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Inflammatory bowel disease and tobacco smoke – a case-control study

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Abstract

A case-control study was carried out in Stockholm, Sweden between 1984 and 1987 to evaluate the association of cigarette smoking and exposure to environmental tobacco smoke during childhood and the subsequent development of inflammatory bowel disease. Information on smoking was obtained by a postal questionnaire. The relative risk of Crohn's disease in current smokers compared with those who had never smoked was 1·33 (95% confidence limits 0·7; 2·6) in men and 4·99 (2·7; 9·2) in women; the corresponding results for ulcerative colitis were 0·96 (0·5; 1·8) and 0·72 (0·4; 1·4). The relative risk of ulcerative colitis in recent exsmokers compared with those who had never smoked was 2·18 (0·9; 5·0). Furthermore, an increase in the risk of Crohn's disease was found in those who were exposed to environmental tobacco smoke during childhood, the relative risk being 1·50 (1·0; 2·3). The corresponding relative risk of ulcerative colitis was 0·98 (0·6; 1·5).

The aetiologies of Crohn's disease and ulcerative colitis are largely unknown. Previous epidemiological studies have indicated that cigarette smokers have an increased risk of Crohn's disease,[1–6] and a decreased risk of ulcerative colitis.[2–10] A greater risk of ulcerative colitis among exsmokers has also been reported.[3–7 10] In addition, it has been reported that patients with inflammatory bowel disease come from non-smoking households more often than healthy subjects do.[7] Although one study did not find any strong confounding effect of coffee or alcohol,[10] it is possible that these factors, as well as other suggested risk factors such as the intake of sugar and use of oral contraceptives among women, may help to explain the association between smoking and inflammatory bowel disease.[4 5 11]

The aim of this study was to evaluate the associations between current and former cigarette smoking and environmental tobacco smoke (passive smoking) during childhood and inflammatory bowel diseases while controlling for potential confounding from other suggested risk factors for the diseases.

Methods

SELECTION OF STUDY SUBJECTS

This case-control study was based on the population in Stockholm County who were aged 15–79 years between 1980 and 1984 and had listed phone numbers. Patients were restricted to those identified by us within four years of the date of diagnosis. Control subjects were randomly sampled from the study population.

Effort was made to identify all new patients with Crohn's disease and ulcerative colitis diagnosed in the study population. Information, including discharge diagnosis, on all patients admitted to hospitals in Stockholm County is stored in a central computerised register, from which the patients in this study were recruited. Hence, patients who were not admitted to hospital could not be included.

Medical records for all potential cases were examined to confirm the diagnosis. In Crohn's disease, the diagnostic criteria were defined using the scoring table suggested by Lennard-Jones.[12] The diagnostic criteria for ulcerative colitis included a history of bloody diarrhoea, typical sigmoidoscopy findings, and characteristic microscopy changes on biopsy specimen.[13] Information on the time of onset of symptoms and definite diagnosis, and extent of disease at diagnosis was extracted from the medical records. The extent of disease was evaluated by endoscopy in ulcerative colitis and by endoscopy or radiography, or both, in Crohn's disease. A total of 260 patients with Crohn's disease and 292 with ulcerative colitis were identified. After restriction to patients whose medical records were located within four years of the date of diagnosis, who were aged 15–79 years at the time of diagnosis, and who had listed phone numbers, 184 patients with Crohn's disease and 181 with ulcerative colitis were left (see Table I).

From the population register in Stockholm County Council, an age (within five year age groups) and sex stratified random sample of 390 control subjects with listed phone numbers was selected. The number of control subjects was

TABLE I *Status of subjects in case-control study*

	Crohn's disease	*Ulcerative colitis*	*Control*
Total	260	292	
Patients excluded:			
Age outside the range	8	23	
Medical records not located within four years of diagnosis	52	66	
Unlisted phone number	16	22	
Subjects contacted (%)	184 (100)	181 (100)	390 (100)
Subjects who did not participate (%):			
Refusals	25 (14)	28 (15)	67 (17)
Other causes	7 (4)	8 (4)	18 (5)
Subjects who participated (%)	152 (83)	145 (80)	305 (78)
Sex:			
Men	63	82	147
Women	89	63	158
Age at diagnosis*:			
≤29	68	56	114
30–49	50	59	125
≥50	34	30	66
Year of diagnosis:			
1980	20	21	
1981	37	33	
1982	31	34	
1983	33	32	
1984	31	25	

*Age in 1982 among controls.

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TABLE II *Relative risk of Crohn's disease among smokers, according to sex, and in relation to smoking status reported five years retrospectively*

Smoking status	No of subjects		Relative risk*	95% Confidence limits
	Cases	Controls		
Men				
Never smoked	27	72	1·00	Reference group
Exsmoker	9	22	1·23	0·5; 3·1
Current smoker: No of cig/day†	24	51	1·33	0·7; 2·6
1–19	17	40	1·20	0·6; 2·5
20+	5	7	2·22	0·6; 7·8
Duration of smoking (yrs)				
1–10	7	19	0·75	0·3; 2·1
11+	17	32	2·04	0·9; 4·5
Women				
Never smoked	21	84	1·00	Reference group
Exsmokers	3	15	1·02	0·3; 4·0
Current smoker: No of cig/day†	65	58	4·99	2·7; 9·2
1–19	58	47	5·44	2·9; 10·3
20+	5	8	2·91	0·8; 10·1
Duration (yrs)				
1–10	29	17	7·78	3·4; 17·9
11+	36	41	3·72	1·9; 7·5

*Multiple logistic regression relative risk estimates. Adjustment for age.
†Four cases and seven controls were excluded from these analyses because of inability to recall the number of cigarettes smoked per day five years ago.

chosen so that the age and sex distribution was similar to that of the two patient series together.

COLLECTION OF EXPOSURE INFORMATION

Exposure information was obtained by a postal questionnaire, which was followed by a telephone interview to clarify and complete the questionnaire. The exposure information was collected after the patients were diagnosed, and the questionnaires were sent to the subjects up to four years after the definitive diagnosis (1984–7). In 63, 94, and 100%, the questionnaires were received within two, three, and four years of diagnosis, respectively.

The subjects were asked if they had ever smoked regularly. Those who had smoked were asked for how long they had smoked; during which calendar years they had smoked throughout life; and the number of cigarettes, cigars, and amount of pipe tobacco smoked per day five years previously. This information was used to distinguish exsmokers from current smokers five years previously. Exsmokers were classified according to the length of time since they last smoked up until five years before answering the questionnaire. Those who had smoked five years previously were classified according to how long they had smoked and how many cigarettes they smoked per day five years ago. Those who smoked only a pipe or cigars were excluded from the analyses (n=6).

Exposure to passive smoking during childhood (0–15 years of age) was determined by the following question: 'How many people smoked regularly in your home during your childhood (0–15 years old)?'

Retrospective information on the consumption five years ago of additional sugar in coffee, cakes, sweets, coffee, and alcohol was also collected as was information on oral contraceptive use in women.

Questionnaires were sent intermittently to an equal number of patients and control subjects. Those who did not respond were reminded to do so by letter and eventually by telephone. When the questionnaires were returned, an interviewer contacted the respondents to complete and clarify the responses. The interviewer was not aware of the study design nor of the specific hypotheses. Our intention was also to keep the respondents uninformed about the specific purposes of the study. They were told that this study was aimed at investigating the association of environmental factors and health in general. Some of the respondents, however, requested more specific information, which was then given to them (n=47). Separate analyses were performed with this group excluded.

SUBJECTS

Table I shows the distribution of patients and control subjects by age, gender, and year of diagnosis. Of 184 patients with Crohn's disease, 181 with ulcerative colitis, and 390 control subjects selected, 83, 80, and 78% respectively responded to the questionnaire. The distribution of cases of Crohn's disease by extent of disease among respondents was: ileum involvement (32%), ileocaecal involvement (43%), and colon involvement (24%). The corresponding figures for ulcerative colitis were: proctitis (15%), left sided (to right flexure) colitis (46%), and total colitis (39%).

DATA ANALYSIS

The two patient groups were analysed separately and compared with the entire series of control subjects one at a time. Confounding was controlled for by stratification. Unconditional maximum likelihood estimates of the relative risks were obtained by using multiple logistic regression analysis with dummy variables indicating the different strata. The estimated standard deviations of the regression coefficient estimates were used to assess 95% confidence limits.[14] These are shown in brackets together with relative risk estimates.

Results

CROHN'S DISEASE

Table II shows a 1·3 times increase in men and a five fold increase in women in the risk of developing Crohn's disease among current smokers compared with those who have never smoked. This relative risk increased both with daily cigarette consumption and duration of smoking in men but not in women. The risks for former smokers compared with those who had never smoked were 1·2 in men and 1·0 in women. Adjustment for consumption of additional sugar in coffee, cakes, sweets, coffee, alcohol, and oral contraceptive use (among women) did not change these results and these analyses are therefore not presented here.

ULCERATIVE COLITIS

Table III shows that both male and female exsmokers have a 60% greater risk of ulcerative colitis than those who have never smoked. Five years after stopping smoking the relative risk in men was estimated at 1·2 and in women at 1·5. The risk of ulcerative colitis among current

TABLE III *Relative risk of ulcerative colitis among smokers, according to sex, and in relation to smoking status reported five years retrospectively*

Smoking status	*No of subjects*		*Relative risk**	*95% Confidence limits*
	Cases	*Controls*		
Men				
Never smoked	40	72	1·00	Reference group
Exsmoker: years since last use†	16	22	1·60	0·7; 3·5
1–4	7	4	3·57	0·9; 13·5
5+	9	17	1·24	0·5; 3·2
Current smoker	26	51	0·96	0·5; 1·8
Women				
Never smoked	36	84	1·00	Reference group
Exsmokers: years since last use	10	15	1·60	0·6; 4·2
1–4	6	9	1·64	0·5; 5·1
5+	4	6	1·54	0·4; 6·3
Current smoker	17	58	0·72	0·4; 1·4
Total				
Never smoked	76	156	1·00	Reference group
Exsmokers: years since last use	26	37	1·47	0·8; 2·6
1–4	13	13	2·18	0·9; 5·0
5+	13	23	1·14	0·5; 2·5
Current smokers	43	109	0·80	0·5; 1·3

*Multiple logistic regression relative risk estimates. Adjustment for age and, when relevant, for sex.
†One of the controls was excluded because of inability to recall when he stopped smoking.

TABLE IV *Relative risks of Crohn's disease and ulcerative colitis according to sex and in relation to exposure to passive smoking during childhood*

Exposed to passive smoking†		*No of subjects*		*Relative risk**	*95% Confidence limits*
		Cases	*Controls*		
Crohn's disease					
No	Men	20	60	1·00	Reference group
	Women	24	62	1·00	Reference group
	Total	44	122	1·00	Reference group
Yes	Men	40	85	1·37	0·7; 2·6
	Women	65	94	1·59	0·8; 3·0
	Total	105	179	1·50	1·0; 2·3
Ulcerative colitis					
No	Men	30	60	1·00	Reference group
	Women	29	62	1·00	Reference group
	Total	59	122	1·00	Reference group
Yes	Men	51	85	1·16	0·7; 2·1
	Women	33	94	0·84	0·4; 1·6
	Total	84	179	0·98	0·6; 1·5

*Multiple logistic regression relative risk estimates. Adjustment for age, smoking, and, when relevant, sex.
†Two patients with ulcerative colitis and one control subject were excluded from these analyses because of inability to recall if they have been exposed to environmental tobacco smoke during childhood.

smokers compared with those who have never smoked was 1·0 among men and 0·7 among women.

ENVIRONMENTAL TOBACCO SMOKE

Table IV suggests that regular exposure to passive smoking in the household during childhood (0–15 years of age) may be associated with an increased risk for Crohn's disease. This association was seen in both men and women. Confounding by their own cigarette smoking was controlled for by separate evaluation of the relative risk among those who had never smoked. The relative risks were estimated at 1·16 (0·5; 2·8) among men and 2·50 (0·9; 6·9) among women. Passive smoking during childhood did not clearly affect the risk of ulcerative colitis.

Discussion

RECALL BIAS

Like previous case-control studies on smoking and inflammatory bowel disease, the present study included patients diagnosed several years beforehand. This means that information on smoking was collected retrospectively, which is a possible source of bias. If the tendency to over or underreport previous smoking is the same in patients and controls, the relative risk will be biased towards unity. However, Crohn's disease and ulcerative colitis affect the bowel and maybe also the smoking habits. A change in cigarette consumption influences retrospective information in the direction towards the current consumption.[15]

If a larger proportion of patients than control subjects stopped smoking some time before the questionnaire was answered, a larger proportion of the patients will report that they did not smoke five years ago. This could lead to an underestimation of the increase in risk of Crohn's disease in current smokers, and of ulcerative colitis in exsmokers, but the more likely outcome would be an overestimation of the decrease in risk of ulcerative colitis in current smokers compared with those who have never smoked. If patients have reduced their cigarette consumption in relation to control subjects, they would tend to underestimate their previous smoking in relation to the controls. To some extent, this might explain the inverse dose-response association (amount and duration) of current smoking in Crohn's disease among women.

Patients and controls were asked about their smoking habits using the same questionnaire and under similar circumstances. This probably makes the comparison between patients and control subjects a more accurate one than in previous studies where patients had the onset of disease or diagnosis as a reference point in time and the control subjects were simply asked about present smoking[3] or smoking during a certain period of time.[14,6] The fact that some of the respondents were informed about the specific purpose of the study could have introduced a bias. Separate analyses were performed with this group excluded but the results were similar to those presented.

SELECTION BIAS

The study was restricted to those with listed phone numbers in order to improve the response rates. In Sweden, about 90% of the population have a listed phone number. The prevalence of current smokers in our control group was equal to corresponding figures in a population survey (36%).[16] Furthermore, the restriction to people with listed phone numbers applied to the entire study population and thus to patients as well as control subjects. It is unlikely that any bias was introduced by this restriction since the aetiology may be assumed to be similar for those with listed and unlisted phone numbers.

Nearly all patients with Crohn's disease in Stockholm are admitted to hospital within a few years of onset. It is likely, however, that a few patients with mild ulcerative colitis are never admitted to inpatient care. We believe that this number is small because our diagnostic criteria were more strict than in some previous popula-

tion based studies of ulcerative colitis.[17 18] Some patients were missed because their medical records were not located until after four years. This was due to administrative problems and is unlikely to be related to smoking habits of the patients.

Unlike some of the previous studies which have used hospital control subjects, we used controls selected from the general population. This ought to minimise any bias due to selection of controls.

Most non-respondents simply refused to participate and this proportion was nearly equal in patients and control subjects (Table I). Although smokers might be less willing to participate than non-smokers, it is only if patients and control subjects differ in this respect that the relative risk will be affected.

CONFOUNDING

Previously suggested risk factors for inflammatory bowel disease were accounted for but this left the results materially unchanged.

FINDINGS

One of the findings in this study was a fivefold increase in the risk of Crohn's disease in women who were currently smoking. Except for Harries's study,[7] in which no association with Crohn's disease was found among either women or men, the reported relative risk in previous studies has ranged between two and eight.[1-6] In women, a negative dose-response association with the number of cigarettes smoked per day and duration of smoking was observed. The small number of women who smoked 20 cigarettes or more per day render the estimates imprecise in this group but this does not explain the inverse dose-response association with duration of smoking. Similar results with regard to the number of cigarettes smoked have previously been seen,[3 5 6] but the explanation is not clear.

There has recently been renewed interest in gut permeability as an important factor in the aetiology of Crohn's disease.[19] The biological explanation for an increase in relative risk among smokers is unclear but gut permeability among smokers is obviously one of the factors that should be investigated further.

This study found only a limited increase in the risk of Crohn's disease in current male smokers compared with men who had never smoked. There is some evidence in previous studies of a weaker association between current smoking and Crohn's disease among men than women,[1 4 5] although these studies still indicate some increased risk among men. In contrast, other studies showed that the relative risk among men did not differ from that among women.[3 6]

An increased risk of ulcerative colitis among exsmokers than in those who had never smoked was observed. The increase was greater for recent exsmokers than for those who had stopped smoking some time ago. The results, although based on small numbers, indicate that the increase in risk among exsmokers decreases towards the risk among those who have never smoked over time. A previous report comparing exsmokers with those who have never smoked, found that exsmokers who quit smoking one to six years previously were at higher risk than those who had given up for longer.[20] The production of mucus in the large bowel is essential for mucosal defences. Non-smoking ulcerative colitis patients have lower mucus production than their counterparts who smoke.[21] Stopping smoking may reduce mucus production, leading to a period of increased risk of inflammatory processes before the mucus production is restored.

Women who currently smoke may have a slight reduction in the risk of ulcerative colitis compared with women who have never smoked but this does not apply to men. Previous studies have found a more pronounced decline in risk.[2-10] We suggest that some of the previous findings might be explained by systematic errors caused by the use of hospital controls and retrospective questioning.[11]

The finding regarding exposure to passive smoking during childhood suggests a slightly increased risk of Crohn's disease but not of ulcerative colitis. If patients overreport exposure of others smoking during childhood compared with control subjects, this would tend to exaggerate the increased risk, but there is no reason to believe that this would be more common in Crohn's disease than in ulcerative colitis patients. To ensure that confounding from cigarette smoking was sufficiently controlled, a separate relative risk estimate among those who had never smoked was also assessed, but the association persisted when the material was so restricted. Franceschi *et al*,[3] did not find any particular association with the smoking of relatives or spouses, whereas Harries *et al*[7] found that patients with ulcerative colitis as well as Crohn's disease came from non-smoking households. However, their control subjects were selected from orthopaedic department patients in whom smokers as well as passive smokers might be over represented.

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