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Tobacco and myocardial infarction in middle-aged women: a study of factors modifying the risk

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Abstract. Janzon E, Hedblad B, Berglund G, Engström G (Department of Community Medicine; and Department of Medicine, Malmö University Hospital, Malmö, Sweden). Tobacco and myocardial infarction in middle-aged women: a study of factors modifying the risk. *J Intern Med* 2004; **256**: 111–118.

Background. Although myocardial infarction (MI) is strongly related to smoking, few have studied why some smokers are more vulnerable than others. This study explored how the risk of MI in current and former smokers is modified by other cardiovascular risk factors.

Methods. Incidence of MI (fatal and nonfatal) amongst 10619 women, 48.3 ± 8.2 years old, were studied in relation to smoking, hypertension, hypercholesterolaemia, diabetes, marital status and occupational level over a mean follow-up of 14 years.

Results. Of the 3738 smokers, one-third had at least one major biological risk factor besides smoking; 228 women had MI during follow-up. Smoking and hypertension showed a synergistic effect on incidence of MI. The adjusted relative risks (RR) were 12.2 (95% CI: 7.5–19.8) for smokers with

hypertension, 5.3 (CI:3.3–8.1) for smokers with normal blood pressure and 2.4 (CI:1.4–4.3) for never-smokers with hypertension (reference: normotensive never-smokers). The corresponding RRs for diabetic smokers and diabetic never-smokers were 19.0 (CI: 10.2–35.4) and 8.8 (CI: 4.4–17.4), respectively (reference: nondiabetic never-smokers). In terms of attributable risks, hypertension, hypercholesterolaemia and diabetes accounted for 12.9, 11.5 and 7.2%, respectively, of MI in female smokers. Low socio-economic level and being unmarried accounted for 19.6 and 1.6%, respectively.

Conclusions. Although smoking is a major risk factor for MI, the risk varies widely between women with similar tobacco consumption. The results illustrate the need of a global risk factor assessment in female smokers and suggest that female smokers should be targets both for intensified risk factor management and programmes to stop smoking.

Keywords: cholesterol, hypertension, myocardial infarction, occupation and marital status, smoking, women.

Introduction

The concept of 'a multifactorial web of causation' implies the presence of complex interactions of factors and circumstances, which may increase or reduce the risk of disease. The cardiovascular hazards associated with smoking are well established [1] and tobacco prevention has been identified as an important public health strategy. A vast number of potentially preventable factors and circumstances are associated with the occurrence of myocardial infarction (MI) [2]. Only a few studies on

cardiovascular risk factors focus on women [3–5]. The combined effects of smoking and other risk factors on incidence of MI in women have not been extensively studied.

In a previous follow-up of women who were invited to the cardiovascular screening programme, in the city of Malmö in Sweden, it was reported that 71% of the incidence of MI could be attributed to smoking. Yet 11 years after the baseline examination almost 98% of the smokers remained free from disease [6]. To what extent differences in other cardiovascular risk factors account for the

differences in vulnerability amongst smokers has received relatively little scientific attention. This study explored whether the differences in cardiovascular risk amongst smokers and ex-smokers can be explained by hypertension, hypercholesterolaemia, diabetes, marital status and occupational level.

Methods

Subjects

The cohort included 10 902 women, who were examined between 1977 and 1991 at the Department of Preventive Medicine, Malmö, Sweden, as a screening for cardiovascular risk factors. Complete birth cohorts were invited. The overall attendance rate was 71% [6, 7]. After excluding women with a history of MI or stroke ($n = 176$), complete information on smoking, hypertension, cholesterol and diabetes was available for 10 619. The women were 28–58 years old (mean age: 48.3 ± 8.2 years) when they attended the health examination programme. Women with hypertension, lipid disorders or diabetes were referred for further examination and treatment. Smokers were advised to quit, but received no help to achieve that [8]. The health service authority of Malmö approved the screening programme and all participants gave their written consent.

Screening examination

A self-administered questionnaire was used for a comprehensive interview on life style and medical history. The questionnaire was revised several times during the study period 1977–91, some questions were deleted and others were added. Hence there were different numbers of subjects answering the various questions.

Smoking habits. Women who answered 'yes' to the question 'Are you a smoker?' or 'Are you a daily smoker?' were considered to be smokers. Women who reported that they had stopped smoking were considered to be ex-smokers. Women who did not report any history of smoking were never-smokers [7].

Tobacco consumption amongst daily smokers was classified as low consumption (<10 cigarettes day⁻¹, $n = 2618$), medium consumption (≥ 10 but <20 ,

$n = 591$) and high consumption (≥ 20 cigarettes day⁻¹, $n = 156$). Information on consumption was missing in 373 smokers. They were classified as medium consumers in order not to drop them in the analyses.

Blood pressure. Blood pressure was measured twice in the right arm in supine position after 10 min rest. A sphygmomanometer with a rubber cuff of appropriate size was used. The average of two measurements was used. Hypertension was defined as a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 95 mmHg or pharmacological treatment of hypertension [9].

BMI. Body mass index (BMI) was calculated as weight/height² (kg m⁻²).

Blood glucose and cholesterol. Serum cholesterol levels after an overnight fast were analysed with standard methods at the laboratory of the hospital. Hypercholesterolaemia was defined as cholesterol concentrations ≥ 6.5 mmol L⁻¹ (251 mg dL⁻¹) [10].

Blood glucose after an overnight fast was analysed with standard methods [11]. Women who had fasting whole blood glucose ≥ 6.7 mmol L⁻¹ or reported treatment of diabetes were considered to have diabetes mellitus [12].

Hormone replacement therapy. Information about hormone replacement therapy (HRT) was obtained in the questionnaire by the question 'Do you take any hormone replacement therapy for menopause inconveniences?' The answering alternatives were 'yes' or 'no'. Information on hormone replacement was missing in 2721 women (24.9%) as the question was not administered during the whole period [13].

Occupation and marital status. Information on occupation and marital status was obtained by data linkage with the national population census database from Statistics Sweden and categorized according to an earlier study from the present cohort [14]. As the number of MI was limited, the women were divided only into two occupational groups. High-level nonmanual workers ($n = 570$), medium-level nonmanual workers ($n = 1365$) and self-employed ($n = 311$) (socio-economic index, SEI, codes 46–89) were categorized as 'high' occupa-

tional groups. Low-level nonmanual workers ($n = 2901$), skilled manual workers ($n = 588$), unskilled manual workers ($n = 4125$), pensioners ($n = 203$) and unspecified occupational groups [housewives, students, unemployed (SEI codes 11–36, 91–99)] ($n = 448$) formed 'low' occupational groups [14, 15]. Information on occupation was missing in 108 women. The women were divided into those who were married or cohabiting ('married') ($n = 7032$), and those who were divorced, widows or unmarried ('single' $n = 3566$) [12]. Information on marital status was missing for 21 women.

Incidence of cardiac events. Acute MIs (ICD-9 code 410) and deaths due to ischaemic heart disease (ICD-9 code 410–414) were counted as cardiac events [16]. New cases of nonfatal MI were retrieved from the Malmö Myocardial Infarction register and from the Swedish Myocardial Infarction register [17, 18]. Information on deaths from all causes and deaths due to ischaemic heart disease was retrieved by data linkage with the Swedish Causes of Deaths register [19]. Information on emigration was retrieved by data linkage with the population register at the Swedish National Bureau of Statistics. All subjects were followed from the baseline examination until death, cardiac event, emigration out of Sweden, or to 31 December 1998. Mean follow-up time was 14.0 ± 4.5 years (range 0.5–21.9 years).

Statistics

Cox proportional hazards model was used to assess the relative contribution of different risk factors on cardiac event rates. Plots of the cardiac event rates over time, in different categories of risk factors, confirmed the fit of the proportional hazard model. To evaluate interaction we used the synergy index (SI) according to Rothman [20], Hallquist *et al.* and Lundberg *et al.* [21, 22]. The formula for the SI was

$$SI = (RR_{AB} - 1) / (RR_A + RR_B - 2),$$

where RR_A and RR_B are the adjusted relative risks (RR) associated with risk factors A and B, respectively, and RR_{AB} is the RR for those exposed to both risk factors. An SI above unity means a positive interaction. If the SI is 1, it indicates no interaction. It was computed from logistic beta-coefficients after adjustments for systolic blood pressure, age, BMI,

cholesterol, diabetes (yes versus no), occupation (high versus low), marital status (single versus married) and HRT (yes, no, missing). Gauss approximation was used to calculate the confidence intervals.

The attributable risk (AR), i.e. the proportion of cardiac events amongst smokers that were attributable to hypertension, hypercholesterolaemia and diabetes, were calculated according to the formula

$$AR = [b(r - 1)] / [b(r - 1) + 1]$$

where b is the proportion of smokers with the risk factor, and r the age-adjusted RR [23].

Results

Prevalence of risk factor

Smoking habits. There were 4846 (45.6%) women who were never-smokers, 2035 (19.2%) were ex-smokers and 3738 (35.2%) were current smokers. A total of 2618 women had low tobacco consumption, 591 had medium consumption, and 156 women had high consumption. Missing information on tobacco consumption was found for 373 women.

The distribution of risk factors in relation to smoking habits is presented in Table 1.

Cardiac events in relation to smoking habits. A total of 49 never-smoking women had a cardiac event (crude rate: 0.73/1000 person-years). Twenty-seven (1.0/1000 person-years) of the ex-smokers, and 152 (2.83/1000 person-years) of the current smokers had a cardiac event during the follow-up.

The age-adjusted RR for never-smokers, ex-smokers and current smokers were 1.0 (reference), 1.4 (95% CI: 0.9–2.3) and 4.7 (CI: 3.4–6.5).

After adjustment for age, BMI, hypertension, cholesterol, diabetes, HRT, marital status and occupation, the RR for ex-smokers and smokers were 1.5 (CI: 0.96–2.5) and RR 5.0 (CI: 3.6–6.9), respectively (reference: never-smokers).

Cardiac events in relation to smoking and other risks factors. In this cohort 1715 women had hypertension, 881 of them were treated for hypertension. The risk-factor-adjusted RRs were 12.2 (95% CI: 7.5–19.8) for smokers with hypertension, 5.3 (CI: 3.3–8.1) for smokers with normal blood pressure and 2.4

Table 1 Prevalence and distributions of different risk factors in 10 619 women in relation to smoking habits

	Never-smokers (<i>n</i> = 4848)	Ex-smokers (<i>n</i> = 2035)	Current smokers (<i>n</i> = 3738)
Age (year)	50.5 ± 6.6 (28.3–57.6)	49.8 ± 7.3 (28.2–57.2)	48.3 ± 8.2 (28.2–56.9)
Blood pressure (mmHg)			
Systolic	127 ± 16 (90–240)	125 ± 16 (80–210)	121 ± 16 (80–250)
Diastolic	83 ± 9 (50–130)	82 ± 9 (50–115)	79 ± 9 (45–125)
Hypertension (%)	19.2	16.4	12.0
Treated hypertension (%)	9.9	7.5	6.7
Blood lipids			
Cholesterol (mmol L ⁻¹)	5.8 ± 1.0 (2.4–14.6)	5.8 ± 1.0 (2.8–9.7)	5.8 ± 1.0 (2.9–13.9)
Triglycerides (mmol L ⁻¹)	1.0 ± 0.57 (0.2–11.2)	1.0 ± 0.57 (0.2–13.8)	1.2 ± 0.62 (0.3–6.9)
Diabetes (%)	2.2	2.0	2.3
BMI (kg m ⁻²)	25 ± 4	24 ± 4	23 ± 4
Hormone replacement therapy (%)	11.5	13.3	12.1
Occupation, low (%)	77.5	72.1	81.4
Civil status, married (%)	77.4	73.2	64.6
Number of risk factors ^a (%)			
None	61.5	64.5	58.7
One	31.5	29.7	30.0
Two	6.6	5.6	5.0
Three	0.4	0.2	0.3

Values are shown as percentages, mean ± SD or (range).

^aHypertension, hypercholesterolaemia or diabetes.

Table 2 Cox proportional analysis of cardiac event rate amongst 10 619 women in relation to smoking habit and hypertension, high cholesterol and diabetes

	Never-smoker	Ex-smoker	Current smoker	Never smoker	Ex-smoker	Current smoker
Blood pressure	Normotension (<160/95)			Hypertension (≥160/95)		
Medium and heavy smokers				27.7		
Events, <i>n/n</i> (%)	27/3914 (0.7)	19/1701 (1.2)	107/3289 (3.3)	22/952 (2.4)	8/334 (2.4)	45/449 (10.0)
SBP (mmHg)	122.6 ± 12.8	121.3 ± 12.7	117.7 ± 12.9	146.2 ± 16.7	146.0 ± 16.4	144.6 ± 19.0
Treatment for hypertension (%)	0	0	0	51.4	45.8	55.5
RR (95% CI) ^{abdefg}	1.0	1.8 (0.99–3.2)	5.3 (3.3–8.1)	2.4 (1.4–4.3)	2.7 (1.1–6.0)	12.2 (7.5–19.8)
Cholesterol	Normal cholesterol (<6.5 mmol L ⁻¹)			High cholesterol (≥6.5 mmol L ⁻¹)		
Medium and heavy smokers				23.6		
Events, <i>n/n</i> (%)	28/3665 (0.8)	17/1564 (1.1)	89/2762 (3.2)	21/1181 (1.8)	10/471 (2.1)	63/976 (6.5)
RR (95% CI) ^{abcefg}	1.0	1.6 (0.9–2.9)	5.6 (3.6–8.6)	1.8(1.02–3.2)	2.4 (1.2–5.0)	8.2 (5.2–12.9)
Diabetes	No diabetes			Diabetes		
Medium and heavy smokers				29.4		
Events, <i>n/n</i> (%)	38/4738 (0.8)	24/1994 (1.2)	137/3653 (3.8)	11/108 (10.2)	3/41 (7.3)	15/85 (17.6)
RR (95% CI) ^{abcdfg}	1.0	1.7 (1.01–2.8)	6.0 (4.1–8.6)	8.8 (4.4–17.4)	7.8 (2.4–25.6)	19.0 (10.2–35.4)

RR, relative risk. CI, 95% confidence interval. Adjusted for ^aage + hormone replacement, ^bbody mass index, ^chypertension, ^dcholesterol, ^ediabetes, ^foccupation and ^gmarital status.

(CI: 1.4–4.3) for never smoking women with hypertension (reference: normotensive never-smokers) (Table 2).

When women with blood pressure treatment were excluded from the analysis, the RR in smokers with hypertension and in never-smokers with hyperten-

sion was 15.2 (CI: 8.6–27.1) and 2.4 (CI: 1.2–5.0), respectively.

The adjusted RR for diabetic smokers and diabetic never-smokers were 19.0 (CI: 10.2–30.6) and 8.8 (CI: 4.4–17.4), respectively (reference: nondiabetic never-smokers) (Table 2).

The adjusted RR for smoking women with high cholesterol was 8.2 (CI: 5.2–12.9) and for never-smokers with high cholesterol 1.8 (CI: 1.0–3.2) (Table 2).

The proportion of medium and high consumers of tobacco in smokers with and without hypertension and diabetes is presented in Table 2. As the proportion of high consumers was lower in hypertensive and diabetic smokers, when compared with the normotensive and nondiabetic groups, higher tobacco consumption could not explain the increased risk in these groups.

Occupation and marital status. The RR of cardiac event in women with low occupation was 1.2 (CI: 0.5–2.7) amongst never-smokers and 6.1 (CI: 2.8–13.0) amongst smokers (Table 3).

The RR of cardiac events in women living alone was 0.8 (CI: 0.4–1.7) amongst never-smokers and 5.0 (CI: 3.3–7.6) amongst smokers (Table 3).

There was a higher proportion of high and medium consumers of tobacco amongst smokers from low socio-economic circumstances and amongst women living alone (Table 3).

Interaction between risk factors. The SI was significant for smoking in combination with hypertension (SI: 1.97, CI: 1.3–3.0) after adjustments for age, BMI, cholesterol, diabetes, HRT, occupation and marital status. SI was above 1 for smoking in combination with high cholesterol (SI: 1.35, CI: 0.91–2.01), diabetes (SI: 1.41, CI: 0.70–2.83), low occupation (SI: 1.23, CI: 0.64–2.36), and marital status (SI: 1.14, CI: 0.71–1.81) but did not reach significance.

Attributable risks. Hypertension, hypercholesterolaemia and diabetes accounted for 12.9, 11.5 and 7.2%, respectively, of the cardiac events in female smokers. Living alone and low occupation accounted for 1.6 and 19.6%, respectively, of the cardiac events in female smokers.

Discussion

Smoking is one of the major risk factors for MI and premature death amongst women [3–5]. However, the risk varies widely between smokers with similar tobacco consumption. There was a statistically significant interaction between smoking and hyper-

Table 3 Cox proportional analysis of cardiac event rates amongst 10 619 women in relation to smoking habits, marital status and occupation

Occupation level	Never smoker	Ex-smoker	Current smoker	Never smoker	Ex-smoker	Current smoker
Medium and heavy smokers (%)	High			Low		
Events, n/n (%)	7/1051 (0.7)	5/556 (0.9)	23.6	42/3754 (1.1)	22/1467 (1.5)	29.3
RR (95% CI) ^{a,b,c,d,e,f}	1.0	1.4 (0.4–4.6)	17/639 (2.7) 4.9 (2.0–11.9)	1.2 (0.5–2.7)	1.8 (0.8–4.3)	6.1 (2.8–13.0)
Civil status	Married			Not married		
Medium and heavy smokers (%)	40/3703 (1.1)	20/1481 (1.4)	11.7	9/1083 (0.8)	7/542 (1.3)	18.5
Events, n/n (%)	1.0	1.4 (0.8–2.4)	97/2395 (4.1) 4.7 (3.2–6.9)	0.8 (0.4–1.7)	1.5 (0.7–3.3)	5.0 (3.3–7.6)
RR (95% CI) ^{a,b,c,d,e,f}						

RR, relative risk; CI, 95% confidence interval. Adjusted for ^aage + hormone replacement, ^bbody mass index, ^chypertension, ^dcholesterol, ^ediabetes, ^foccupation and ^gmarital status.

tension for the risk of cardiac events. The joint effects of smoking and diabetes or smoking and cholesterol also tended to be higher than expected from risk addition. The results illustrate the need of a global risk factor assessment in order to identify women who need intensified risk factor management, including a targeted programme to stop smoking.

The results also illustrate the risk reduction in ex-smokers when compared with those who continue to smoke. For all risk factors, the risk was substantially lower for women who had stopped smoking. Although no information on duration of smoking was available, and although many ex-smokers may have re-started smoking, we can conclude that smoking cessation is associated with a substantial risk reduction independently of the levels of other risk factors.

The prevalence of the major cardiovascular risk factor, i.e. hypercholesterolaemia, hypertension and diabetes, was similar or higher amongst the never-smokers when compared with the smokers in this cohort. However, although this was a rather young female cohort, approximately one-third of the smokers had at least one additional risk factor. The heterogeneity amongst female smokers is also illustrated by the fact that cholesterol ranged from 2.9 to 13.2 mmol L⁻¹ and systolic blood pressure from 80 to 250 mmHg. Hence, although the major biological risk factors generally do not cluster with smoking, a substantial proportion of smokers are exposed to at least one additional risk factor, which substantially may increase the cardiovascular risk.

There was a significant interaction between smoking and hypertension, and the risk for cardiac events amongst hypertensive smokers was approximately two times higher than what could be expected from additive effects. The risk was even higher amongst hypertensive smokers without blood pressure treatment. A recent study reported a significant interaction between smoking and family history of hypertension [24]. Although an increased blood pressure can be observed immediately after smoking a cigarette [25, 26], smoking is associated with a lower blood pressure in most epidemiological studies [27]. This could only partially be explained by a lower body weight in smokers [28–30]. In the present cohort, the proportion of heavy smokers was somewhat lower amongst smokers with hypertension when compared with smokers with normal

blood pressure. Systolic blood pressure was somewhat lower in hypertensive smokers when compared with hypertensive never-smokers. This would, if anything, reduce the risk difference between the groups. Differences with respect to blood pressure, tobacco consumption and other risk factors cannot explain the synergistic effect between smoking and hypertension in this study.

Due to the limited number of cardiac events, the participants were categorized into high and low occupation level, which obviously is a crude categorization. Several previous studies have reported associations between different socio-economic indicators and mortality, cardiac events and prevalence of cardiovascular risk factors [31, 32]. As the proportion of housewives is high in many countries, most studies on occupation have focused on men. However, a Finnish study suggested that occupation is an equally good indicator for cardiovascular risk factors in men and women [33]. In this study, the differences were small between the RR for cardiac event in smokers with low occupation and in smokers with high occupation. There were, as often discussed in the literature, more smokers amongst women with low occupation level and they also had higher tobacco consumption [34].

A questionnaire was used to identify smokers and ex-smokers. There was however no question about occasional smoking. Occasional smokers could therefore be misclassified as never-smokers. Occasional smoking is however less common in middle-aged women when compared with young groups [35]. Moreover, misclassification of occasional smokers as never-smokers would bias the results towards null findings. As 373 smoking women did not report consumption they were coded into the medium consumption group. Many of them might have been high consumers of tobacco. The proportion with missing information showed no significant difference between women with hypertension and normal blood pressure, and it is unlikely that misclassification of tobacco consumption explain the increased risk in hypertensive smokers. We have no information on age of initiation of smoking, but according to Danish surveys, almost all smokers start before 18 years of age [36, 37]. The smokers in this middle-aged cohort had then, probably, been smoking at least 9–10 years. We have no information on smoking cessation during follow-up. The higher cardiac

event rate amongst women with other risk factors could thus reflect a greater unwillingness or lack of ability to give up smoking. No systematic attempt was made to convince or help smokers who participated in the health examination to quit. However, it is likely that many smokers with diabetes and hypertension were advised by their doctors to stop smoking, and that the cessation rates if anything were higher in these groups [38, 39].

Conclusion

Smoking is one of the major risk factors for MI and premature death. The risk varies widely between women with similar tobacco consumption. The results illustrate the need of a global risk factor assessment in order to identify women who need intensified risk factor management, including a targeted programme to stop smoking.

Conflict of interest statement

No conflict of interest was declared.

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