European Journal of Epidemiology **10**: 361–366, 1994.

Cigarette smoking and acute myocardial infarction

A case-control study from the GISSI-2 trial

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Accepted in revised form 2 May 1994

Abstract. To make a further quantitative assessment of the relationship between cigarette smoking and the risk of myocardial infarction, a multicentric case-control study was conducted in Italy between September 1988 and June 1989 within the framework of the GISSI-2 trial. Ninety hospitals in various Italian Regions participated. 916 cases of acute myocardial infarction with no history of ischaemic heart disease and 1106 controls admitted to hospital for acute conditions not related to known or suspected risk factors for ischaemic heart disease were studied. Relative risks (RR) and 95% confidence intervals (CI) of myocardial infarction according to various measures of tobacco smoking, were adjusted for identified potential confounding factors using multiple logistic regression. Compared to lifelong non-smokers, the RR was 1.3 (95% CI 1.0 to 1.9) for ex-smokers, 2.0 (95% CI 1.4 to 2.9) for current smokers of less than 15 cigarettes per day, 3.1 (95% CI 2.2 to 4.2) for 15–24 cigarettes per day and 4.9 (95% CI 3.4 to 7.1) for 25 or more cigarettes per day. No trend in risk was evident for the duration, the RR being around 3 for subsequent categories. There was a significant interaction between smoking and age. Below the age 45, smokers of 25 or more cigarettes per day had a 33 times higher risk than non-smokers, compared to 7.5 at in the age group 45–54, 4.4 between the ages 55–64 and 2.5 at the age of 65 or over. The risk estimates were higher in women (RR for $\geq$ 25 cigarettes per day = 10.1), in subjects in the lowest cholesterol tertile (RR = 11.9), with no history of diabetes (RR = 6.8), hypertension (RR = 9.5), no family history ischaemic heart disease (RR = 9.1) and low body mass index (RR = 9.3). The importance of smoking is confirmed as a cause of acute myocardial infarction: about 50% of all nonfatal infarctions in this Italian population could be attributable to cigarette smoking. The relative risks for smokers were higher at a younger age, in women and in subjects with a low baseline risk for other risk factors.

Key words: Cigarette smoking, Myocardial infarction

Introduction

There is substantial evidence that cigarette smoking is associated with ischaemic heart disease (IHD). Ex-smokers carry a substantially lower risk than current smokers and, a few years after stopping, ex-smokers have a risk approaching that of never smokers [1, 2]. There is, however, still some uncertainty in the quantification of risk. Most published work on smoking and IHD is based on cohort studies [1], where exposure to cigarette smoking is recorded several years before the event. Thus, misclassification of smoking status at the time of onset of disease is possible, and may have led to an underestimation of the real risk associated with cigarette smoking.

A few case-control studies on myocardial infarction have been conducted, particularly in young women, in whom the risk associated with oral contraceptive use had to be verified, and the incidence of the disease was too low for cohort studies [3–5]. In those studies, the increase in risk related to smoking was generally higher than in studies of males. This difference might be explained in terms of a different study design (cohort/case-control), or of a real difference between men and women, or of a different age distribution in various datasets. In several studies the relative risk of IHD of current smokers compared to non-smokers decreased with age [1, 2] and some studies suggested that smoking only slightly increases the risk of IHD at later ages [6, 7]. Since stopping smoking is more frequent among older people [8, 9], the misclassification of ex-smokers as current smokers might be greater in older ages and could thus have led to a greater underestimation of the risk of older smokers.

To clarify the role of smoking for different sexes and age groups, it is important to collect data from studies with different designs. Therefore, we analyzed the relation between smoking and risk of AMI using data from a large Italian case-control study.

Subjects and methods

The present study was conducted between September 1988 and June 1989 in 90 hospitals located in various regions of Italy, all participating in the GISSI-2 study, a randomized clinical trial of 12,490 subjects [10], in which streptokinase versus alteplase and heparin versus no heparin were compared in the treatment of AMI. The design of this investigation has already been described [11].

The cases were 916 subjects included in the GISSI-2 study, admitted to hospital for a confirmed episode of AMI and with no history of IHD. The median age was 57 years (range 24–74).

Controls were subjects admitted to the same hospitals where cases were identified, for acute conditions not related to known or potential risk factors of AMI. Subjects with history of IHD, or admitted for neoplastic, cardio-, cerebro-vascular or any other chronic conditions were excluded from the control group. This consisted of 1106 subjects, 44.3% of whom were admitted for traumatic conditions, 11.2% for non-traumatic orthopaedic disorders, 24.9% for surgical conditions and 19.6% for other miscellaneous illnesses, such as ear, nose, throat or dental disorders. Controls were frequency-matched to cases for age, sex and hospital. Their median age was 57 years (range 23–74). Less than 3% of subjects approached (cases and controls) refused to be interviewed.

A standard questionnaire was administered to cases and controls by trained interviewers, including questions on socio-demographic factors, smoking habits, diet, coffee and alcohol consumption, physical activity, history of selected conditions and family history of cardio- and cerebro-vascular events. For 614 cases and 792 controls a measure of serum cholesterol levels was also obtained. Questions on smoking included smoking status (never/ex/current) and, for current and ex-smokers, number of cigarettes, cigars and pipes smoked per day, duration of smoking, brand of cigarettes principally used and, for ex-smokers, time since stopping.

Statistical analysis. Relative risks (RR) of myocardial infarction, and the corresponding 95% confidence intervals (CI) for various categories of smokers compared to never smokers were estimated by the odds ratio described by Mantel & Haenszel [12] with allowance for age and sex, and by multiple logistic regression models [13]. Included in the regression equations were terms for age, sex, education, serum cholesterol level, history of diabetes and hypertension, family history of IHD, coffee and alcohol consumption, and body mass index. The significance of the linear trends in risk was assessed, respectively, by the test given by Mantel [14], and by comparing the difference of the deviances of the models with and without the relevant term to the chi-squared distribution with one degree of freedom [13]. On the basis of the distribution of smokers among cases and of the corresponding multivariate RR, population attributable risks were computed, i.e. the proportion of cases that would have been avoided if the given exposure(s) had not been present in the population. The method described by Bruzzi et al. [15] implies knowledge of the risk estimates and of the joint distribution of the risk factors in the population of cases only, and thus can be used for data from hospital-based case-control studies.

Results

Table 1 presents the distribution of cases and controls according to selected covariates. The two groups

Table 1. Distribution of 916 cases of acute myocardial infarction (AMI) and 1106 controls according to socio-demographic variables and history of selected conditions, Italy 1988–1989

Variable	AMI		Controls	
	No.[a]	%	No.[a]	%
Sex				
Males	801	87.4	976	88.2
Females	115	12.6	130	11.8
Age (years)				
< 45	116	12.7	160	14.5
45–54	233	25.5	280	25.4
55–64	356	38.8	412	37.3
⩾ 65	211	23.0	254	23.0
Education (years)				
< 7	504	55.6	744	68.2
7–11	242	26.7	221	20.3
⩾ 12	160	17.7	126	11.5
Cholesterol tertile (cutpoints)				
1 (< 187 mg/dl)	132	14.4	336	30.4
2 (187–225 mg/dl)	212	23.1	256	23.1
3 (⩾ 226 mg/dl)	270	29.5	200	18.1
Unknown	302	33.0	314	28.4
Diabetes				
No	811	88.5	1021	92.3
Yes	105	11.5	85	7.7
Hypertension				
No	664	72.5	922	83.4
Yes	252	27.5	184	16.6
Family History of AMI				
No	705	77.0	995	90.0
Yes	211	23.0	111	10.0
Coffee consumption (cups/day)				
< 3	477	52.1	808	73.1
⩾ 3	439	47.9	298	27.0
Body mass index (kg/m^2)				
< 25	324	35.4	505	45.7
⩾ 25	591	64.6	601	54.3

[a]In some cases the sum of strata does not add up to the total because of missing values.

were well comparable in terms of sex and age. Cases tended to be more educated, had higher cholesterol levels, were more frequently diabetic and hypertensive, more frequently had relatives with IHD, drank more coffee and had a higher body mass index.

The distribution of cases and controls according to the number of cigarettes smoked per day and duration of smoking by sex is given in Table 2. Among males, 10% of cases and 22% of controls were lifelong non-smokers and 21% of cases and 30% of controls were former smokers. The corresponding figures for females were 60% and 84% for never smokers and 5% in both groups for ex-smokers. Thus, AMI cases were more frequently current smokers (69% of males and 35% of females versus 48% of male and 11% of female controls) and tended to smoke more cigarettes than controls.

The corresponding relative risks are presented in Table 3. Compared to lifelong non-smokers, ex-smokers had a relative risk of 1.3 (95% CI 1.0 to 1.9), and the overall risk of current smokers was 2.9 (95% CI 2.2 to 3.9). The risk was 2.0 (95% CI 1.4 to 2.9) for current smokers of less than 15 cigarettes/day, 3.1 (95% CI 2.2 to 4.2) for those smoking 15–24 cigarettes per day and 4.9 (95% CI 3.4 to 7.1) for smokers of 25 or more cigarettes per day. The trend in risk with number of cigarettes per day was highly significant. No trend in risk was evident across categories of duration, the risk being around 3 for all categories (⩽ 30, 31–40, > 40 years). Nonetheless, the trend in risk including non-smokers was significant on account of the marked difference in risk between smokers and non-smokers.

Table 4 presents the estimated relative risk of AMI

Table 2. Distribution of 916 cases of acute myocardial infarction (AMI) and 1106 controls according to sex, number of cigarettes smoked and duration of smoking, Italy 1988–1989

	Males		Females	
	AMI	Controls	AMI	Controls
Never smokers	81 (10.1)	211 (21.6)	69 (60.0)	109 (83.8)
Ex-smokers	166 (20.7)	294 (30.1)	6 (5.2)	7 (5.4)
Current smokers:				
Cigarettes/day				
< 15	83 (10.4)	121 (12.4)	15 (13.0)	9 (6.9)
15–24	229 (28.6)	230 (23.6)	22 (19.1)	4 (3.1)
⩾ 25	239 (29.8)	111 (11.4)	3 (2.6)	1 (0.8)
Unknown	1 (0.1)	3 (0.3)	–	–
Pipe/cigar	2 (0.2)	6 (0.6)	–	–
Duration of smoking (years)				
⩽ 30	168 (30.0)	152 (15.6)	15 (13.0)	9 (6.9)
31–40	169 (21.1)	143 (14.7)	7 (6.1)	2 (1.5)
> 40	217 (27.1)	176 (18.0)	18 (15.7)	3 (2.3)

Table 3. Estimated relative risk (RR) of acute myocardial infarction and 95% confidence intervals (CI) according to number of cigarettes smoked and duration of smoking, Italy 1988–1989

	MH[a] (95% CI)	MLR[b] (95% CI)
Never smokers	1[c]	1[c]
Ex-smokers	1.5 (1.1–2.1)	1.3 (1.0–1.9)
Current smokers:	3.2 (2.4–4.1)	2.9 (2.2–3.9)
Cigarettes/day		
< 15	2.0 (1.4–2.8)	2.0 (1.4–2.9)
15–24	3.1 (2.3–4.1)	3.1 (2.2–4.2)
⩾ 25	6.7 (4.8–9.3)	4.9 (3.4–7.1)
χ^2 trend[d]	138.80[e]	84.68[e]
Duration of smoking (years)		
⩽ 30	3.7 (2.6–5.3)	3.1 (2.1–4.7)
31–40	3.4 (2.4–4.7)	3.0 (2.1–4.2)
> 40	3.3 (2.4–4.5)	3.1 (2.2–4.3)
χ^2 trend[d]	64.95[e]	47.79[e]

[a] Mantel-Haenszel estimates adjusted for age and sex.
[b] Multiple logistic regression estimates adjusted for age, sex, education, serum cholesterol, history of diabetes and hypertension, family history of ischaemic heart disease, coffee consumption and body mass index.
[c] Reference category.
[d] Ex-smokers excluded.
[e] $p < 0.01$.

for smokers, relative to non-smokers, in strata of selected covariates. There was a significant interaction between smoking and age, i.e. the trend in risk was significantly steeper at younger ages than at older ones. Below age 45 smokers of 25 or more cigarettes per day had a 33 times higher risk than non-smokers, compared with 7.5 at age 45–54, 4.4 at age 55–64 and 2.5 at age 65 or over. The risks appeared higher in women and in subjects in the lowest cholesterol tertile, with no history of diabetes or hypertension, no family history of IHD and lower body mass index. However, the interactions between smoking and these covariates were not statistically significant.

Discussion

This case-control study on acute myocardial infarction, conducted in the framework of the GISSI-2 randomized clinical trial [10], further confirms the importance of smoking as a cause of the disease. The relative risks associated with smoking appeared to be higher in subjects with lower baseline risk: younger people, women, not diabetic or hypertensive, subjects without family history of ischaemic heart disease and with a lower body mass index.

Our study found no trend in risk with increasing duration. Thus, the risk of AMI seemed to be essentially determined by the smoking habits shortly before diagnosis.

The choice of hospital controls to analyze smoking has been criticized, since smokers may be admitted to hospital more frequently than non-smokers and may stay there longer [16]. This could lead to an overrepresentation of smokers in the control group as compared to the general population and, hence, to an underestimation of the relative risk associated with smoking. However, we excluded from the control group all subjects admitted for diagnoses known or potentially related to smoking. Furthermore, cases of AMI included in this study lived long enough to be admitted to hospital and interviewed, and therefore do not represent the whole population

Table 4. Estimated relative risk[a] of acute myocardial infarction according to the number of cigarettes in strata of selected covariates, Italy 1988–1989

	Never smokers[b]	Ex smokers	Current smokers (cigarettes/day)			χ^2 trend[c]
			< 15	15–24	⩾ 25	
Age (years)						
< 45	1	2.0	3.8	8.7	32.8	64.89[d]
45–54	1	1.7	1.7	3.4	7.5	50.52[d]
55–64	1	1.6	1.7	3.2	4.4	36.53[d]
⩾ 65	1	0.8	2.4	1.6	2.5	3.05
Sex						
Males	1	1.4	1.8	2.7	6.0	116.10[d]
Females	1	1.3	2.3	10.9	10.1	20.16[d]
Education (years)						
< 7	1	1.3	1.6	3.0	5.4	68.42[d]
⩾ 7	1	1.6	2.1	3.1	8.2	69.99[d]
Cholesterol tertile (mg/dl)						
1 (< 187)	1	3.8	5.6	5.3	11.9	24.88[d]
2 (187–225)	1	0.9	1.5	3.0	5.9	28.82[d]
3 (⩾ 226)	1	1.3	1.4	2.9	5.6	27.88[d]
Diabetes						
No	1	1.4	1.8	3.1	6.8	131.58[d]
Yes	1	2.6	7.9	4.8	4.0	5.49[e]
Hypertension						
No	1	1.7	2.2	3.9	9.5	150.61[d]
Yes	1	1.1	1.8	1.9	1.7	3.75
Family history of ischaemic heart disease						
No	1	2.0	2.3	3.6	9.1	126.72[d]
Yes	1	0.8	1.5	2.5	2.9	13.49[d]
Coffee consumption (cups/day)						
< 3	1	1.1	1.9	2.3	4.2	38.59[d]
⩾ 3	1	2.4	2.1	4.1	7.2	59.43[d]
Body mass index (kg/m^2)						
< 25	1	1.8	2.7	3.7	9.3	64.74[d]
⩾ 25	1	1.4	1.7	2.9	4.7	64.27[d]

[a] Multiple logistic regression estimates adjusted for age and sex (when appropriate).
[b] Reference category.
[c] Ex-smokers excluded.
[d] $p < 0.01$.
[e] $p < 0.05$.

of AMI cases, but only nonfatal ones. However, the association with smoking was seen even in cohorts whose endpoint was mortality from IHD [1, 2]. Thus it seems unlikely that the observed association is affected by substantial bias.

The fact that smokers have a higher risk of myocardial infarction is well established [1]. We estimated a relative risk of 4.9 for heavy smokers (25 cigarettes/day or more) relative to non-smokers, which may seem higher than those reported in several cohort studies like the ones of the Pooling Project, whose estimated relative risk for more than one pack/day was around 3 [1, 2]. The higher risks in our study might be due to a lower misclassification of current and ex-smokers in case-control studies compared to cohort studies, where exposure is ascertained some time before the disease occurs. Other cohort investigations, however, such as the American Nurses Health Study [17] showed relative risks for smoking comparable to those of the present study, at least in women.

Our data thus suggest that smoking has an even greater effect than estimated in previous cohort studies. These, however, should be viewed with caution, in consideration of the different diagnoses considered in the various studies (AMI/HD/cardiovascular disease), of the different cutpoints of number of cigarettes chosen, and of the different age composition of the populations under study.

In our study, like in previous ones [1, 2, 6, 7, 18], the risks associated with smoking were considerably higher at younger ages. It has been suggested that smoking is not a relevant risk factor at older age [1], but we found that the relative risk of heavy smokers was over 2 even after 65 years of age, indicating that smoking is an important risk factor even in older

subjects, particularly when absolute (and not only relative) risk is considered.

When analyzed in strata of other risk factors, the effect of smoking appeared more marked in subjects at lower risk from other risk factors, i.e. in women [3–5, 17] and in those who were not diabetic or hypertensive, had no family history of IHD, had low serum cholesterol and a lower body mass. This might be because smoking is the major casual agent in those who are not exposed to other risk factors, and therefore, most cases are attributable to it.

In conclusion, this case-control study on myocardial infarction further confirms that smoking causes AMI, not only at younger ages, but also in older subjects, and suggests that the relative risk associated with smoking (and hence the population attributable fraction) might be even higher than previously estimated. Assuming that the cases were representative of the general Italian population of AMI cases, in fact, smoking would account for 49% – almost half – of nonfatal myocardial infarctions in Italy [15].

Acknowledgements

GISSI-EFRIM was supported through a main grant from Bayer Italy S.p.A. Financial support was also received from Squibb Italy S.p.A. and Italfarmaco S.p.A. We acknowledge the contribution of the Italian League Against Tumors, Milan, and Mrs Angela Marchegiano Borgomainerio. Mrs Judy Baggott, Mrs M. Paola Bonifacino and the G. A. Pfeiffer Memorial Library staff provided helpful editorial assistance.

References

1. US Department of Health and Human Services. The health consequences of smoking. Cardiovascular disease. A report of the Surgeon General. Rockville, MD, 1983.
2. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chron Dis 1978; 31: 201–306.
3. Mann JI, Doll R, Thorogood M, Vessey MP, Waters WE. Risk factors for myocardial infarction in young women. Br J Prev Soc Med 1976; 30: 94–100.
4. Slone D, Shapiro S, Rosenberg L, Kaufman DW, Hartz SC, Rossi AC, et al. Relation of cigarette smoking to myocardial infarction in young women. N Engl J Med 1978; 298: 1273–1276.
5. Gramenzi A, Gentile A, Fasoli M, D'Avanzo, Nergi E, Parazzini F, La Vecchia C. Smoking and myocardial infarction in women: A case-control study from northern Italy. J Epidemiol Community Health 1989; 443: 214–217.
6. Hammond EC. Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr 1966; 19: 127–204.
7. Strobel M, Gsell O. Mortality in relation to tobacco smoking. Nine years of observation in Swiss physicians. Helv Med Acta 1965; 32: 547–592.
8. Kabat GC, Wynder EL. Determinants of quitting smoking. AM J Publ Health 1987; 77: 1301–1305.
9. Nergi E, Pagano R, La Vecchia C. Determinants of stopping cigarette smoking in Italy. Rev Epidemiol Sante Publ 1989; 37: 337–344.
10. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: A factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Lancet 1990; 336: 65–71.
11. Negri E, Santoro L, D'Avanzo B, Nobili A, La Vecchia C, GISSI-EFRIM, GISSI-2. Body mass and acute myocardial infarction. Prev Med 1992; 21: 292–301.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719–748.
13. Breslow NE, Day NE. Statistical methods in cancer research, vol. 1: The analysis of case-control studies. IARC Sci Publ 1980; 32.
14. Mantel N. Chi-square tests with one degree of freedom. Extensions of the Mantel-Haenszel procedure. J AM Stat Assoc 1963; 58: 690–700.
15. Bruzzi P, Green SB, Byer DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. AM J Epidemiol 1985; 122: 904–914.
16. La Vecchia C, Pagano R, Negri E, Decarli A. Smoking and prevalence of disease in the 1983 Italian National Health Survey. Int J Epidemiol 1988; 17: 50–55.
17. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987; 317: 1303–1309.
18. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. BMJ 1976; 2: 1525–1536.

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