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Risk factors for ulcerative colitis: A population-based, case–control study in Spain

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Abstract

Background: Environmental factors seem to be very important in the aetiology of Ulcerative Colitis (UC), with smoking, contraceptive use, and hygiene being the factors most commonly linked to disease.
Aim: To analyse the association between different risk factors and development of UC in our community.
Patients and methods: This is a case–control, population-based study. The UC population consists of an inception-case population of all cases diagnosed, using Lennard–Jones criteria, in our community from 1st February 1992 to 31st January 1995 that were prospectively included. Controls were selected from healthy population and matched with patients for age, sex and rural/urban habitat. We used the SPSS/PC+ software, EpiInfo and Statistix for statistical analysis, giving the rates as point estimates and 95% confidence intervals (95%CI) or as mean ± standard deviation in quantitative variables. For multivariate analysis we used conditional logistic regression.
Results: 205 patients were diagnosed of UC. 38 patients (18.5%) with UC were smokers, compared with 84 (40.8%) controls ($p<0.001$). Smoking behaved as a protector factor for UC (OR = 0.55 (CI 95% 0.33–0.92) and ex-smoker acted as a risk factor (OR = 1.94 (CI 95% 1.14–3.34). After the multivariate analysis, both associations were maintained. We did not detect statistical differences in the analysis of previous appendectomy, childhood hygiene or oral contraceptive use. Five of the 12 cases with family aggregation had first-degree relatives and 7 of them second-degree relatives. None of the controls had previous IBD history ($p=0.0002$).
Conclusion: Ex-smoking and previous family history of inflammatory bowel disease appeared as risk factors for developing ulcerative colitis while current smoking behaved as a protective factor in this population.

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are complex diseases, in which uncontrolled intestinal inflammation

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seems to result from a combination of genetic and environmental factors.[1] Even in these years of rapid emergence of genetic data,[2] it is clear that external factors do have a key influence in the phenotype of these diseases: the dynamic of changes in populations appears to be mainly determined by environment.[3] Data on smoking are particularly interesting, because as shown in twin studies, this factor appears to modulate the genotype to result in the very different phenotypes of UC versus CD, being "protective" for UC and "promoter" for CD.[4] Besides smoking,[5–8] previous appendectomy has also been shown to protect from UC in several epidemiological studies, as shown in a meta-analysis[9]; and on the other side, the use of oral contraceptive has been suggested as a risk factor.[10] Hygiene in infancy, a factor difficult to separate from familial aggregation,[11] could be a risk factor for CD, data on UC are more scarce.[12]

We do report the analysis of these factors in an inception-case cohort of patients with UC, compared to a healthy control population matched for age, sex and rural/urban residence.

2. Participants and methods

2.1. Cases and controls

This is a case–control and population-based study. Patients were all UC cases (Lennard–Jones criteria[13]) diagnosed in our community (Aragón, Spain, 47,719 km^2 and 1.187.546 inhabitants) from 1st February 1992 to 31st January 1995. Controls were selected from healthy population, and matched for age, sex and urban/rural residence. Urban was defined as living in a town with >25,000 inhabitants. Detailed data on epidemiological methods and incidence have been previously reported.[14] In brief, we first reviewed the clinical records of all patients. Then we designed a questionnaire to be fulfilled by both, cases and controls. Questions included cigarette consumption, date of beginning and ending smoking and number of cigarettes/day; previous appendectomy; oral contraceptive use and family history of inflammatory bowel disease. We also asked them about the number of persons living in their houses during their infancy (until 18 years old), number of bathrooms and existence or not of hot water, as indirect variables of childhood domestic hygiene. Patients and controls were all contacted personally by one of investigators (BS, CLM) who fulfilled all the questionnaires. The reference date for calculations was the time of diagnosis. To avoid recall bias, almost all questionnaires (>90%) were obtained less than one year after diagnosis, and clinical records were used for quality control.

Table 1 Characteristics of 205 cases and their age, sex, urban/rural matched controls

	Cases	Controls	
Age ($X \pm SD$)	34.9 ± 15.42	35.5 ± 15	Matched
Sex	128m/77f	128m/77f	Matched
Urban/rural	122u/83r	122u/83r	Matched
	205	205	

$X \pm SD$: mean ± standard deviation.
m: male u: urban.
f: female r: rural.

Table 2 Bivariate analysis

	Cases	Controls	p value
Smokers (%)	38 (18.5)	84 (40.8)	$p=0.01$
Ex-smokers (%)	63 (30.7)	43 (20.9)	$p=0.009$
Appendectomy (%)	11 (5.4)	6 (2.9)	NS
IBD history (%)	12 (5.9)	0	$p=0.0002$
Contraceptives (%) (77 females)	14 (18.2)	7 (9.09)	NS

NS: not significant.

2.2. Analysis

Data were first collected in a personal database (Filemaker 3.0). We then used the SPSS/PC+ software, v. 6.1 (SPSS Inc., Chicago, IL), EpiInfo and Statistix tools for all our statistical analysis.

Explanatory variables in the main adjusted analysis included: age; sex; current cigarette smoking; previous appendectomy; oral contraceptive use; number of persons/house, number of bathrooms and existence of hot water in infancy; and family history of IBD. The rates are given as point estimates and 95% confidence intervals (95% CI) or as mean ± standard deviation in quantitative variables.

The possible association of clinical factors was first tested by bivariate analysis using chi-square test for proportions and Student's t-test for means. We then tested 33 different models performing a multivariate analysis (conditional logistic regression) including as exploratory variables those with a $p<0.20$ in our bivariate analysis, considering ulcerative colitis as dependent variable and the rest of studied variables as independent.

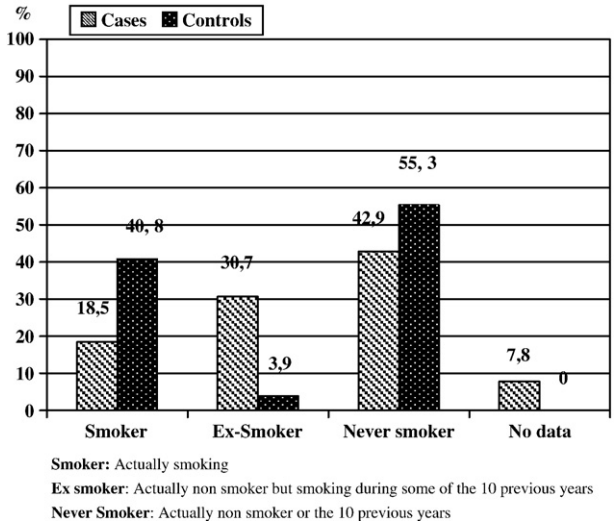

Figure 1 Comparing "smoking" between cases and controls. Smoker: actually smoking. Ex smoker: actually non-smoker but smoking during some of the 10 previous years. Never smoker: actually non-smoker or the 10 previous years.

3. Results

205 patients were diagnosed of UC in Aragón from 1st February 1992 to 31st January 1995. Table 1 shows the characteristics of cases and their age, sex and urban/rural matched controls. The age range was from 13 to 92 years, well matched with that of controls, as expected. Table 2 shows our bivariate analysis of all variables studied.

3.1. Smoking

We defined current smoker as a person consuming cigarettes at the time of the study or those who left the habit in the last year; ex-smoker as the one who has consumed cigarettes during the last 10 years but does not since at least one year; and non-smoker as the one who never smoked or has stopped smoking for more than 10 years. As Fig. 1 shows, 38 UC patients (18.5%) were current smokers, compared with 84 (40.8%) controls ($p=0.01$); 63 patients were ex-smokers (30.8%) compared with 43 (20.9%) of our controls ($p=0.009$). So, according with our bivariate analysis, current cigarette smoking behaved as a protector factor for development of ulcerative colitis with an OR=0.55 (IC 95% 0.33–0.92) and the fact of being ex-smoker behaved as a risk factor with an OR=1.94 (IC 95% 1.14–3.34). These analysis remained all significant at the 0.05 level after multivariate analysis.

In Calkins meta-analysis of selected studies[6] we can observe a dose-response pattern with a decreasing risk of ulcerative colitis with increasing usage of cigarettes when we analyse and subdivide the smoker group by the number of cigarettes. However, making a quantitative analysis in our patients, in patients smoking less than 10 cigarettes/day we can see an OR=6.44; IC 95%: 1.91–21.73 $p=0.011$; behaving as a protective factor against ulcerative colitis disappearing this association in smokers of more than 20 cigarettes/day.

3.2. Appendectomy

11 patients of the 205 cases (5.4%) had previous appendectomy, with surgery at a mean age of 20.45±13.28. In our bivariate analysis we did not detect statistical differences with a "protector" but not significant: OR=0.54.

3.3. Contraceptives

Of the 77 women in each group of our study, just 21 (27.3%) had taken oral contraceptives during the year of the diagnosis or the year before (14 in the case group (18.2%) and 7 (9%) in the control group). Data about the time of consuming were available in these 14 women, being between 2 to 89 months with a mean of 24 months. In our analysis, we do not detect significant differences, though the odds ratio tends to show a risk factor in this group: $p=0.469$; OR=1.429 (IC 95% 0.5438–3.753).

3.4. IBD familial history

12 patients (10 males, 2 females) diagnosed of UC had previous family history of inflammatory bowel disease: 11 of them had previous family history of UC and just 1 of them had a relative with CD. Five patients had first-degree relatives (offspring or parents), and 7 had second-degree relatives. None of the controls had previous IBD history ($p=0.0002$). Trying to study this variable in a multivariate analysis we can't give any results due to the few cases reported which limits seriously the power of the statistical tests.

3.5. Childhood hygiene

Roughly the same proportion of those diagnosed of UC colitis answered in their questionnaires to have hot water in their houses than that of the controls (52.9 versus 53.2% (NS)). Neither the number of bathrooms nor the number of persons living in the house during the infancy (<18 years old) showed any difference between cases and controls.

4. Discussion

Of course, our study is limited by the number of cases and controls included, and so results are to be interpreted with caution. However, our data were obtained prospectively with a very careful protocol, and this is a population-based study of an inception-case series; so we think it can add valuable evidence to the available literature.

Smoking relation to Inflammatory Bowel Diseases (IBD) has been confirmed in a very recent, high-quality meta-analysis: current smoking is a risk factor for CD (OR=1.76) and a protective factor for UC (OR=0.58), and former smoking is a risk factor for UC (OR=1.79).[15] These pooled data from literature are very similar to that obtained in our study (see Table 2). In fact, some very recent interesting reports suggest also that there is a strong interaction between smoking and genetic factors. For instance, in monozygotic twins with IBD if one gets CD and the other UC, smoking appears as the key determinant factor.[5] Moreover, smoking seems to be a key risk factor for familial, but not sporadic CD.[16] Taken together these epidemiological observations are the clearest evidence of genetic–environmental interactions we do currently have in IBD. Perhaps because of small numbers, we were unable to confirm the dose-effect previously shown by Calkins.[5] However, our finding of an effect of a relatively small dose (<10 cigarettes per day) is not unexpected, as even passive smoking has been linked to IBD.[17] Time is important in life and, of course, in IBD,[18] and recent evidence also suggest that not only *how much* but also *when* did the patient smoke can significantly modify the clinical phenotype in UC,[19] so more research is clearly needed.

Our data on appendectomy, contraceptive use and familial aggregation are consistent with published data. It is very clear that 205 patients is a small population to confirm or discard these associations, but the similarity of our numbers and those published by other groups,[20] confirm the validity of our data.

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