Acute myocardial infarction: association with time since stopping smoking in Italy

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Abstract

Study objective **– The study aimed to investigate the relationship between years since stopping smoking and the risk of acute myocardial infarction.**

Design **– This was a hospital based, multicentre, case-control study conducted in Italy between September 1988 and June 1989 within the framework of the GISSI-2 clinical trial.**

Setting **– Over 80 coronary care units in various Italian regions participated.**

Subjects **– A total of 916 incident cases of acute myocardial infarction, below age 75 years, and with no history of ischaemic heart disease, and 1106 control subjects admitted to the same hospitals for acute, non-neoplastic, cardiovascular or cerebrovascular conditions that were not known or suspected to be related to cigarette smoking took part in the study.**

Main outcome measures and results **– Measures were relative risk (RR) estimates of acute myocardial infarction according to the time since stopping smoking and adjusted for identified potential confounding factors. Compared with never smokers, the multivariate RRs were 1·6 (95% confidence interval (CI) 0·8,3·2) for subjects who had given up smoking for one year; 1·4 (95% CI 0·9,2·1) for those who had stopped for two to five years; 1·2 (95% CI 0·7,2·1) for six to 10 years; and 1·1 (95% CI 0·8,1·8) for those who had not smoked for over 10 years. The estimated RR for current smokers was 2·9 (95% CI 2·2,3·9). The risks of quitters were higher for heavier smokers and those below age 50 years, while no difference emerged in relation to the duration of smoking, sex, and other risk factors for myocardial infarction.**

Conclusions **– These results indicate that there is already a substantial drop in the risk of acute myocardial infarction one year after stopping. The risk in exsmokers, however, seemed higher (although not significantly) than that of those who had never smoked, even more than 10 years after quitting. This could support the existence of at least two mechanisms linking cigarette smoking with acute myocardial infarction – one involving thrombogenesis or spasms that occurs over the short term, and another involving atherosclerosis that is a long term effect.**

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It is well established that cigarette smoking increases the risk of acute myocardial infarction and of ischaemic heart disease in general.[1] Furthermore, exsmokers are at a substantially lower risk of myocardial infarction than current smokers, so inducing smokers to give up smoking is important for the prevention of ischaemic heart disease.[1] There are, however, some unanswered questions concerning the quantification of the risk reduction associated with stopping smoking. In particular, the relationship between the time since stopping and myocardial infarction and whether former smokers may in due course achieve the same risk as non-smokers are still uncertain. Besides their major relevance to public health, answering these questions may help elucidate the biological mechanisms of tobacco-related infarction risk.[1]

We therefore decided to investigate the relationship between the time since stopping smoking and the risk of acute myocardial infarction using data from a large case-control study conducted in Italy. Since a case-control study is able to provide accurate information on events and changes in risk factor exposure that occur in the short term before the event, this is the most appropriate design to investigate the pattern of risk with time since stopping smoking.

Methods

Between September 1988 and June 1989 we conducted a case-control study of acute myocardial infarction within the framework of the GISSI-2 study – this was a randomised clinical trial of alteplase *versus* streptokinase and heparin *versus* no heparin in the treatment of myocardial infarction.[2] Eighty hospitals spread all over Italy participated in this study. The design of this investigation has already been described.[3,4]

SUBJECTS

Cases were 916 subjects aged below 75 years, randomised to the GISSI-2 trial, who had been admitted to hospital for a confirmed first episode of acute myocardial infarction (according to the standard WHO criteria),[5] but had no history of ischaemic heart disease. Altogether 801 were men and 115 women; their median age was 57 years, and the age range was 24 to 74 years.

Controls were patients admitted to the same hospitals for acute conditions that were not related to tobacco smoking or to other known or suspected risk factors for acute myocardial

infarction. We excluded all subjects with a history of ischaemic heart disease and all those whose primary diagnosis on hospital admission was a cardiovascular, cerebrovascular, neoplastic, or any other chronic condition. These exclusion criteria, however, applied only to the primary admission diagnosis. This control group consisted of 1106 subjects (976 men and 130 women), 44% of whom had been admitted for traumatic conditions, 11% for non-traumatic orthopaedic disorders, 25% for surgical conditions, and 20% for other miscellaneous illnesses, such as ear, nose and throat or dental disorders. Their median age was 57 years (range 25–74). Controls were frequency-matched to cases by age, sex, and area of residence. Fewer than 3% of all subjects approached (cases and controls) refused to be interviewed.

INTERVIEWS

Trained interviewers, ad hoc instructed and tested for reliability and validity, administered a structured questionnaire to cases and controls during their stay in hospital. Four interviewers collected data from Lombardy and two from each of the other nine participating regions. The case or control status was known to the interviewers. However, this was a broadly oriented study of risk factors for acute myocardial infarction and hence the attention of the interviewer and interviewee was not specifically focused on any single issue. The interviewers received the same structured training in order to standardise data collection in various centres. Data checking and quality control were centralised and were carried on interactively throughout the study period. Questions concerned sociodemographic factors; lifestyle habits; consumption of coffee, alcohol, and a few indicator foods; selected indicators of physical activity; history of selected conditions; and family history of cardiovascular and cerebrovascular diseases. The average duration of the interview was approximately 30 minutes. Measurements of serum cholesterol concentrations were available for 614 cases and 792 controls only.

Information was collected specifically on smoking status (never/ex/current); age at starting smoking; number of cigarettes, cigars, and pipes usually smoked per day; duration of the habit in years; lifelong history of various brands of cigarettes principally smoked; and years since stopping smoking. Exsmokers were considered those subjects who had given up for at least one year. The time since quitting smoking was divided into four levels (<2, 2–5, 6–10, and >10 years).

STATISTICAL ANALYSIS

Mantel-Haenszel odds ratios, and the corresponding 95% confidence intervals (CI), adjusted for sex and age in decades, were used to estimate relative risks (RR) of acute myocardial infarction according to the time since quitting smoking.[6] In addition, multiple logistic regression models were fitted to control simultaneously for several potential confounding factors and to obtain risk estimates in relation to selected covariates.[7] Included in the regression models were terms for sex; age, in decades; and, whenever indicated, years of education (three levels); body mass index (<25; 25–30; $\geqslant 30$ kg/m^2); history of diabetes and hypertension; family history of acute myocardial infarction; serum cholesterol concentration (quartiles, plus one category for missing information); and coffee consumption (0–1, 2, 3, 4, or more cups per day). To analyse the effect of stopping smoking for smokers, models including terms for number of cigarettes smoked were also fitted. Tests for interaction between the time since quitting smoking and other covariates were based on the comparison of the difference between the deviances of the models with and without interaction terms to the χ^2 distributions with degrees of freedom equal to the number of interaction terms.[7]

Results

Table 1 shows the distribution of cases and controls according to sex, age, and selected covariates. The two groups were comparable in terms of age and sex distribution, but cases tended to be better educated; more frequently overweight, hypertensive, and diabetic; had higher serum cholesterol concentrations; more frequently reported a history of acute myocardial infarction in relatives; and drank more coffee.

The distribution of cases and controls according to smoking status (never/ex/current), and for exsmokers the time since quitting, and the corresponding relative risks are presented in table 2. There was a considerable excess of current smokers among cases of acute

Table 1 Distribution of 916 cases of acute myocardial infarction (AMI) and 1106 controls according to sex, age, and selected covariates. Italy, 1988–89.

Covariate	Cases		Controls	
	No	(%)	No	(%)
Sex:				
Men	801	(87·4)	976	(88·2)
Women	115	(12·6)	130	(11·8)
Age (y):				
<40	55	(6·0)	62	(5·6)
40–49	167	(18·2)	207	(18·7)
50–59	305	(33·3)	373	(33·7)
60–69	323	(35·3)	382	(34·5)
70–74	66	(7·2)	82	(7·4)
Education (y):				
<7	514	(56·1)	759	(68·6)
7–11	242	(26·4)	221	(20·0)
⩾12	160	(17·5)	126	(11·4)
Body mass index (kg/m^2):				
<25	322	(35·2)	498	(45·0)
⩾25	594	(64·8)	608	(55·0)
Serum cholesterol (mg/dl):				
<205 (median)	227	(24·8)	477	(43·1)
⩾205	387	(42·3)	315	(28·4)
Unknown	302	(33·0)	314	(28·4)
Hypertension:				
No	664	(72·5)	922	(83·4)
Yes	252	(27·5)	184	(16·6)
Diabetes:				
No	811	(88·5)	1021	(92·3)
Yes	105	(11·5)	85	(7·7)
Family history of AMI:				
No	705	(77·0)	995	(90·0)
Yes	211	(23·0)	111	(10·0)
Coffee consumption (cups/d):				
<3	477	(52·1)	808	(73·1)
⩾3	439	(47·9)	298	(26·9)

Table 2 Distribution of 916 cases of acute myocardial infarction (AMI) and 1106 controls, estimated relative risks, and 95% confidence intervals (CI) according to years since stopping smoking. Italy, 1988–89.

	No of cases	*No of controls*	*Relative risk (95% CI)*	
	(%)	*(%)*	*M-H**	*MLB†*
Never smokers	150 (16·4)	320 (28·9)	1‡	1‡
Time since quitting (y):				
1	18 (2·0)	29 (2·6)	1·4 (0·8,2·8)	1·6 (0·8,3·2)
2–5	57 (6·2)	94 (8·5)	1·5 (1·0,2·3)	1·4 (0·9,2·1)
6–10	32 (3·5)	61 (5·5)	1·1 (0·7,1·8)	1·2 (0·7,2·1)
>10	65 (7·1)	117 (10·6)	1·1 (0·7,1·6)	1·1 (0·8,1·8)
Current smokers	594 (64·8)	485 (43·9)	3·4 (2·6,4·4)	2·9 (2·2,3·9)

* Mantel-Haenszel odds ratios adjusted for age and sex.
† Estimates from a multiple logistic regression model including terms for age, sex, education, body mass index, serum cholesterol level, history of diabetes and hypertension, family history of AMI and coffee consumption.
‡ Reference category.

myocardial infarction as compared with controls (65% *v* 44%). The Mantel-Haenszel odds ratio adjusted for age and sex, relative to never smokers, was 1·4 (95% CI 0·8,2·8) for subjects who had given up smoking for one year, 1·5 (95% CI 1·0,2·3) for two to five years, 1·1 (95% CI 0·7,1·8) for six to 10 years, and 1·1 (95% CI 0·7,1·6) for over 10 years, while the odds ratio for current smokers was 3·4 (95% CI 2·6,4·4). The corresponding estimates from the logistic model, adjusted for all identified potential confounding factors, were 1·6, 1·4, 1·2, and 1·1 respectively for exsmokers across various time since quitting groups, and 2·9 for current smokers.

Table 3 analyses the RR in subjects who had given up smoking compared with those who had never smoked, grouped according to the number of cigarettes smoked per day and duration of the habit. Within each stratum the estimates were based on smaller numbers of cases, so random variation was larger. In all categories of current and former smokers, however, the RR were higher for subjects who had smoked 20 or more cigarettes per day than for those smoking less than 20, although the formal test for interaction was not statistically significant. No clear pattern emerged in relation to the duration of smoking.

Table 4 shows the risks of former smokers (those who had given up for five or less and more than five years) and of current smokers in relation to selected covariates. For both current and exsmokers, risk estimates were higher at a younger age: below 50 years of age the risk was 3·3 for subjects who stopped within five years and 1·8 for those who had given up for six years or more, compared with nonsmokers, but above age 50 the estimates were 1·4 and 1·3 respectively. For current smokers, the corresponding relative risks were 8·8 and 2·6. The interaction between age and the time since quitting smoking was not, however, statistically significant. The risks in relation to sex, education, body mass index, hypertension, and family history of acute myocardial infarction confirmed a systematic tendency for the RR to decline with time since stopping.

Table 3 Estimated relative risk (and 95% confidence interval) of acute myocardial infarction according to years since stopping smoking in relation to number of cigarettes and duration of smoking. Italy, 1988–89.*

	No of cigarettes/d		*Duration of smoking (y)*	
	<20	*≥20*	*<30*	*≥30*
Never smokers	1†	1†	1†	1†
Time since stopping (y):				
1	1·4 (0·6,3·5)	1·7 (0·8,4·0)	2·5 (0·7,8·3)	1·4 (0·7,3·0)
2–5	1·4 (0·8,2·5)	1·7 (1·0,2·8)	1·5 (0·8,2·9)	1·6 (1·0,2·6)
6–10	1·1 (0·5,2·3)	1·5 (0·8,2·8)	1·2 (0·6,2·6)	1·4 (0·8,2·6)
>10	0·9 (0·5,1·6)	1·9 (1·2,3·0)	1·4 (0·9,2·2)	1·0 (0·5,2·0)
Current smokers	2·3 (1·7,3·1)	4·1 (3·0,5·4)	3·5 (2·4,5·1)	3·2 (2·4,4·3)

* Estimates from multiple logistic regression models including terms for age and sex.
† Reference category.

Table 4 Estimated relative risk (and 95% confidence interval) of acute myocardial infarction (AMI) according to years since stopping smoking in relation to selected covariates. Italy, 1988–89.*

	Never smokers	*Years since stopping*		*Current smokers*
		≤5	*>5*	
Age:				
<50	1†	3·3	1·8	8·8
≥50	1†	1·4	1·3	2·6
Sex:				
Men	1†	1·5	1·4	3·1
Women	1†	2·5	0·7	5·8
Education (y):				
<7	1†	1·6	1·2	3·0
≥7	1†	1·5	1·6	3·8
Body mass index (kg/m^2):				
<25	1†	3·1	1·1	4·1
≥25	1†	1·1	1·5	3·1
History of hypertension:				
No	1†	1·9	1·6	4·5
Yes	1†	1·2	1·1	1·8
Family history of AMI:				
No	1†	1·7	1·4	3·6
Yes	1†	1·1	1·4	2·3

* Estimates from multiple logistic regression models including terms for age and sex, when appropriate.
† Reference category.

Table 5 Estimated relative risk (and 95% confidence interval) of acute myocardial infarction according to years since stopping smoking. Italy, 1988–89.*

	Relative risk	*(95% CI)*
Current smokers	1†	
Time since stopping (y):		
>1<2	0·5	(0·3,1·0)
2–5	0·5	(0·4,0·7)
6–10	0·4	(0·3,0·7)
>10	0·4	(0·3,0·6)

* Estimates from a multiple logistic regression model including terms for age, sex, and number of cigarettes.
† Reference category.

Table 5 gives the RR for subjects who had stopped smoking, relative to current smokers, adjusted for age, sex, and also the number of cigarettes smoked. The risk estimates were 0·5 for subjects who had given up for five years or less and 0·4 for six or more years. For all categories of former smokers the risks were significantly lower than for current smokers.

Discussion

In this large Italian case-control study the RR of acute myocardial infarction was already significantly lower in exsmokers than in current ones one year after quitting. The RR tended to decrease with the time since quitting and to become close to that of never smokers after 10 years without smoking.

A similar pattern of risk for former smokers, reduced in respect of current smokers, and declining asymptotically to that of non-smokers, has been observed in several prospective studies.[8-12] In three previously published case-control investigations, the risk of acute myocardial infarction declined steeply to reach that of never smokers after three years.[13-15] In a prospective study from the UK, the risk for quitters was lower than that of current smokers at least five years after stopping, but after more than 20 years it was still about twice that of never smokers.[16] The apparent discrepancy between case-control and cohort studies has been attributed to the fact that in cohort studies some quitters may start smoking again, and hence the risk of quitters may be inflated by misclassification of some current smokers as exsmokers.[13] Our data, however, are also consistent with the findings of prospective studies.

Smoking increases the risk of acute myocardial infarction through several different mechanisms. It contributes to the development of coronary atherosclerosis and induces an imbalance between myocardial oxygen supply and demand, coronary artery spasms, hypercoagulation, increased platelet adhesiveness and aggregation, and a decreased ventricular fibrillation threshold.[1,17] Thus, the effects of smoking are both long and short term. Giving up smoking should, in principle, eliminate almost immediately the acute effects, but the atherosclerotic damage would persist even after quitting.

This study shows a prompt and substantial drop in risk for former smokers when compared with current smokers, which is already evident one year after quitting: this can be attributed to the elimination of the acute effects of cigarette smoking. The risk of former smokers remained higher, however, than that of never smokers, for several years at least after quitting.

In this and previous work, the sample size was not large enough to establish whether the risk of former smokers reaches that of never smokers after a defined number of years or whether it remains slightly raised. In principle, however, the risk should remain at least moderately high, and reach that of never smokers only asymptotically.

In our study, the risk estimates for former smokers, like those for current smokers, were higher at a younger age and directly related to the number of cigarettes smoked. These findings agree with most previous work.[1] However, in contrast with some other studies,[1] we did not observe any material difference in risk with the duration of smoking both for current and for exsmokers.

With regard to possible sources of bias, we took care to eliminate from the comparison group all subjects admitted to hospital for conditions known or suspected to be related to smoking, which could have led to an underestimation of the smoking associated relative risks. Furthermore, the results were consistent in separate analyses across major different diagnostic categories of controls (traumas, other orthopaedic, surgery, other miscellaneous). Our cases survived long enough to be interviewed, so they do not represent the whole population with acute myocardial infarction, but only those who did not die. However, several cohort investigations which considered ischaemic heart disease mortality as an endpoint yielded comparable results. Among the strengths of the study are the almost complete participation, the comparable interview setting for cases and controls, the accurate diagnosis for cases,[2] and the ascertainment of smoking status at the exact moment of the myocardial infarction.

In conclusion, therefore, the most important indication from this study, on a public health level, is the substantial drop in the risk of acute myocardial infarction after stopping smoking: about two thirds of the excess risk could be eliminated after one year only. Furthermore, the observation that the RR of former smokers could only asymptotically reach that of never smokers has interesting implications for our understanding of the tobacco-related biological mechanisms of infarction risk.

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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 Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990;**336**:65–71.
3 Negri E, Santoro L, D'Avanzo B, Nobili A, La Vecchia C. Body mass and acute myocardial infarction. *Prev Med* 1992;**21**:292–301.
4 Negri E, Franzosi MG, La Vecchia CL, Santoro L, Nobili A, Tognoni G. Tar yield of cigarettes and risk of acute myocardial infarction. *BMJ* 1993;**306**:1567–70.
5 WHO. *Ischemic heart disease registers: report of the Fifth Working Group.* Copenhagen: World Health Organization, 1971.
6 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;**22**:719–48.
7 Breslow NE, Day NE. *Statistical methods in cancer research.* Vol. 1: The analysis of case-control study. Lyon: IARC Science Publications, 1980:32.
8 Hammond EC, Horn D. Smoking and death rates. Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. *JAMA* 1958;**166**:1294–308.
9 Hammond EC. Smoking in relation to the death rates of one million men and women. In: Haenszel W, ed. Epidemiological approaches to the study of cancer and other chronic diseases. *Monogr Natl Cancer Inst* 1966;**19**:127–204.
10 Cederlof R, Friberg L, Hrubec Z, Lorich U. *The relationship of smoking and some social covariables to mortality and cancer morbidity. A ten year follow-up in a probability sample of 55,000 Swedish subjects age 18 to 69.* Parts I and II. Stockholm: Karolinska Institute, 1975:91.
11 Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *BMJ* 1976;**2**:1525–36.
12 Rogot E, Murray JL. Smoking and causes of death among

US veterans: 16 years of observation. *Public Health Rep* 1980;**95**:213–22.
13 Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. *N Engl J Med* 1985;**313**:1511–14.
14 Rosenberg L, Palmer JR, Shapiro S. Decline in the risk of myocardial infarction among women who stop smoking. *N Engl J Med* 1990;**322**:213–17.
15 Dobson AJ, Alexander HM, Heller RF, Lloyd DM. How soon after quitting smoking does risk of heart attack decline? *J Clin Epidemiol* 1991;**44**:1247–53.
16 Cook DG, Shaper AG, Pocock SJ, Kussick SJ. Giving up smoking and the risk of heart attacks. A report from the British Regional Heart Study. *Lancet* 1986;ii:1376–80.
17 US Department of Health and Human Services. *Reducing the health consequences of smoking. 25 years of progress*. A report of the Surgeon General: Rockville, MD, 1989.