ISCHEMIC HEART DISEASE

Smoking Cessation and Risk of Myocardial Reinfarction in Coronary Patients: a Nested Case-Control Study

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Introduction and objectives. Smoking cessation reduces mortality in coronary patients. The aim of this study was to estimate association measures between the risk of occurrence of fatal or non-fatal reinfarction in patients who either continue to smoke or stop after a first infarction and are treated with secondary prevention measures.

Patients and method. The study was a case-control (1:1) design nested in a cohort of 985 coronary patients under the age of 76 years who were not treated with invasive procedures and survived more than 6 months after the first acute myocardial infarction. Cases were all patients who suffered reinfarction (n = 137) between 1997 and 2000. A control patient was matched with each case by gender, age, hospital, interviewer, and the secondary prevention timeframe.

Results. Patiehts who smoke after the first acute myocardial infarction had an odds ratio (OR) of 2.83 (95% CI, 1.47-5.47) for a new acute myocardial infarction. Adjustment for lifestyle, drug treatment, and risk factors (family history of coronary disease, high blood pressure, hypercholesterolemia, and diabetes mellitus) did not change the OR (2.80 [95% CI, 1.35-5.80]). Patients who quit smoking had an adjusted OR of 0.90 (95% CI, 0.47-1.71) compared with non-smokers before the first acute myocardial infarction. Continued smoking had an adjusted OR of 2.90 (95% CI, 1.35-6.20) compared to quitting after the first acute myocardial infarction.

Conclusion. The risk of acute myocardial infarctions is three times higher in patients who continue to smoke after an acute coronary event compared with patients who quit. The risk of reinfarction in patients who stop smoking is similar to the risk of non-smokers before the first infarction.

Key words: *Myocardial infarction. Prevention. Coronary disease. Smoking. Lifestyle.*

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Abandono del tabaco y riesgo de nuevo infarto en pacientes coronarios: estudio de casos y controles anidado

Introducción y objetivos. Dejar de fumar reduce la mortalidad en pacientes coronarios. El objetivo de esta investigación fue estimar las medidas de asociación entre la aparición de un reinfarto fatal o no fatal y el mantenimiento o el abandono del hábito tabáquico tras un primer infarto, en pacientes sometidos a medidas de prevención secundaria.

Pacientes y método. Estudio de casos y controles (1:1) anidados en una cohorte de 985 pacientes coronarios, menores de 76 años, no tratados con procedimientos invasivos o quirúrgicos, que sobrevivieron más de 6 meses tras el primer infarto. Los casos (n = 137) fueron todos los pacientes con un reinfarto entre 1997 y 2002, emparejados con los controles por sexo, edad, hospital, entrevistador y tiempo de prevención secundaria.

Resultados. El hábito de fumar después del primer IAM presentó una *odds ratio* (OR) de 2,83 (intervalo de confianza [IC] del 95%, 1,47-5,47) para un nuevo IAM. El ajuste del modelo por otros estilos de vida, tratamientos farmacológicos y factores de riesgo (antecedentes familiares de enfermedad coronaria, hipertensión arterial, hipercolesterolemia y diabetes mellitus) mantuvo la OR (2,80 [IC del 95%, 1,35-5,80]). Los que dejaron de fumar presentaron una OR ajustada de 0,90 (IC del 95%, 0,47-1,71) respecto a los no fumadores, mientras que los que continuaron fumando presentaron una OR ajustada para un nuevo IAM de 2,90 (IC del 95%, 1,35-6,20) respecto a los que dejaron de fumar.

Conclusiones. El mantenimiento del tabaquismo después de un IAM se asocia con un riesgo triple de padecer otro infarto respecto a los pacientes que dejan de fumar. El abandono del hábito tabáquico equipara el riesgo al de los no fumadores antes del primer infarto.

Palabras clave: *Infarto de miocardio. Prevención. Enfermedad coronaria. Tabaco. Estilo de vida.*

ABBREVIATIONS

OR: odds ratio
CI: confidence interval
AMI: acute myocardial infarction

INTRODUCTION

A healthy lifestyle is the foundation for primary prevention, hence changes in diet and physical exercise and the cessation of smoking form the basis in of therapy patients with established heart disease.[1] Most studies of measures recommended for secondary prevention of coronary heart disease analyze the efficacy of programs aimed at favoring changes in lifestyle or at increasing the percentage of patients treated with drugs shown to be effective at delaying progression of coronary heart disease.[2]

Smoking has been related with physiopathologic mechanisms of cardiovascular disease, such as raised concentrations of carboxyhemoglobin and increases in fibrinogen and platelet aggregability, as well as changes in vascular reactivity and a reduction in plasma levels of high density lipoprotein (HDL-C).[3-6] These changes, either alone or in combination, favor the appearance of arterial lesions, which lead to progression of arteriosclerosis and an increased risk of thrombosis.

Most of the evidence regarding the cardiovascular benefits of smoking cessation comes from randomized studies which included patients with prior cardiovascular disease. A meta-analysis has recently been published of cohort studies analyzing the benefit of smoking cessation in patients with coronary heart disease. The main finding was a combined odds ratio (OR) of 0.54 (95% confidence interval [CI], 0.46-0.62) for death, regardless of sex, study period, observation period and geographic zone, although the risk of non-fatal reinfarction was not studied.[7]

Only one clinical trial examining the efficacy of multiple risk factor management has shown significant results for smoking cessation.[8] The duration of hospital stay and intensive counseling during recovery from the acute episode are important for achieving higher rates of sustained smoking cessation.[9]

This study was designed to analyze the effectiveness of our usual program of secondary prevention counseling in reducing the risk of coronary disease, especially relating to smoking cessation after a first AMI, which is still considered to be one of the main cardio-vascular risk factors.[10,11]

PATIENTS AND METHODS

This 1:1 case-control study included 274 coronary patients from a cohort of 985 with a firm diagnosis of AMI from 1980 to 2000 in the Hospital de Navarra. Patients were included if they were younger than 76 years of age, they survived more than 6 months after the acute event, and they had received no invasive therapeutic procedure or aorto-coronary bypass. Diagnosis of all infarctions was made according to criteria of the MONICA project[12] (two or more ECGs with definite changes; an ECG with suggestive changes and abnormal enzymes; or characteristic symptoms and abnormal enzymes). Cases were considered those patients with fatal or nonfatal reinfarction from January 1997 to December 2000 (n=142; men, 90.5%). Data collection was made at the time of the second infarction. The medical charts were reviewed to ensure compliance with all the study criteria. The two patients who refused to participate in the study and the three with inadequate control data (see below) were excluded from the analysis, giving a final total of 137 patients interviewed (96.5% of the initial sample).

One control patient was paired with each case for the same age (±5 years) and sex. The controls were from the same cohort of patients; i.e., all had had just one myocardial infarction (based on the criteria as mentioned above) and after the same secondary prevention period as their corresponding case (±10%) presented no symptoms of coronary disease progression. Data from controls were obtained when they were matched with their corresponding case. The data base was ordered by age and the first control who matched the reference case was chosen. If a control refused to participate (9 patients), the next suitable control in the data base was chosen.

The interviews were carried out by two doctors (EMZ and IEI) and one nurse (BSA), who all received prior training in a pilot study. Each case-control pair was interviewed by the same researcher. The interview was conducted after explaining the reasons for the study and obtaining informed consent. The questionnaire contained information concerning the following aspects: previous diseases (1 question), family history of cardiovascular disease (1 question), work after the first infarction (3 questions), family and social integration (3 questions), personal attitudes (2 questions, about feelings of stress and perfectionism) and drug

TABLE 1. **Number and percentage of cases and controls in each category according to smoking status**

	Cases	Controls
Nonsmoker before and after first AMI	51 (37.2%)	54 (39.4%)
Quit smoking after first AMI	48 (35.0%)	67 (48.8%)
Continued smoking after first AMI	38 (27.7%)	16 (11.7%)
Total	137 (100%)	137 (100%)

AMI: acute myocardial infarction.

therapy after the first myocardial infarction (8 questions). Questions about lifestyle before and after the first infarction included: smoking (4 questions), physical exercise (10 questions), dietary habits (5 questions) and sexual activity (2 questions). The patients were asked about compliance with the recommended changes in self-care and about the type and frequency of visits to their cardiologist, family doctor, and primary care nurse (13 questions).

If the patient had died (29 cases and 6 controls), or when the patient was unable to maintain a telephone conversation due to deafness or cognitive deterioration (6 cases and 5 controls), the interview was conducted with a close family member. In these cases, the matching control patient was also interviewed through a close family member.

Data were recorded in a Microsoft Access data base, and data for the possible control patients were obtained from a Microsoft Excel data base. Statistical analysis was made using SPSS, version 10.0. The odds ratios were calculated by conditional logistic regression analysis, with the case/control as the dependent variable. Binary logistic regression models were adjusted to study mortality, with death as the dependent variable. Percentage differences were calculated with EpiInfo, version 6.04b.

RESULTS

Mean age was 69.8 years for cases and 69.7 years for controls. The mean time to reinfarction in the cases was 7.15±0.51 years. Only 10 cases had a reinfarction 14 years or more after the first AMI. The study concentrated on lifestyle, drug therapy, and medical and nursing care during the period between the first infarction and entry to the study, i.e. the time of the most recent infarction in the cases or the time of pairing in the controls, to determine the duration of secondary prevention.

For the variable «smoker» in the initial analysis, the cases and controls were classified as smokers or nonsmokers after their first infarction. For the second conditional logistic regression model they were classified as "nonsmokers before and after first infarction", "ceased smoking after first infarction" and "continued smoking after first infarction". The number of patients included in each category is shown in Table 1.

Table 2 shows possible confounding variables for cases and controls, as well as percentages differences. Stopping work after the first infarction was associated with a lower frequency of smoking

TABLE 2. **Variables which could confound analysis of smoking cessation after a first infarction**

	Controls			Cases		
	Nonsmoker (%)	Quit smoking (%)	Continue smoking (%)	Nonsmoker (%)	Quit smoking (%)	Continue smoking (%)
Family history	29.6	26.9	18.8	35.3	35.4	31.6
Married	88.9	88.1	75.0	80.4	91.7	78.4
Primary education	85.2	76.1	87.5	84.3	79.2	73.7
Retired	37.0	41.8	68.8b	31.4	52.1	65.8a
Feelings of stress	16.7	16.4	50.0b	25.5	22.9	23.7
Perfectionism	70.4	70.1	68.8	64.7	68.8	57.9
High blood pressure	40.7	55.2	31.2	47.1	45.8	55.3
Dyslipidemia	40.7	52.2	75.0a	47.1	43.7	50.0
Diabetes	24.1	25.4	12.5	35.3	22.9	13.2a
Antihypertensive therapy	31.5	53.7	31.3	37.3	37.5	39.5
Cholesterol-lowering drugs	35.2	42.4	62.5	25.5	40.4	39.5
Antidiabetic agents	22.2	20.9	12.5	23.5	22.9	10.5
Walking	85.2	91.0	75.0	80.4	87.5	71.1
Dietary changes	87.0	88.1	68.8	56.9	68.8	42.1
Compliance with recommendations	77.8	83.6	43.8b	86.3	87.5	60.5b

[a]P<.05 compared with nonsmokers. [b]P<.05 compared with nonsmokers and those who quit smoking.

TABLE 3. **Odds ratio (OR) and 95% CI of a second myocardial infarction after a first myocardial infarction according to smoking status (yes/no)**

	OR (95% CI)
Crude analysis[a]	2.83 (1.47-5.47)
Adjusted for lifestyle[b]	2.96 (1.47-5.95)
Further adjusted for drug therapy[c]	3.20 (1.56-6.56)
Further adjusted for family and personal history[d]	2.80 (1.35-5.80)

[a]Paired by age, sex, hospital, interviewing doctor and duration of secondary prevention period. [b]Adjusted for walking, dietary changes and compliance with recommendations after a first myocardial infarction. [c]Further adjusted for drug therapy (antihypertensive drugs, cholesterol lowering drugs and antidiabetic agents). [d]Further adjusted for family history of coronary heart disease and for the presence of high blood pressure, dyslipidemia and diabetes.

cessation, as well as with greater difficulty stopping smoking in the controls, who reported a subjective feeling of stress, which was not reported by the cases. Moreover, the proportion of patients who failed to follow treatment advice adequately was greater among those who continued smoking after their first infarction. This is consistent with the responses to the survey.

Smoking after the first infarction was associated with a reinfarction, with an OR of 2.83 (95% CI, 1.47-5.47). Interestingly, after adjusting the statistical model for variables related with walking and dietary modification after the first infarction, as well as for self-reported compliance with medical recommendations for secondary prevention, the OR rose to 2.96 (95% CI, 1.47-5.95). Likewise, inclusion in the model of drug therapy regimens (antihypertensive drugs, lipid lowering drugs and antidiabetic agents) increased the OR of a reinfarction to 3.20 (95% CI, 1.56-6.56). However, after including family history of heart disease and risk factors (hypertension, dyslipidemia and diabetes), the final OR was 2.80 (95% CI, 1.35-5.80) (Table 3).

In comparison with nonsmokers, both before and af-

ter the first infarction, the decision to quit smoking resulted in an OR for reinfarction of 0.82 (95% CI, 0.4-1.42). After adjusting for other lifestyle factors, compliance with recommendations, drug therapy and risk factors (family history, hypertension, dyslipidemia and diabetes) the OR was 0.90 (95% CI, 0.47-1.71) (Table 4). Those patients who continued smoking after the first infarction had an OR for reinfarction of 3.06 (95% CI, 1.53-6.13) compared with those who quit smoking. After adjustment for other lifestyle factors, compliance with the recommendations, drug therapy, high blood pressure, hypercholesterolemia, diabetes and family history, the OR fell to 2.90 (95% CI, 1.35-6.20) (Table 4).

In an attempt to evaluate the risk of a further infarction in relation to the number of cigarettes smoked per day, the conditional logistic regression model was adjusted, using the number of cigarettes divided by 5 as an independent variable. After inclusion of the same variables as mentioned above, those patients who continued smoking after the first infarction had an additional risk of reinfarction of 39.5% for each 5 cigarettes smoked per day (data not shown).

The OR of death was 3.07 (95% CI, 1.13-8.33) for those patients who continued smoking compared with those who quit smoking after their first infarction.

DISCUSSION

This study examined several factors influencing secondary prevention in coronary patients after a first AMI, including counseling aimed at smoking cessation. An observational study is the only possible design due to ethical difficulties arising with planned intervention studies. No differences were found in the incidence of reinfarction between patients who quit smoking and those who had never smoked. Those patients who continued smoking after their first myocardial infarction had a three-fold risk of a second infarc-

TABLE 4. **Measures of association (OR and 95% CI) for reinfarction in patients who quit smoking vs nonsmokers and patients who continued smoking vs those who quit**

	Quit smoking vs nonsmokers	Continue smoking vs quit smoking
Crude analysis[a]	0.82 (0.47-1.42)	3.06 (1.53-6.13)
Adjusted for lifestyle[b]	0.86 (0.48-1.53)	3.13 (1.50-5.53)
Further adjusted for drug therapy[c]	0.89 (0.48-1.66)	3.34 (1.57-7.08)
Further adjusted for family and personal history[d]	0.90 (0.47-1.71)	2.90 (1.35-6.20)

[a]Paired by age, sex, hospital, interviewing doctor and duration of secondary prevention period. [b]Adjusted for walking, dietary changes and compliance with recommendations after a first myocardial infarction. [c]Further adjusted for drug therapy (antihypertensive drugs, cholesterol lowering drugs and antidiabetic agents). [d]Further adjusted for family history of coronary heart disease and for the presence of high blood pressure, dyslipidemia and diabetes.

tion compared to those who quit smoking.

Previous studies have compared the effect of cardiac rehabilitation programs and lifestyle changes with usual standards of care.[1,2,13] Although programmed interventions resulted in a better prognosis for these patients, none of the seven clinical trials of secondary prevention which analyzed the effect of smoking cessation and other preventive measures on the incidence of reinfarction detected any significant differences in coronary events, and only one study showed an increased rate of smoking cessation in the experimental group.[2]

Preventive intervention programs do not always improve health outcome,[14] and it is not easy to apply proven preventive measures to daily practice.[15,16] Other randomized trials have promoted interventions to improve social support, quality of life and care, but with uncertain results.[2,17]

This study was designed to determine the effectiveness of secondary prevention measures in patients with coronary heart disease. Treatment and counseling were provided by family doctors and primary care nurses, with occasional visits by the cardiologist. Standards of clinical management of coronary patients are constantly being improved.[18] The matched design of this case-control study, with one of the criteria being the duration of the secondary prevention period, was aimed at eliminating a possible cohort effect resulting from varying access to the increasing evidence supporting protective therapy. Our results, therefore, reflect the permanent updating of preventive measures as they become incorporated into patient care.

Although we included a variable to attempt to adjust for variations in patients´ adhesion to counseling, it had the logical limitations associated with subjective self-referral. The reliability of this variable can be seen from the fact that patients who continued smoking reported a lower percentage of adaptation to the recommended treatment. Of note, too, was the fact that the control group patients who were unable to quit smoking reported a greater percentage of stress. This association has been seen by others.[19] For other lifestyles, the smokers walked less often and introduced fewer changes into their diet, although these differences were not statistically significant. The least healthy lifestyles, therefore, were generally found in the same patients.

Because patients who die shortly after an acute coronary event do not have the opportunity to implement measures of secondary prevention or to benefit from health education activities, we excluded those who survived less than six months after a first infarction.

The beneficial effect of smoking cessation has been studied extensively in relation to the reduction in mortality after an infarction.[20-22] Several cohort studies of coronary patients, collected in a meta-analysis, found different benefits regarding mortality after cessation of smoking. Four of these studies reported no significant individual differences, though the combined risk showed a reduction in mortality of 46%.[7]

Few studies analyze the incidence of fatal or non-fatal infarction in coronary patients in relation with smoking. Hedback et al[23] found a statistically significant reduction in the percentage of patients having a reinfarction among those who ceased smoking, after both five- and ten-year follow-up. However, no multivariate risk analysis was done. In our study, the dependent variable was the occurrence of a further infarction, either fatal or non-fatal. This event was clearly related with smoking, independently of other risk factors; with the analysis showing protection for those who ceased smoking and an increased risk for those who continued. A similar effect was reported by Rea et al,[24] who demonstrated that the longer the cigarette-free period the greater the protection.

Multivariate OR in our study (smokers vs nonsmokers) revealed a possible protective role of the independent variables related with other habits (exercise and diet) and with drug therapy, as the OR rose from 2.83 to 3.39. Thus, any change towards a beneficial lifestyle or the incorporation of protective treatment would reduce the risk in those patients who were unable to quit smoking. Although this protection has been shown with specific drugs, such as beta blockers among the group of antihypertensive agents,[25] our patients were questioned about the use of any antihypertensive drug in order to facilitate their response over the telephone. The same applies to statins,[26] which are the drugs most often prescribed for hypercholesterolemia during the period of secondary prevention, although few patients were able to identify their generic name.

Hermanson et al[27] found a significant OR of 1.7 for fatal infarction in patients who continued smoking. Using mortality as a dependent variable in our study showed that patients who continued smoking had a significantly increased risk of death, with an OR of 3.07 compared to those who quit smoking. However, our study was not designed to analyze mortality in patients with coronary heart disease.

The most important limitation in our study is probably the credibility of the responses given by the patients over the telephone, especially those related to smoking. Previous studies have relied on the cotinine assay for validation,[28] but this was not possible in our

study due to its design. Nevertheless, telephone interviews are not incompatible with obtaining exact responses, as the interview is conducted voluntarily with a stranger. The same can be said for the other responses concerning lifestyle and treatment.

Another factor could be the validity of responses given by close relatives. An attempt to control for this bias was made by interviewing the same type of relative in the control patient, so that the comparative analysis should still be valid. To avoid interviewer bias, both the case and the control were interviewed by the same person. The characteristics of this study, nested in the same cohort of patients, and the pairing between cases and controls according to age, sex, hospital, interviewer and duration of the secondary prevention period, strengthens the validity of our results. Patients with a prior bypass or angioplasty were excluded from the study in order to eliminate bias resulting from therapy which could interfere with the natural course of the disease or with the benefits of secondary prevention recommendations. Patients with reinfarction within six months of the initial event were also excluded, as a shorter period of secondary prevention can be considered insufficient.

Previous studies have either examined the effects of intervention programs or analyzed mortality in cohorts of patients with coronary heart disease according to smoking habits.[2,7] Our observational study of current secondary prevention also provides a multivariate analysis of the association between preventive measures and the incidence of reinfarction in patients with coronary heart disease.

CONCLUSIONS

Patients who have had a first myocardial infarction are liable to have another. Those who quit smoking have a three-fold reduction in risk of a second coronary event compared to those who continue smoking. Secondary prevention of coronary heart disease requires responding to the difficulty encountered by some patients with smoking cessation. Any effort aimed at this will reduce morbidity and mortality in patients with coronary heart disease. Counseling about smoking cessation should take place in different areas, although primary care nurses, after adequate training, will probably be able to achieve high rates of smoking cessation.[29]

ACKNOWLEDGEMENTS

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