

Active and Passive Smoking, Chronic Infections, and the Risk of Carotid Atherosclerosis

Prospective Results From the Bruneck Study

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Background and Purpose—Susceptibility of the vasculature to the injurious effects of smoking varies substantially, with some smokers developing severe premature atherosclerosis and others remaining free of advanced atheroma until high ages. The present study sought to estimate the contribution of chronic infections to the variability of atherosclerosis severity among smokers.

Methods—In the community-based Bruneck Study, 5-year changes in carotid atherosclerosis were assessed by high-resolution ultrasound. Early atherogenesis was defined by the development of nonstenotic plaques and advanced atherogenesis by the development/progression of vessel stenosis >40%.

Results—The risk of early atherogenesis strongly relied on lifetime smoking exposure and remained elevated long-term after cessation of smoking. Remarkably, current and ex-smokers faced an increased atherosclerosis risk only in the presence of chronic infections (odds ratios [95% CIs], 3.3 [1.8 to 6.2] and 3.4 [1.8 to 6.3]; $P < 0.001$ each), whereas current, past, and nonsmokers without infections did not differ substantially in their estimated risk burden (odds ratios [95% CIs], 1.4 [0.8 to 2.4], 0.9 [0.6 to 1.6], and 1.0 [reference group]). In analogy to first-hand smoking, subjects exposed to environmental tobacco smoke were found to be vulnerable to the manifestation of chronic infection, and only those infected experienced a high atherosclerosis risk. The risk of advanced atherogenesis showed a dose-response relation with the number of daily cigarettes, returned to normal shortly after cessation of smoking, and emerged as independent of infectious illness.

Conclusions—Our study provides the first epidemiological evidence that the proatherogenic effects of cigarette smoking are mediated in part by the chronic infections found in smokers. A better understanding of the vascular pathogenetic mechanisms of smoking may offer novel clues for disease prevention supplementary to the primary goal of achieving long-term abstinence. (*Stroke*. 2002;33:2170-2176.)

Key Words: atherosclerosis ■ cigarette smoking ■ infection ■ inflammation

There is overwhelming evidence that cigarette smoking is a risk factor for atherosclerotic vascular diseases.¹⁻⁸ Less consensus, however, prevails on the nature of the underlying pathogenetic mechanisms. Most of the proposed proatherogenic actions of smoking, such as interference with blood coagulation, induction of endothelial dysfunction, and promotion of lipid peroxidation, reverse themselves shortly after cessation of smoking,⁹⁻¹³ which is in contrast to the emerging epidemiological evidence of a long-term or even irreversible risk burden of atherosclerosis in ex-smokers.^{1-3,6,8} In recent years chronic infection has been implicated in the etiology of atherosclerosis.^{14,15} Such a pathomechanism may be relevant to the development of vessel pathology among smokers because of the facilitating effects of smoking on the manifestation of various types of persistent infectious illness.¹⁶⁻²¹

The present study sought to investigate the association of first- and second-hand smoking with early and advanced stages of atherogenesis and to assess the role of chronic infectious illness in this scenario. Additional analyses will focus on the benefit of smoking cessation.

Subjects and Methods

Study Subjects

The Bruneck Study is a prospective population-based survey of the epidemiology and etiology of atherosclerosis. The survey area is located in northern Italy (Bolzano Province). Agriculture, tourism, commerce, and light industry are the main sources of income. Geographic remoteness causes low population mobility (<0.2% per year). On the prevalence day (May 1, 1990), 4793 permanent residents aged 40 to 79 years were registered in the community of

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Bruneck. The official population register contains information obtained from the national census and is continuously updated regarding births, deaths, and changes of residence. The study population was recruited between July and November 1990 as a sex- and age-stratified random sample of all inhabitants aged 40 to 79 years (125 women and 125 men in the 5th to 8th decades, each). A total of 93.6% participated, with data assessment completed in 919 subjects. During follow-up (1990 to reevaluation from July to October 1995), a subgroup of 63 individuals died or moved away. In the remaining population, follow-up was 96.5% complete ($n=826$).^{8,22-24} The study protocol was approved by a local ethics committee.

Clinical History and Examination

Smoking behavior was ascertained by participant self-report. Subjects were allocated to 1 of 3 categories: current or active smokers, past or ex-smokers (abstinence from smoking for >30 days), or nonsmokers (<100 cigarettes in the past lifetime and no regular smoking in the weeks before the baseline and follow-up evaluation). The average amount of smoking was expressed as cigarettes per day. "Pack-years" were calculated as the number of packs per day multiplied by the years of smoking. Subjects, who did not change their smoking behavior during the follow-up period, gave highly consistent responses on smoking status (smokers, ex-smokers, nonsmokers), severity (1 to 5, 6 to 10, >10 cigarettes per day), and time interval since quitting (if applicable) (1 to 5, 6 to 10, >10 years) in the 1990 and 1995 evaluations (weighted κ coefficients >0.8). Exposure to environmental tobacco smoke (ETS), referred to as passive smoking, was assessed in a structured interview and coded present if exceeding 1 hour per week. This threshold was arbitrarily defined because of the lack of a well-established biological limit and matches the threshold used in a comparable large population survey.¹ Regular alcohol consumption was quantified in terms of grams per day. Hypertension was defined as a blood pressure (mean of 3 measurements) $\geq 160/95$ mm Hg or the use of antihypertensive drugs. Diabetes mellitus was coded present for subjects with fasting glucose levels ≥ 7.8 mmol/L and/or a 2-hour value (oral glucose tolerance test) ≥ 11.1 mmol/L. Socioeconomic status was defined on a 3-category scale on the basis of information about the occupational status of the person with the highest income in the household and the educational level of the subject.¹⁴

Subjects with a chronic infection or condition known to be associated with recurrent episodes of infectious exacerbation (chronic obstructive pulmonary disease [COPD]) were identified in a 2-phase screening procedure, as detailed elsewhere.^{14,24} The first step involved a self-reported medical and medication history, clinical examinations, spirometry, extensive laboratory tests, and a detailed review of the Bruneck Hospital databases and medical records provided by general practitioners. The situation in Bruneck is unique in that the whole area is served by a single hospital that houses the only x-ray facilities and laboratory for blood tests and microbiological examinations in the region. Whenever the data were inconclusive, individuals were referred for further optional (confirmatory) examination in a second step. Diagnosis of common infections was established by an expert committee including specialists from various medical fields (eg, internal medicine, pulmonology, nephrology, gastroenterology). Bronchitis was defined as chronic when a cough with expectoration lasted for ≥ 3 months in >2 consecutive years (World Health Organization definition). The diagnosis of COPD required spirometric documentation of airway obstruction (forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] ratio <0.70) and the presence of compatible symptoms such as dyspnea, cough, or expectoration. Urinary tract infection was regarded as recurrent in the case of ≥ 3 documented episodes within a 2-year period. Other chronic infections were ascertained by a procedure that closely resembles the extensive diagnostic practice in clinical routine and thus warrants highest possible accuracy.¹⁴ Screening identified 268 subjects with ≥ 1 of the following conditions: COPD with recurrent infectious exacerbation ($n=141$), chronic bronchitis ($n=86$), chronic upper respiratory infection ($n=3$), chronic/recurrent urinary tract infection ($n=34$), periodontitis

($n=19$), chronic skin infection and ulcer ($n=14$), and chronic gastrointestinal infection ($n=7$).

Laboratory Methods

Blood samples were drawn after an overnight fast and 12-hour abstinence from smoking. In subjects with acute infections, blood drawing was delayed for at least 6 weeks. All laboratory parameters were assayed by standard methods, as extensively described previously.^{8,14,22-24}

Scanning Protocol and Definition of Ultrasound End Points

The ultrasound protocol involves the scanning of the left and right internal (bulbous and distal segments) and common carotid arteries (proximal and distal segments).^{22,23} Atherosclerotic lesions were defined with the use of 2 ultrasound criteria: wall surface (protrusion into the lumen or roughness of the arterial boundary) and wall texture (echogenicity). The maximum axial diameter of plaques was assessed in each of the 8 vessel segments (intraobserver coefficient of variation [CV], 10% and 15%, depending on the vessel segment), and an atherosclerosis score was calculated by adding all diameters (CV, 13.5% [reproducibility sample $n=100$; for details, see References 22 and 23]). In subjects free of atherosclerosis, the score was zero.

Scanning was performed twice in 1990 and 1995 by the same experienced sonographer, who was unaware of the subjects' clinical and laboratory characteristics. During the 1995 reevaluation the sonographer was blinded to the results of the first assessment.

Early atherogenesis was defined as the occurrence of new plaques in previously normal vessel segments^{8,22,23} and was assessed in subjects with and without preexisting carotid atherosclerosis. Thresholds of 0.7 mm (common carotid artery) and 1.0 mm (internal carotid artery) were introduced in the definition of incident atherosclerosis as a minimum plaque diameter requirement because smaller lesions were difficult to distinguish from focal/diffuse wall thickening.²² Advanced atherogenesis was assumed when the increase in plaque diameter exceeded twice the measurement error and a narrowing of the lumen >40% occurred.^{8,22,23} As detailed elsewhere, the cutoff of 40% appeared to be a biological threshold in our population, at which marked changes in the growth kinetics of plaques (continuous, slow, and diffuse growth versus occasional and focal prominent lesion expansion), risk profiles (conventional versus procoagulant risk factors), and vascular remodeling process (compensatory or overcompensatory versus insufficient or even absent) occurred as indicative of a switch in the underlying pathogenetic mechanisms from conventional atherogenesis to atherothrombosis.

Reproducibility of the ultrasound categories was "near perfect" (κ coefficient >0.8, as derived from 2 independent measurements performed by the same sonographer in a reproducibility sample of 100 subjects).

Statistical Analysis

Differences in the means of vascular risk attributes and markers of inflammation according to smoking status were examined with ANOVA. The association of smoking and chronic infection with early/advanced atherogenesis was assessed by logistic regression analysis.²⁵ In these equations, subjects' categories (according to smoking and infection status) were treated as sets of indicator variables. Base models were controlled for age and sex (\pm baseline atherosclerosis score). Multivariate equations were fitted with the use of a forward stepwise selection procedure, applying the default setting of SPSS-X statistical software.⁸

Regression-standardized risks of chronic infection according to the pack-years of smoking and exposure to ETS were calculated with the marginal method of the regression adjustment technique.²⁶

Results

In this study cohort, 453 (54.8%) were never smokers, 212 (25.7%) past smokers, and 161 (19.5%) current smokers.

Characteristics of Subjects According to Smoking Status and Exposure to ETS

Variable	Nonsmokers* (n=453)	Ex-smokers*			Current* Smokers (n=161)	P	Exposure to ETS (n=121)†
		>10 (n=119)	6–10 (n=43)	0–5 (n=50)			
Demographic variables/lifestyle							
Male sex, No. (%)	136 (30)	100 (84)	35 (81)	39 (78)	106 (66)	<0.001	
Age, y	58.7	59.7	58.9	59.0	53.9	<0.001	
Social status, No. (%)							
Low	308 (68)	55 (46)	25 (58)	31 (62)	89 (55)	<0.001	
Medium	86 (19)	28 (24)	11 (26)	10 (20)	40 (25)		
High	59 (13)	36 (30)	7 (16)	9 (18)	32 (20)		
Alcohol consumption, No. (%)							
Abstainers	294 (65)	31 (26)	15 (35)	16 (32)	52 (32)	<0.001	
1–50 g/d	122 (27)	44 (37)	14 (33)	14 (28)	52 (32)		
51–99 g/d	32 (7)	27 (23)	8 (19)	13 (26)	35 (22)		
≥100 g/d	5 (1)	17 (14)	6 (13)	7 (14)	22 (14)		
Risk factors							
LDL cholesterol, mmol/L	3.7	3.8	3.8	3.7	3.8	0.426	+0.1
HDL cholesterol, mmol/L	1.5	1.6	1.5	1.5	1.4	0.028	–0.1
Lipoprotein(a), μmol/L	0.6	0.4	0.6	0.6	0.6	0.296	–0.2
Hypertension, %	36.2	39.9	37.7	33.5	30.0	0.464	+7.0
Systolic blood pressure, mm Hg	147.9	149.5	144.9	147.9	145.1	0.358	+3.0
Ferritin, pmol/L	339.1	409.2	333.2	333.9	361.8	0.407	+14.4
Body mass index, kg/m ²	25.8	25.7	25.6	25.5	25.3	0.734	+0.5
Diabetes mellitus, %	12.2	7.8	4.0	9.4	8.2	0.344	–1.0
Microalbuminuria, mg/L	27.6	55.4	40.2	44.5	50.5	0.626	+5.5
Hemoglobin, mg/dL	14.3	14.4	14.3	14.2	14.9	0.061	+0.1
Inflammation/infection							
Chronic infection, %	26.4	33.9	37.2	39.4	45.5	<0.001	+9.4‡
C-reactive protein>1 mg/L, %	29.7	34.9	37.2	38.0	41.4	0.057	+4.0‡
C-reactive protein, mg/L	2.4	2.6	2.9	3.7	3.9	0.045	+1.2‡
α ₁ -antitrypsin, μmol/L	35.8	35.7	36.0	36.6	38.6	<0.001	+0.6
White blood cell count, ×10 ⁹ /L	6.2	6.1	6.7	6.9	7.3	<0.001	+0.3‡
Neutrophil count, ×10 ⁹ /L	3.4	3.3	3.7	3.8	4.1	0.060	+0.1
Fibrinogen, μmol/L	8.3	7.9	8.1	8.8	9.3	<0.001	–0.1

*Values are means adjusted for age, sex, alcohol consumption, and social status. Ex-smokers were categorized according to the time elapsed since quitting: 0–5, 6–10, and >10 years. P values are after adjustment for age, sex, alcohol consumption, and social status (ANOVA). P values for demographic and lifestyle variables are unadjusted.

†Values are adjusted differences of given variables between subjects exposed and not exposed to ETS (adjusted for age, sex, alcohol consumption, social status, and active smoking).

‡P<0.05 (adjusted for age, sex, alcohol consumption, social status, and active smoking).

Subjects reporting regular cigarette consumption exhibited lower HDL cholesterol levels than past and never smokers but no other significant changes in classic vascular risk factors (Table). In contrast, laboratory markers of inflammation and the rate of chronic infection were markedly elevated in current smokers and in ex-smokers, even >10 years after cessation of smoking (Table). The unexpected association between nonsmoking and low socioeconomic status is largely explained by the composition of our study population. Both the proportion of smokers and the level of socioeconomic status markedly decrease in the elderly and in women.

Manifestation of chronic infection in current/ex-smokers relied primarily on lifetime exposure to cigarette smoke

($P<0.001$) as well as the subject's age ($P<0.001$) and exposure to ETS ($P<0.05$) (Figure 1).

During the 5-year follow-up, 332 men and women of the 826 study subjects developed new carotid plaques. The risk of incident atherosclerosis showed a strong association with pack-years of smoking (cumulative exposure) (age/sex-adjusted and multivariate odds ratio [95% CI], 1.5 [1.2 to 1.8] and 1.4 [1.1 to 1.8] per 10 pack-years).

The risk of early atherogenesis according to smoking and infection status is detailed in Figure 2. Separate models were fitted in the entire population sample (Figure 2a; n=826) and in those free of carotid atherosclerosis at baseline (Figure 2b; n=500). Remarkably, in both analyses an increased risk was

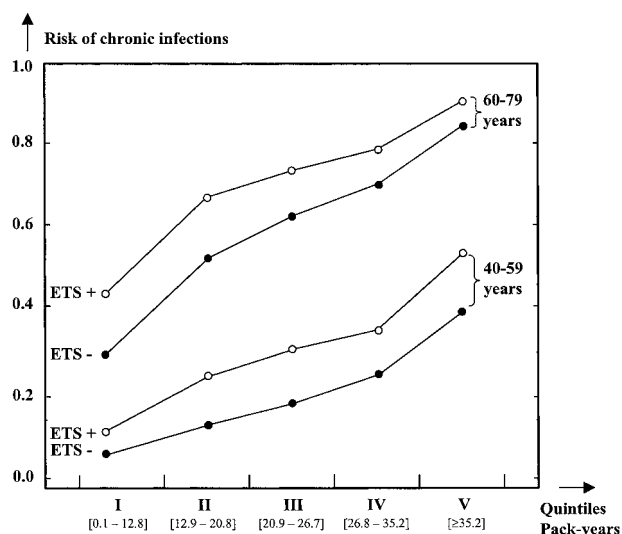


Figure 1. Regression-adjusted risk of chronic infection in current/ex-smokers according to pack-years of smoking ($P<0.001$), age ($P<0.001$), and ETS ($P<0.05$). ETS+ and ETS- indicate subjects exposed and not exposed to environmental tobacco smoke, respectively.

confined to current smokers and ex-smokers with clinical evidence of chronic infection, whereas those without such evidence did not differ from nonsmokers in their estimated

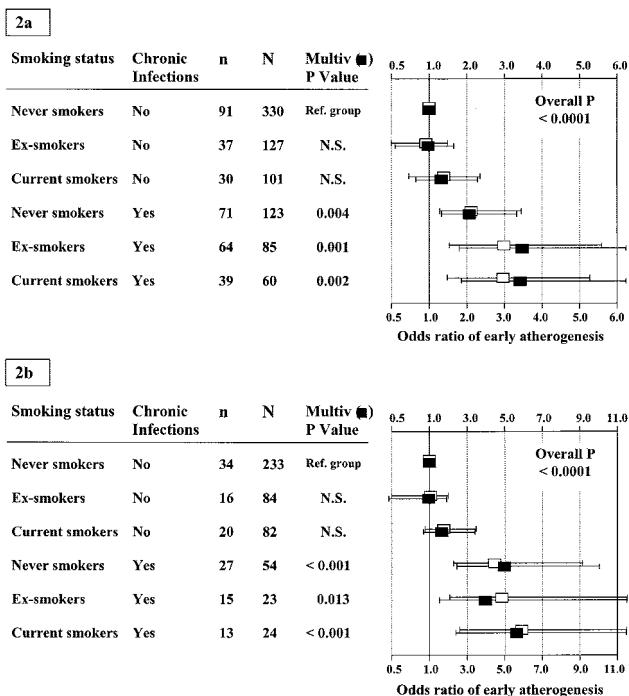


Figure 2. Odds ratios (95% CIs) of early atherosclerosis in the carotid arteries according to smoking and infection status. Separate equations were fitted in the entire population sample (a) and in those free of carotid atherosclerosis at study baseline (b). Odds ratios were adjusted for age, sex, and, in panel a, for baseline atherosclerosis score (□) plus LDL and HDL cholesterol, lipoprotein(a), hypertension, smoking (pack-years), alcohol consumption, ferritin, hypothyroidism, microalbuminuria, social status, impaired glucose tolerance, and diabetes (■). Multiv indicates multivariate; Ref., reference.

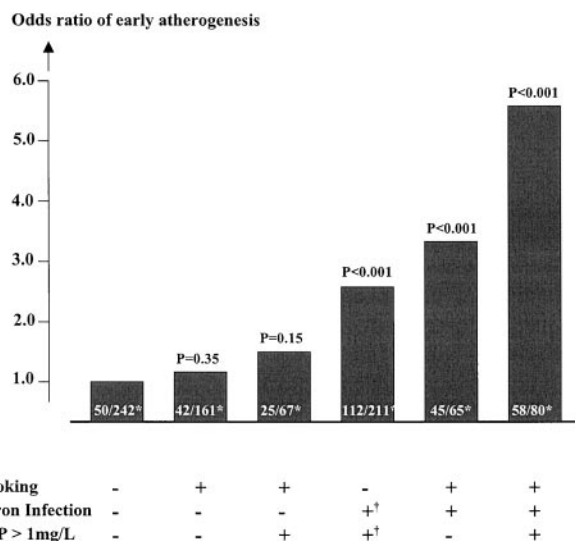


Figure 3. Adjusted odds ratios [95% CIs] of early atherosclerosis in the carotid arteries according to smoking, infection status, and levels of C-reactive protein (CRP). Analysis was conducted in the entire population sample. Adjustment is as described in Figure 2. *Numbers of subjects with early atherosclerosis per number of subjects at risk; †chronic infection or CRP >1 mg/L or both. Chron indicates chronic.

risk burden. Analogous findings were obtained when laboratory markers of bacterial infection such as seropositivity to *Chlamydia pneumoniae*, one of the most common pathogens, were substituted for the clinical definition of infection status. Adjusted odds ratios (95% CIs) for seronegative nonsmokers, ex-smokers, and current smokers were 1.0, 1.4 (0.6 to 3.3), and 1.6 (0.7 to 3.8) and for seropositive nonsmokers, ex-smokers, and current smokers were 1.8 (1.1 to 3.0), 1.9 (1.0 to 3.4), and 2.9 (1.6 to 3.6), respectively ($P<0.01$). Finally, exclusion of all subjects with COPD (ie, the chronic infection variable now subsumes primary infectious disorders only) had little effect on the results obtained.

Figure 3 additionally takes into account the presence of laboratory evidence of systemic inflammation. In brief, current/ex-smokers with chronic infection and a prominent inflammatory response faced an atherosclerosis risk higher than that in smokers with infection but low C-reactive protein (which was still highly significant). Smokers with high C-reactive protein but no clinically overt infection tended to be at an increased risk as well, but differences to nonsmokers did not reach a conventional level of statistical significance.

Adjustment of the analyses for a wide range of risk factors and potential confounders, including age, sex, social status, and alcohol consumption, did not essentially affect the risk estimates obtained (Figure 2), nor did an adjustment for manifest cardiovascular disease and medication. In accordance with these findings, results were virtually identical when the analyses were restricted to alcohol abstainers or subgroups defined by sex or age (40 to 59 versus 60 to 79 years).

The time course of changes in the risk burden after cessation of smoking is visualized in Figure 4a. Notably, in ex-smokers with chronic infection the risk of early atherosclerosis remained consistently elevated, even >10 years after

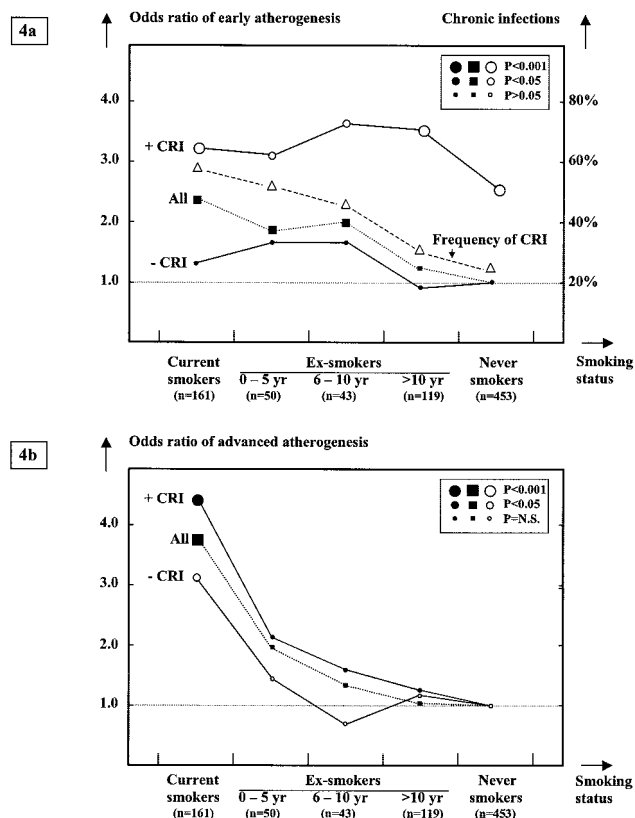


Figure 4. Changes in adjusted odds ratios for early (a) and advanced (b) atherosclerosis in the carotid arteries after smoking cessation. +CRI and -CRI indicate subjects with and without chronic infection, respectively. The size of the symbols (● □) indicates the significance of the odds ratios in the various subject categories.

cessation. In the overall group of ex-smokers, a continuous decline in atherosclerosis risk with an increasing time interval since cessation corresponded to the equally lower rate of chronic infection in this subgroup.

A total of 92 men and women of 326 subjects with preexisting atherosclerosis showed incident/progressive carotid stenoses >40% (advanced atherosclerosis). This process, which was shown to primarily arise from atherothrombosis,^{8,22,23} was strongly associated with the amount of current smoking (odds ratios [95% CI], 2.5 [1.1 to 6.3], 3.2 [1.3 to 8.2], and 4.3 [1.7 to 10.4] for 1 to 5, 6 to 10, and >10 cigarettes per day) and less so with pack-years (odds ratio [95% CI], 1.2 [1.1 to 1.4] per 10 pack-years).⁸ Contrary to the early stage of atherosclerosis, the risk of advanced atherosclerosis appeared to return to normal shortly after cessation and emerged as largely independent of the presence or absence of chronic infection (Figure 4b). In the multivariate analysis, odds ratios (95% CIs) for subjects with and without chronic infection were as follows: current smokers 4.1 (1.6 to 10.1) and 3.1 (1.3 to 7.5), ex-smokers 1.5 (0.6 to 3.7) and 1.1 (0.4 to 2.9), and never smokers 1.0 (0.4 to 2.3) and 1.0 (reference group).

Exposure to ETS (passive smoking) was reported by 121 subjects, half of whom were past or active smokers as well. There was a nonsignificant tendency for HDL cholesterol

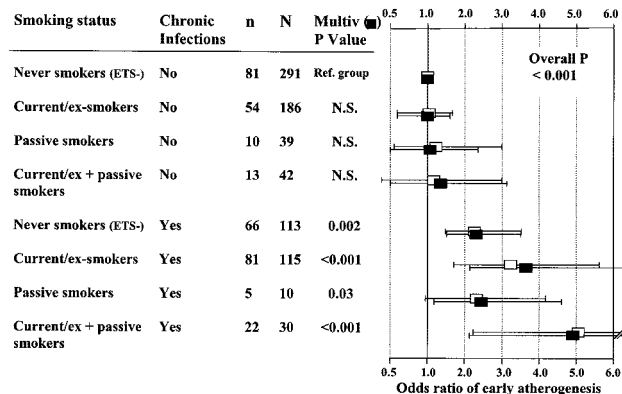


Figure 5. Adjusted odds ratios (95% CIs) of early atherosclerosis in the carotid arteries according to active and passive smoking and infection status. Adjustment is as described in Figure 2. Abbreviations are as defined in Figures 1 and 2.

levels to be lower among passive smokers, whereas all other classic vascular risk predictors were distributed equally in subjects with and without exposure to ETS. As the only abnormalities significantly linked to ETS, the rate of chronic infection and levels of some laboratory markers of infection/inflammation were elevated (Table). Exposure to ETS conferred an increased risk of early (odds ratio [95% CI], 1.3 [1.0 to 1.8]) and advanced atherosclerosis (odds ratio [95% CI], 1.5 [1.0 to 2.2]). Again, the excess risk of early atherosclerosis was confined to passive smokers with chronic infection (Figure 5).

Discussion

In our study the association of smoking with early and advanced stages of atherosclerosis was found to differ in terms of scale and reversibility.

Early Atherosclerosis

Cigarette smokers faced a substantially increased risk of early atherosclerosis, with the risk burden being cumulative and exceeding the active smoking period. From an etiologic point of view, this observation is remarkable. When ex-smokers remain at high risk of atherosclerosis,^{1-3,6,8} it cannot (or cannot only) be smoke ingredients and the reversible adverse effects on vascular risk factors, endothelial function, and lipid peroxidation⁹⁻¹³ that are atherogenic but rather a process associated with smoking, which persists and proceeds independently after cessation. The only abnormalities reported to persist for a long time after smoking cessation are the overrepresentation of chronic infection and elevation of markers of systemic inflammation.^{16-21,27-29} Actually, smoking facilitates the occurrence of chronic bronchitis,¹⁹ COPD with recurrent infectious exacerbation,¹⁸ periodontitis,^{20,21} and persistent infection with *C pneumoniae* and *Helicobacter pylori*^{16,17} and was reported to stimulate a prominent inflammatory response to various infectious agents.^{19,29} Chronic infectious diseases in turn have been implicated in the etiology of atherosclerosis and may thus play a central role in the chain of events linking smoking and vessel pathology.^{14,15} Our study contributes strong epidemiological evidence of such a pathomechanism. Only current and ex-smokers with clinical or serological evidence of chronic infection faced a

several-fold risk of early atherogenesis, whereas those without experienced a low base risk not significantly different from that of lifetime nonsmokers (Figure 2).

Alternative interpretations of our data deserve consideration as well. The association obtained may arise in part from an inverse sequence of events, ie, the promotion of infections by severe prevalent atherosclerosis. Moreover, it cannot be ruled out that the preferential association between pack-years of smoking and early atherogenesis reflects a cumulative or time-dependent exposure to other yet unknown risk factors or that a third factor exists that amplifies the risk of chronic infections and of atherosclerosis without both diseases being causally related. Relevance of the primary interpretation, however, appears to be low in our community-based population sample given the strong associations observed in subjects free of atherosclerosis at study baseline (Figure 2b), while the latter interpretation thus far lacks any epidemiological or experimental support.

Chronic inflammation of nonbacterial origin is also likely to contribute to the atherosclerosis risk among smokers, especially in the presence of COPD. The data presented in Figure 3, however, and the fact that the key findings were not essentially affected by the exclusion of subjects with COPD indicated a higher priority for the chronic infection condition.

Advanced Atherogenesis

The present study yields evidence of a dose-response association between smoking and the advanced, putatively atherothrombotic stage in vessel pathology.⁸ The risk burden appeared to decrease soon after cessation (Figure 4b), consistent with the fact that the prothrombotic properties of smoking, evident at both the platelet and coagulation levels, are reversible shortly after cessation.^{8,9,30,31} Chronic infection status was not independently associated with advanced atherogenesis in our study cohort¹⁴ and, accordingly, did not explain the relation evident between smoking and atherothrombosis.

Second-Hand Smoking

Despite the comparatively low exposure to smoke ingredients, passive smoking was considered harmful because of the high toxicity of side-stream smoke and the lack of systemic adaptation in terms of an upregulated antioxidant defense.³² In our cohort the group of passive smokers faced an increased risk of early atherogenesis (odds ratio, 1.3). As we found with active smoking, excess atherosclerosis risk was confined to passive smokers with manifest infection (Figure 5). On the basis of these results, the hypothesis may be generated that ETS renders individuals susceptible to (respiratory) infection (either by affecting alveolar antimicrobial defense or by contact with the high infection load of first-hand smokers) and that such infections mediate an increased risk of carotid atherosclerosis.

Methodological Considerations

The present study has several strengths, including its prospective design, representativity of the general community, availability of all clinical and laboratory data required for chronic infection status to be defined,¹⁴ and the person-based progres-

sion model capable of differentiating various stages of vessel pathology.^{22,23} As a limitation, the ethnic background of the study population was purely white. Results do not necessarily apply to other ethnicities. A further limitation inherent in all epidemiological investigations in this field is the fact that smoking is self-reported. Denial of smoking may cause smokers to be misclassified as ex- or nonsmokers. In addition, smokers differ from nonsmokers in regard to socioeconomic status and alcohol consumption. Substantial confounding, however, seems unlikely in the present study because of the considerable consistency in the responses on smoking behavior given in 1990 and 1995 (see Subjects and Methods) and the fact that a careful adjustment for prevalent cardiovascular disease, vascular risk, and lifestyle factors, including the aforementioned factors, had only a modest impact on the risk estimates obtained.

Conclusions

(1) Regular cigarette smoking predicts a markedly increased risk of both early and advanced stages of atherogenesis in the carotid arteries, making it a particularly harmful risk condition. (2) Smokers have a substantial benefit from cessation in that atherothrombotic properties are soon reversed but may remain at increased risk of atherosclerosis development in case of persistent chronic infection. (3) The present study is among the first to suggest that the proatherogenic effects of first- and possibly also second-hand smoking are mediated in part by the chronic infections that manifest themselves among smokers in close relation to lifetime cigarette exposure.

Expanding insights into the vascular pathogenetic mechanisms of smoking, such as the infection pathway, suggested by this study may be a basis for novel prevention strategies. Owing to the fact that smoking cessation often cannot be realized in clinical practice and that those who successfully quit may remain at increased atherosclerosis risk,^{1-3,6,8} interventions supplementary to the central objective of achieving permanent abstinence would be desirable.

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