation procedure as at baseline. A total of 3734 subjects attended the re-investigation (76% of the eligible population). In the baseline investigation, the self-administered questionnaire was extended with a broader approach concerning psychosocial factors and smoking habits in February 1992. The present study includes those subjects who participated in the baseline investigation between February 1992 and 1994 and in the re-examination (2007–2012) ($n = 3035$). The mean follow-up period was 16.5 ($\pm$1.5) years. After exclusion of 43 subjects with prevalent cardiovascular disease (CVD) at baseline, a total of 2992 constituted the study population (1227 men and 1765 women). Subjects were considered to have CVD at baseline, if they had been treated due to myocardial infarction and/or stroke registered in the national and regional myocardial infarction and stroke register [27,28]. The Ethics Committee at Lund University approved the study (LU 51–90, LU 204–00, Dnr 532/2006 (approved 2007-01-23)).

2.2. Measurement of carotid atherosclerosis

B-mode ultrasound was used to assess early arterial changes. The ultrasound investigations were performed by specially trained and certified sonographers after completion of an extensive training program. The examination procedure has previously been described [29]. In short; the carotid bifurcation area of the right common carotid artery was scanned within a pre-defined window defined as 3 cm of the distal CCA, the bulb and 1 cm of the internal and external carotid artery [29]. By using a specially designed computer-assisted analyzing system, the mean IMT was determined off-line in the far wall of the right distal CCA as the mean thickness over a 10-mm segment proximal to the bifurcation [30]. Furthermore, maximum IMT in the far wall in the bifurcation (i.e., bulb) was assessed. The degree of lumen diameter reduction was determined by visually judging a plaque or plaques on-line and determining the plaque protrusion into the lumen as the lumen reduction measured in percent [29].

2.3. Baseline smoking habits

Risk factors were estimated based on laboratory tests, physical examination, and a self-administered questionnaire handed out at the baseline visit. Details of assessment procedures have been previously reported [31]. Smoking habits were assessed by baseline questionnaire and classified into six categories; never smokers not exposed to ETS, never smokers exposed to ETS, former smokers, intermittent smokers, moderate smokers 1–15 cigarettes/day and heavy smokers >15 cigarettes/day. ETS was assessed as reported exposure to environmental tobacco smoke in living accommodation and/or in the working environment and was classified into “yes” and “no”. Years since smoking cessation among former smokers was assessed through information of years since smoking cessation before baseline investigation.

2.4. Baseline measures of other cardiovascular risk factors

The self-administered questionnaire also gathered data about educational level, alcohol consumption, medical history, and drug medical treatments. Educational level was assessed as educational length and categorized into two groups; <9 years of education and ≥9 years of education. Alcohol consumption was quantified by answers from the questionnaire concerning the consumption of alcohol during the last month. Those with no recorded alcohol consumption during the last year were categorized as abstainers. Risk consumption was defined as having a weekly consumption of pure alcohol ≥96 g/week for women and ≥128 g/week for men. Diabetes mellitus was defined as a self-reported physician's diagnosis of diabetes, use of anti-diabetic medications or a fasting blood glucose level ≥6.1 mmol/L. Antihypertensive treatment and lipid-lowering treatments were self-reported. Physical examination of supine systolic blood pressure was performed after supine rest for 10 min. Blood glucose, total and high density lipoproteins (HDL)-cholesterol was measured according to standard procedures at the Department of Clinical Chemistry, University Hospital Malmö. Low density lipoprotein (LDL)-cholesterol was calculated using Friedewald's formula. The analysis of high sensitive (hs)-C-reactive protein (CRP) was done from frozen plasma samples gathered at the baseline examination using the Tina-quant® CRP latex high sensitivity assay (Roche Diagnostics, Basel, Switzerland) on an ADVIA® 1650 Chemistry System (Bayer Healthcare, NY, USA) [32]. White blood cells count (WBC) was counted using a SYSMEX K1000 automatic counter (Sysmex Europe, Norderstedt, Germany) using fresh heparinized blood [33].

2.5. Statistical analysis

The distribution of CRP was skewed and was therefore log transformed in the analyses. Progression rates of carotid IMT and lumen diameter reduction due to plaque protrusion were calculated as the change between follow-up and baseline measurements divided by the time interval (years) between baseline and follow-up. The association between smoking habit categories and progression rate of IMT and lumen diameter reduction were assessed by multiple linear regression models. Adjustments for covariates were made in three steps. Step one including age, sex and carotid IMT or lumen diameter reduction, respectively, at baseline. In step two additional adjustments were made for educational level, body mass index (BMI), alcohol consumption, LDL, HDL, lipid-lowering medication, diabetes mellitus, systolic blood pressure and antihypertensive medication. In step three additional adjustments were made for CRP and WBC. The analyses were performed using SPSS version 20.0.

3. Results

3.1. Baseline smoking prevalences

Table 1 shows that heavy smokers (>15 cigarettes/day) were generally younger, more often male, less educated, more often had alcohol risk consumption, had lower BMI, lower HDL, higher hs-CRP, higher WBC, and lower systolic blood pressure (SBP), than never smokers