Cigarette Smoking and the Development and Progression of Aortic Atherosclerosis
A 9-Year Population-Based Follow-up Study in Women

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Background. Cigarette smoking has been recognized as an important risk factor for cardiovascular disease in men and women. Whether the increased risk results from an atherogenic effect of smoking is still debated. We examined the relation between cigarette smoking and atherosclerotic changes in the abdominal aorta.

Methods and Results. The association between cigarette smoking and atherosclerotic changes in the abdominal aorta was examined in a population-based cohort of 758 women, initially aged 45 to 64 years. All women were examined radiographically for calcified deposits in the abdominal aorta, which have been shown to represent intimal atherosclerosis. After 9 years of follow-up, atherosclerotic changes, indicating development or progression of plaques, could be demonstrated in 37% of women. A direct association was found between atherosclerotic change and number of cigarettes smoked per day. Compared with women who had never smoked, the relative risks of those who smoked 1 to 9, 10 to 19, and 20 or more cigarettes per day were 1.4 (95% confidence interval, 1.0 to 2.0), 2.0 (1.6 to 2.5), and 2.3 (1.8 to 3.0), respectively, after adjustment for age and other cardiovascular risk factors. Associations of atherosclerotic change with inhaling habit and duration of smoking were borderline significant after number of cigarettes smoked per day was taken into account. Among former smokers, the risk decreased with increasing duration of stopping but a significant excess risk was still observed after 5 to 10 years since quitting (relative risk, 1.6; 95% confidence interval, 1.1 to 2.2).

Conclusions. These follow-up data support the evidence for an effect of cigarette smoking on atherosclerosis. The findings suggest that the rate of atherosclerotic change may be reduced by cessation of smoking, but a residual effect appears to be present for at least 10 years. (Circulation. 1993;88[part 1]:2156-2162.)

Key Words • smoking • atherosclerosis • aorta • radiography

Cigarette smoking has long been recognized as one of the major risk factors for cardiovascular disease in men.1 In the past decade, smoking has also been identified as an important cardiovascular risk factor in women.1,2 Despite the strong support for a causal relationship, understanding of the pathophysiological basis is incomplete. The observations of a rapid reduction in risk of cardiovascular disease after cessation of smoking suggest that acute mechanisms are primarily responsible for the increased risk.3-5 Other studies, however, found an excess risk up to 10 years after quitting,6-9 which indicates that chronic processes are also involved. Autopsy studies have shown a direct association between cigarette smoking and aortic processes of atherosclerosis.9-12 An association has also been found between smoking and coronary atherosclerosis,9,13,14 but negative results have been reported,15,16 and prospective autopsy studies generally failed to find the association.11,17-19 Angiographic studies have been able to show a relation between smoking and coronary atherosclerosis in some20,21 but not in other studies.22,23

A limitation of autopsy and angiographic studies is that the study population is highly selective, which may cause serious bias.25,24 A prospective examination of the relationship in asymptomatic persons would give a clearer picture. A major artery that can be examined with relative ease is the aorta. Calcific densities in the aorta, as detected on radiographs, represent an advanced stage of atherosclerosis25 and have been shown to be related to cardiovascular morbidity and mortality.26,27 In the present follow-up study, we investigated the association between cigarette smoking and atherosclerotic changes in the abdominal aorta during 9 years of follow-up of a population-based cohort of 758 middle-aged women.

Methods

Baseline Study

Between 1975 and 1978, a population-based study on risk factors for chronic diseases was conducted in the
Dutch town of Zoetermeer. All inhabitants of one rural and one urban district of the town were invited for a medical examination. A total of 10,532 individuals participated in the study, of which 1,167 were women aged 45 to 64 years. The response rate among women in this age range was 77%. Information was gathered on risk factors of cardiovascular disease and on the prevalence of some other chronic diseases (locomotor diseases, rheumatoid arthritis). Information was collected by questionnaire, physical examination, radiologic examination, and blood analysis. The questionnaire included questions on life style factors, hormonal status (e.g., age at menopause), medical history, and current use of medication. Blood pressure was measured on the left arm using a random-zero sphygmomanometer. The mean of two readings was used in the analysis. Height and weight were measured without shoes and with indoor clothing. Quetelet index was calculated as weight divided by height squared. Serum total cholesterol was measured by an automated enzymatic method. Radiographs of most joints and joint groups were made among subjects aged 45 years or older.

**Follow-up**

In 1985, all female participants aged 45 to 64 years at baseline were invited for a follow-up examination during which information was obtained on incidence of fractures and some cardiovascular risk factors. Of 1,167 women invited, 71 had died and 87 had moved away during the follow-up period. Of the remaining women, 855 (85%) were reexamined. The mean duration of follow-up was 8.9 ± 0.8 years. Subjects completed a questionnaire that contained questions on a variety of life style factors, including smoking and alcohol consumption, medical history, current use of medication, and past use of replacement estrogens. At the research center, blood was taken, and a radiologic and physical examination were performed, including measurements of blood pressure and height and weight. Women who were alive at follow-up but were not reexamined (n = 241) were slightly older compared with the women who were reexamined. After adjustment for age, they had a higher percentage of current smokers (43% versus 34%, \( P = .02 \)) and slightly higher baseline levels of systolic and diastolic blood pressures, reaching borderline significance. No differences were found in other cardiovascular risk factors. The observed number of deaths was comparable to the expected number of deaths (74) calculated by use of age- and sex-specific national death rates during the follow-up period.

**Measurement of Aortic Atherosclerosis**

Aortic atherosclerosis was diagnosed by radiographic detection of calcific deposits in the abdominal aorta. The technical procedures for radiographic measurements were similar at baseline and follow-up. At each occasion, lateral abdominal films (T12-S1) were made aimed at assessment of the lumbar vertebrae. Films were made at a fixed distance with subjects in a sitting position. Baseline and follow-up films were examined in pairs in an unmasked fashion. Aortic calcifications were considered to be present when linear densities were seen in an area parallel and anterior to the lumbar spine (L1-4). Atherosclerotic change was defined as the occurrence (disappearance) of calcifications or enlargement (reduction) of the calcified area present at baseline. In no subject was a decrease in aortic atherosclerosis observed. In the following text, atherosclerotic change will therefore refer to an increase in atherosclerosis (development or progression of plaques). The extent of atherosclerotic change was graded, but because of relatively small numbers in the categories, severity grades were combined in the analysis of the present study. All films were examined by two independent observers without knowledge of the risk factor status of the subjects. Prior to the scoring a sample of the films was read by the two observers simultaneously to reach agreement on interpretation of the scoring protocol. In case of interobserver difference of independent readings, films were reviewed by both observers simultaneously to reach consensus. The score that was agreed on by both observers was recorded. The percentage of agreement for absence versus presence of atherosclerotic change was 0.88, and the \( \kappa \) statistic was .74. In 59 subjects atherosclerotic change could not be measured because baseline or follow-up films were missing (n = 50) or not readable (n = 9).

**Measurement of Smoking Habits**

Information on smoking habits was obtained by a self-administered questionnaire. At baseline, subjects were asked whether they had smoked at least 100 cigarettes up to the time of investigation and, if so, the age of starting. Current smokers were asked about the number of cigarettes they smoked per day. Former smokers were asked about the number of cigarettes they had smoked at the time of stopping and at what age they had stopped. Both categories of smokers were asked to indicate whether they inhaled the smoke. At follow-up, information was recorded on whether the women were currently smoking and, if so, the number of cigarettes they smoked per day. Information on smoking habits was missing for 9 women.

For the present analysis, current smokers were categorized according to the number of cigarettes smoked per day as reported at baseline (1 to 9, 10 to 19, and 20 or more). These will be referred to as light, moderate, and heavy smokers. Women who reported current smoking at baseline but did not report smoking at follow-up were allocated to a separate group, referred to as quitters. Former smokers were considered to be those who had smoked at least 100 cigarettes but were not smoking at baseline. The remaining women were considered to be never smokers. Seven women who reported at baseline to have never smoked and 9 former smokers reported smoking at follow-up. These 16 women were excluded from the analysis.

**Data Analysis**

Women with missing or nonevaluable data on atherosclerotic change and smoking habits and 15 women who reported a history of a major cardiovascular event at baseline were excluded. The total number of women excluded for one or more reasons was 97, leaving 758 subjects for analysis. Characteristics of smoking categories were adjusted for age by analysis of covariance (continuous variables) or standardized by the direct method, using the age distribution of the whole study population as standard (dichotomous variables). The risk of atherosclerotic change was evaluated for all smoking categories relative to those who had never
TABLE 1. Baseline Characteristics of 758 Dutch Women Aged 45 to 64 Years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.3 (5.6)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.63 (0.06)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.5 (9.6)</td>
</tr>
<tr>
<td>Quetelet index, kg/m²</td>
<td>25.4 (3.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134.3 (18.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82.6 (11.1)</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>6.2 (1.1)</td>
</tr>
<tr>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>35</td>
</tr>
<tr>
<td>Former smokers</td>
<td>15</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>63</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>21</td>
</tr>
<tr>
<td>Aortic atherosclerosis</td>
<td>22</td>
</tr>
</tbody>
</table>

smoked. Because atherosclerotic change was observed in a relatively high percentage of subjects (37%), the odds ratios as derived from logistic regression analysis would be overestimates of the corresponding relative risks. Therefore, a simple model was used, which is directly in terms of relative risk. The model equation is probability (atherosclerotic change) = e^{a_k + \alpha}, in which \( e^a_k \) represents the relative risk of atherosclerotic change for smoking category \( k \) relative to nonsmokers, and \( \alpha \) represents the confounders. The model parameters were estimated by maximization of the likelihood function, using the LE module of the BMDP statistical package.\(^{31}\) Age was included in the models after logarithmic transformation. A limitation of the applied model is that it does not prevent individual predicted probabilities from exceeding 1. In all age-adjusted analyses, predicted probabilities were <1.0. The multivariate model including other risk factors as continuous variables gave probabilities that slightly exceeded 1.0 for 7 subjects. Probabilities of these subjects were set to 1. Because use of replacement estrogens and alcohol consumption were not measured at baseline in all subjects, follow-up measures are reported and included in the multivariate model.

Table 1 shows the baseline characteristics of the study population. The mean age of the population was 53.3±5.7 years. Thirty-five percent were current smokers, and 15% were former smokers. Aortic atherosclerosis was present at baseline in 22% of women. Ninety-nine percent of subjects were postmenopausal at follow-up. Ever use of replacement estrogens and consumption of two or more alcoholic drinks per day were reported at follow-up by 23% and 9%, respectively. Baseline smoking habits are presented in Table 2. During follow-up 84 women quit smoking. After adjustment for age, quitters had smoked fewer cigarettes per day at baseline and had a lower percentage of inhalers than did continuing smokers, with former smokers in-between.

### Smoking and Atherosclerotic Change

During follow-up, atherosclerotic changes (development or progression of plaques) were observed in 284 women (37%). The relative risks of atherosclerotic change according to smoking status are presented in Table 3. The risks increased with increasing number of cigarettes smoked per day. The risk of former smokers was comparable to that of light smokers. Women who quit smoking during follow-up had only a slightly increased risk. Fifty-two percent of quitters did not inhale and smoked fewer than 10 cigarettes per day. In com-

### Results

#### Table 2. Baseline Smoking Habits in Groups of Continuing Smokers, Quitters, and Former Smokers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuing Smokers (n=182)</th>
<th>Quitters* (n=84)</th>
<th>Former Smokers† (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cigarettes per day</td>
<td>13.2 (0.6)</td>
<td>6.7 (0.9)§</td>
<td>10.4 (0.8)§</td>
</tr>
<tr>
<td>Age of starting, y</td>
<td>22.9 (0.6)</td>
<td>24.5 (0.8)</td>
<td>21.5 (0.8)</td>
</tr>
<tr>
<td>Duration of smoking, y</td>
<td>29.4 (0.6)</td>
<td>27.8 (0.9)</td>
<td>19.5 (0.8)§</td>
</tr>
<tr>
<td>Inhaling, %</td>
<td>80.0 (3.1)</td>
<td>39.1 (5.2)§</td>
<td>68.8 (4.7)§</td>
</tr>
</tbody>
</table>

### Table 3. Relative Risks of Atherosclerotic Change by Smoking Status

<table>
<thead>
<tr>
<th>Atherosclerotic Change</th>
<th>Never Smoked (n=381)</th>
<th>1-9 (n=57)</th>
<th>10-19 (n=76)</th>
<th>≥20 (n=49)</th>
<th>Quitters* (n=84)</th>
<th>Former Smokers† (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>112</td>
<td>23</td>
<td>44</td>
<td>32</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>Relative risk (95% CI)‡</td>
<td>1.0]</td>
<td>1.5 (1.1-2.0)</td>
<td>2.0 (1.6-2.5)</td>
<td>2.3 (1.8-2.8)</td>
<td>1.2 (0.9-1.7)</td>
<td>1.6 (1.2-2.0)</td>
</tr>
<tr>
<td>Relative risk (95% CI)§</td>
<td>1.0]</td>
<td>1.4 (1.0-2.0)</td>
<td>2.0 (1.6-2.5)</td>
<td>2.3 (2.8-3.0)</td>
<td>1.1 (0.7-1.5)</td>
<td>1.5 (1.2-2.0)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Subjects who stopped smoking during follow-up.
†Subjects who stopped smoking before the baseline examination.
‡Adjusted for age.
§Adjusted for age, systolic blood pressure, serum total cholesterol, Quetelet index, diabetes mellitus, menopausal status, alcohol consumption, use of replacement estrogens, and duration of follow-up.
¶Reference group.
TABLE 4. Relative Risks of Atherosclerotic Change for Former Smokers by Number of Years Since Quitting

<table>
<thead>
<tr>
<th>Years Stopped</th>
<th>Never Smoked (n=381)</th>
<th>&lt;5 (n=24)</th>
<th>5-9 (n=34)</th>
<th>≥10 (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>112</td>
<td>13</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Relative risk*</td>
<td>1.0†</td>
<td>2.3</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>. . .</td>
<td>1.6-3.3</td>
<td>1.1-2.2</td>
<td>1.0-2.2</td>
</tr>
</tbody>
</table>

*Adjusted for age. †Reference category.

comparison, only 10% of continuing smokers and 24% of former smokers fell in this category. When the group of light, noninhaling smokers (n=44) was excluded, the relative risk of quitters increased to 1.7 (1.3 to 2.3). This suggests that the low overall risk of those who quit during follow-up, as indicated in Table 3, can be ascribed to their light smoking habits.

When analyses were restricted to subjects without aortic atherosclerosis at baseline (n=590), the age-adjusted relative risks of atherosclerotic change were 1.8 (1.1 to 2.9), 2.8 (2.0 to 4.1), and 3.0 (2.0 to 4.7) for light, moderate, and heavy smokers, respectively, and 1.1 (0.6 to 1.8) and 1.7 (1.1 to 2.6), respectively, for quitters and former smokers. Among women with aortic atherosclerosis present at baseline (n=168), atherosclerotic changes were observed in 78% of never smokers and 89% of continuing smokers (age-adjusted relative risk, 1.2; 1.0 to 1.4). Compared with smokers who did not inhale, women who inhaled the smoke (n=147) had a borderline significant excess risk of atherosclerotic change, after number of cigarettes smoked per day was taken into account in multivariate analysis (relative risk, 1.4; 0.9 to 2.0). Borderline significant associations were also found with duration of smoking. Compared with women who had smoked less than 20 years (n=19), the relative risk of women who had smoked 20 to 29 years (n=72) was 1.8 (0.9 to 3.6), and the risk of women who had smoked 30 years or more (n=91) was 1.7 (0.9 to 3.2) after adjustment for age and number of cigarettes smoked per day. The relative risk among former smokers increased with increasing duration of stopping, but a borderline significant excess risk was still seen after 10 years since quitting (Table 4).

Other Risk Factors

Mean (SEM) ages of continuing smokers, quitters and former smokers (52.1 [0.4], 53.0 [0.6], and 52.1 [0.5] years, respectively) were significantly lower compared with never smokers (54.3 [0.3] years) (P<.05). Continuing smokers had a higher baseline level of serum total cholesterol compared with never smokers (6.3 [0.1] versus 6.1 [0.05] mmol/L, P=.06) after adjustment for age. Cholesterol levels of quitters and former smokers were similar to those of continuing smokers. No baseline differences were seen in blood pressure levels. Age-adjusted baseline levels of Quetelet index of continuing smokers (25.0 [0.2] kg/m²) and former smokers (24.9 [0.3] kg/m²) were significantly lower compared with those of never smokers and quitters (25.7 [0.2] and 25.7 [0.4] kg/m², respectively) (P<.05). The percentage of women who reported ever use of postmenopausal hormones at follow-up was slightly but not significantly lower among never smokers (20%) compared with continuing smokers (23%, P=.37), quitters (25%, P=.31), and former smokers (27%, P=.16). The percentage of women with a follow-up report of consumption of two or more alcoholic drinks per day was lower among never smokers (5%) compared with continuing smokers (18%, P<.001), quitters (10%, P=.16), and former smokers (9%, P=.26).

Atherosclerotic change was positively associated with baseline levels of systolic blood pressure (β=0.01 per mm Hg, SE=0.003, P=.0005) and serum total cholesterol (β=0.14 per mmol/L, SE=0.02, P<.0001). No significant overall association was observed between atherosclerotic change and ever use of postmenopausal hormones. The relative risk of atherosclerotic change associated with ever use of postmenopausal hormones, administered orally, among women with natural menopause was 0.7 (95% confidence interval, 0.5 to 1.2). No associations were observed of Quetelet index and alcohol consumption with atherosclerotic change. Adjustment for cardiovascular risk factors did not materially alter the relative risks of atherosclerotic change associated with smoking (Table 3).

Discussion

In this study, cigarette smoking was a strong and independent predictor of atherosclerotic change in middle-aged women during 9 years of follow-up. Before conclusions can be drawn from these data, some methodological issues need to be considered. The first concerns the design of the study. This population-based follow-up study provided estimates of baseline smoking habits that were not influenced by the disease status and allowed to take changes in smoking behavior during follow-up into account. The study does not have the potential biases due to selectivity of the study population that are inherent to autopsy and angiographic studies. Smoking was, however, more prevalent among women lost to follow-up than in those who were reexamined. Selection bias, resulting in an overestimation of the effect estimate, would be present when smoking women who left the study had fewer atherosclerotic changes than smoking women who were reexamined, but this seems unlikely. We have no information on risk factors of the nonresponders to the baseline study. The number of deaths in the baseline cohort, however, was comparable to the expected number of deaths calculated by use of national mortality data, indicating comparability between the responders and general population. Apart from smoking, only slight differences in risk factors were present between those who left the study during follow-up and those who were reexamined. Therefore, we believe that the results of this study can be extrapolated to the general population of middle-aged women.

Second, we need to consider the significance of aortic calcification. The validity of radiographic assessment of aortic calcification for the diagnosis of atherosclerosis has been studied by comparison with assessments made on necropsy material. All subjects with radiographically detected calcified deposits in the abdominal aorta (n=20) were found to have atherosclerosis at necropsy. In 5 of 31 subjects in whom no calcification was diagnosed radiographically, atherosclerotic plaques were
found in the aorta at necropsy.25 The observation that systolic blood pressure and serum cholesterol were associated with aortic calcification further confirms that the measure represents intimal atherosclerosis. The propensity of false-negative misclassification in our study will have resulted in an underscoring of the total number of plaques. The question is how this might have affected the risk estimates. If we assume that smoking affects noncalcified plaque growth and that plaque calcification is determined by other factors that operate equally in smokers and nonsmokers, we will have equal proportions of plaques misclassified in both exposure groups. This nondifferential misclassification of disease status will not have affected the relative risk estimates. However, if smoking also affects plaque calcification, a different proportion of plaques will be misclassified in smokers compared with nonsmokers. This differential misclassification, if present, will have resulted in an overestimation of the risk estimate. Although such an effect seems unlikely, some care should be taken in considering the observed calcified plaques as an estimate of all plaques.

A next question is whether it is justified to make inferences from data of aorta calcification to other vessels. Aortic atherosclerosis has been found to be a predictor of cardiovascular events at various sites,26,27 which supports the concept of generalized atherosclerosis. Furthermore, a close relation has been shown between the presence of aortic plaques and coronary calcium.32 It is possible, however, that the aorta is more vulnerable to the effects of smoking than other arteries. This is supported by the predisposition of smokers to aneurysms of the abdominal aorta and peripheral vascular disease.1,23 Autopsy studies have shown a relatively strong relation of smoking with aortic atherosclerosis,9-12 which was generally more pronounced than the association with coronary atherosclerosis.9,11,16 However, we should consider potential bias in making inferences from comparisons among deaths.11 This may be especially true for cigarette smoking since smoking is not related only to cardiovascular disease death but also to other major causes of death. In studies in which smoking was not or was only moderately associated with coronary atherosclerosis, smoking was reported to occur to a similar extent or more frequently among noncardiovascular disease deaths.11,29 This may result in an underestimation of the relationship between smoking and coronary atherosclerosis because subjects who died of a cause other than cardiovascular disease may have been more resistant to atherosclerotic effects of smoking. This type of bias will have less influence when aortic atherosclerosis is examined because of its weaker relation with a particular cause of death.

Results of angiographic studies examining the association of smoking with coronary atherosclerosis have been inconsistent,20-23 while studies examining the association of smoking with progression of atherosclerosis generally failed to show an effect.34-36 Also, in these studies, potential bias should be considered. Smoking may have acute, nonatherogenic effects on the myocardium that require coronary angiography. Smokers undergoing coronary angiography may therefore have less coronary atherosclerosis than nonsmokers undergoing coronary angiography.37 It has been suggested that smoking may be related to the early development of plaques but not to extension of the affected area22 or, more specifically, progression of existing lesions.28 The scoring protocol that was used in the present study did not allow discrimination between the development of new plaques and progression of existing lesions, but we found that the positive association between smoking and atherosclerotic change was also noticeable in women in whom atherosclerosis was already present at baseline. Among these women, the risk of atherosclerotic change among those who had never smoked was 78%. Because the risk of atherosclerotic change in continuing smokers cannot exceed 100%, the relative risk of smokers compared with never smokers cannot exceed 1.3. The observed relative risk of atherosclerotic change of 1.2 among women with atherosclerosis present at baseline, therefore, does not indicate a weak effect but rather is a consequence of a limitation on the range of relative risks.

A borderline significant association of atherosclerotic change with inhaling habit was found after the number of cigarettes was taken into account in multivariate analyses. Only one autopsy study among men reported on the effect of inhaling the smoke, but it did not adjust for number of cigarettes smoked per day.10 Few studies in men have reported an independent effect of inhaling habit on cardiovascular morbidity and mortality,29 and comparable data for women are absent. Duration of smoking has been shown to be associated with atherosclerosis at autopsy10 and with cardiovascular morbidity and mortality1 but is generally considered to be of less importance after the number of cigarettes is taken into account.40 In the present study, we found an independent, borderline significant effect of duration of smoking. Women who had smoked for 20 or more years had an excess risk of atherosclerotic change compared with those with a shorter duration of smoking, but no further increase in risk was observed with increasing duration of smoking beyond 30 years.

The possibility of bias, caused by factors that are associated with both cigarette smoking and atherosclerosis, needs to be considered. Differences between smoking categories in baseline levels of serum cholesterol and Quetelet index were adjusted for by multivariate analyses. Alcohol consumption and use of postmenopausal hormones were measured at follow-up only. Smoking was positively associated with alcohol consumption, and slight differences between smoking categories were present for use of postmenopausal hormones. Alcohol consumption was not associated with an increased risk of atherosclerotic change. This suggests the presence of an alternative mechanism for the protective effect of moderate alcohol consumption on cardiovascular disease.41 As is supported by data showing that the relationship is independent of serum levels of low-density and high-density lipoprotein cholesterol.42 Epidemiological studies suggest a protective effect of postmenopausal hormone use on cardiovascular disease.43 The results of the present study are compatible with a protective effect of postmenopausal hormone use on atherosclerotic change, but the effect was not strong and lacked statistical significance. Therefore, potential differences in baseline levels of alcohol consumption and postmenopausal hormone use between smoking categories are not likely to have affected the observed risk estimates.
The reduced cardiovascular risk in past compared with current smokers is a consistent finding among studies. Those who stop smoking are not a representative selection of smokers, and concern has been expressed about possible differences in baseline levels of other risk factors. Only some studies have been able to measure risk factors of smokers before they quit. In agreement with the observations in these studies, the reduced risk of atherosclerotic change that was observed among quitters compared with continuing smokers in the present study could not be ascribed to differences in baseline levels of blood pressure and serum cholesterol. A careful interpretation of the difference is risk estimates between quitters and continuing smokers is needed because of differences in smoking habits. In the present study among middle-aged women, 52% of quitters were light, noninhaling smokers compared with only 10% among continuing smokers and 24% among former smokers. Exclusion of light, noninhaling smokers resulted in a notable increase in the risk of quitters.

A relatively fast disappearance of the excess risk of myocardial infarction after cessation of smoking has been found in several studies but some remaining excess risk of cardiovascular disease up to 10 to 15 years after quitting has also been reported. Compared with never smokers, we observed a significant excess risk of atherosclerotic change until 10 years after quitting. This may be compatible with a cascade of the atherosclerotic process caused by early vessel wall damage. Several mechanisms have been suggested. The occurrence of endothelial alterations after nicotine and carbon monoxide exposure has been suggested by animal experiments, but results are inconsistent and studies in experimental animals have so far generally failed to demonstrate atherosclerotic effects similar to that observed in humans.

In summary, the present follow-up study in women provides evidence for an effect of smoking on atherosclerosis. The risk of atherosclerotic change decreased with increasing time since quitting, but a residual effect appeared to be present for at least 10 years. This observation supports the view that in addition to acute cigarette smoking may have prolonged effects on the vessel wall. The finding underlines the need to stop smoking at an early age and gives additional support to measures for prevention of uptake of smoking in the young.

Acknowledgments

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References


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