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

Eva Negri, Carlo La Vecchia, Barbara D’Avanzo, Alessandro Nobili, Romano Giuseppe La Malfa on behalf of the GISSI-EFRIM investigators

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 ex-smokers, 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.

It is well established that cigarette smoking increases the risk of acute myocardial infarction and of ischaemic heart disease in general. 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. 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.

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. Eighty hospitals spread all over Italy participated in this study. The design of this investigation has already been described.

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), 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
disease, and all those
whose primary diagnosis on hospital admis-
sion was a cardiovascular, cerebrovascular,
nonalastic, 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 miscel-
naneous 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 con-
trols during their stay in hospital. Four inter-
viewers 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 fac-
tors; lifestyle habits; consumption of coffee,
alcohol, and a few indicator foods; selected
indicators of physical activity; history of
selected conditions; and family history of car-
diovascular and cerebrovascular diseases.

Information was collected specifically on
smoking status (never/ex/current); age at start-
ingsmoking; 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
cyres 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 corre-
sponding 95% confidence intervals (CI),
adjusted for sex and age in decades, were used
to estimate relative risks (RR) of acute myocar-
dial infarction according to the time since quitti-
iming.6 In addition, multiple logis-
tic regression models were fitted to control
simultaneously for several potential confound-


ing 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; > 30 kg/m²); history of diabetes
and hypertension; family history of acute myo-
cardial infarction; serum cholesterol con-
centration (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 $\chi^2$ 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, and
frequently reported a history of acute myocar-
dial infarction in relatives; and drank more
coffee.

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

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>801 (87-4)</td>
<td>976 (88-2)</td>
</tr>
<tr>
<td>Women</td>
<td>115 (12-6)</td>
<td>130 (11-8)</td>
</tr>
<tr>
<td>Age (y):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>55 (6-0)</td>
<td>62 (5-6)</td>
</tr>
<tr>
<td>40–49</td>
<td>167 (18-2)</td>
<td>207 (18-7)</td>
</tr>
<tr>
<td>50–59</td>
<td>305 (33-3)</td>
<td>373 (33-7)</td>
</tr>
<tr>
<td>60–69</td>
<td>323 (35-5)</td>
<td>382 (34-5)</td>
</tr>
<tr>
<td>70–74</td>
<td>66 (7-2)</td>
<td>82 (7-4)</td>
</tr>
<tr>
<td>Education (y):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7</td>
<td>514 (56-1)</td>
<td>759 (68-6)</td>
</tr>
<tr>
<td>7–11</td>
<td>242 (26-4)</td>
<td>221 (20-0)</td>
</tr>
<tr>
<td>≥ 12</td>
<td>160 (17-5)</td>
<td>126 (11-4)</td>
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<tr>
<td>Body mass index (kg/m²):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>322 (35-2)</td>
<td>498 (45-0)</td>
</tr>
<tr>
<td>≥ 25</td>
<td>594 (64-8)</td>
<td>608 (55-0)</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 205 (median)</td>
<td>227 (24-8)</td>
<td>477 (43-1)</td>
</tr>
<tr>
<td>≥ 205</td>
<td>387 (42-5)</td>
<td>315 (28-4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>302 (33-0)</td>
<td>314 (28-4)</td>
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<td>Hypertension:</td>
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<td></td>
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<tr>
<td>No</td>
<td>646 (72-5)</td>
<td>922 (83-4)</td>
</tr>
<tr>
<td>Yes</td>
<td>252 (27-5)</td>
<td>184 (16-6)</td>
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<tr>
<td>Diabetes:</td>
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<td></td>
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<tr>
<td>No</td>
<td>811 (88-5)</td>
<td>1021 (92-5)</td>
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<tr>
<td>Yes</td>
<td>105 (11-5)</td>
<td>85 (7-7)</td>
</tr>
<tr>
<td>Family history of AMI:</td>
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<td></td>
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<tr>
<td>No</td>
<td>705 (77-0)</td>
<td>995 (90-0)</td>
</tr>
<tr>
<td>Yes</td>
<td>211 (23-0)</td>
<td>111 (10-0)</td>
</tr>
<tr>
<td>Coffee consumption (cups/d):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3</td>
<td>477 (52-1)</td>
<td>808 (73-1)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>439 (47-9)</td>
<td>298 (26-9)</td>
</tr>
</tbody>
</table>


477 (52-1) | 808 (73-1) |
| ≥ 3 | 439 (47-9) | 298 (26-9) |
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 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 more, 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 low 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. In three previously published case-control investigations, the risk of acute myocardial infarction declined steeply to reach that of never smokers after three years. 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. 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. 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. 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. However, in contrast with some other studies, 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 (trauma, 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 end-point 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, 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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