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,4,9 and a decreased risk of ulcerative colitis.5,9 A greater risk of ulcerative colitis among exsmokers has also been reported.7-9 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.4,11

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

The 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 Lenard-Jones.17 The diagnostic criteria for ulcerative colitis included a history of bloody diarrhoea, typical sigmoidoscopy findings, and characteristic microscopy changes on biopsy specimen.18 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 II  Relative risk of Crohn’s disease among smokers, according to sex, and in relation to smoking status reported five years retrospectively

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>No of subjects</th>
<th>Relative risk*</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>27</td>
<td>72</td>
<td>1:00</td>
</tr>
<tr>
<td>Exsmoker</td>
<td>9</td>
<td>22</td>
<td>0:5; 3:1</td>
</tr>
<tr>
<td>Current smoker: No of cig/day†</td>
<td>1-19</td>
<td>24</td>
<td>1:33</td>
</tr>
<tr>
<td></td>
<td>1-19</td>
<td>17</td>
<td>1:20</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>5</td>
<td>2:22</td>
</tr>
<tr>
<td>Duration of smoking (yrs)</td>
<td>1-10</td>
<td>7</td>
<td>0:75</td>
</tr>
<tr>
<td></td>
<td>1-10</td>
<td>17</td>
<td>2:04</td>
</tr>
<tr>
<td></td>
<td>11+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>21</td>
<td>84</td>
<td>1:00</td>
</tr>
<tr>
<td>Exsmokers</td>
<td>3</td>
<td>15</td>
<td>0:3; 4:0</td>
</tr>
<tr>
<td>Current smoker: No of cig/day†</td>
<td>1-19</td>
<td>65</td>
<td>4:99</td>
</tr>
<tr>
<td></td>
<td>1-19</td>
<td>58</td>
<td>5:44</td>
</tr>
<tr>
<td></td>
<td>20+</td>
<td>5</td>
<td>2:91</td>
</tr>
<tr>
<td>Duration (yrs)</td>
<td>1-10</td>
<td>29</td>
<td>7:78</td>
</tr>
<tr>
<td></td>
<td>1-10</td>
<td>36</td>
<td>3:72</td>
</tr>
</tbody>
</table>

*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.

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, alcohol, and oral contraceptive use (among women) did not change these results and these analyses are therefore not presented here.

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...
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 overestimation 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 smoking1 or smoking during a certain period of time.16 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.

SELECTIVE 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%).18 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-
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, 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. 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, 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. 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, 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.

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. 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. 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. We suggest that some of the previous findings might be explained by systematic errors caused by the use of hospital controls and retrospective questioning.

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 childhood 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 found no particular association with the smoking of relatives or spouses, whereas Harries et al 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 overrepresented.

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