Rectocolite hémorragique

Appendectomy, smoking habits and the risk of developing ulcerative colitis: a case control study in private practice setting

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Summary

Objectives — The strongest environmental factors identified for ulcerative colitis (UC) are cigarette smoking and appendectomy. However, most studies have been performed using case-controls from hospital-based populations. The purpose of this study was to compare the history of previous appendectomy and smoking habits in a group of patients with UC and a control group, followed by gastroenterologists in private practice.

Methods — We performed a case control study in which 100 physicians recruited UC-patients and age and sex matched controls. Data were collected during a single visit. Based on a standardized questionnaire, UC patients and controls were divided into never, former or current smokers, and into subjects with or without a previous history of appendectomy.

Results — One hundred and ninety eight age- and sex-matched pairs of UC patients and controls were included. The prevalence of appendectomy in the UC-patients and control group was 12% and 46%, respectively. The pairwise-matched OR of ulcerative colitis for previous appendectomy was 0.10 (95% CI, 0.05-0.21) (P<0.0001). The OR for former and never smokers versus current smokers was 2.40 (95% CI, 1.31-4.38) (P=0.004). In UC-patients, the OR of family history of UC compared with controls was 2.80 (95% CI, 1.01-7.77) (P=0.048).

Conclusions — This case-control study confirmed a strong negative correlation between both appendectomy and tobacco smoking, and ulcerative colitis in patients followed-up by gastroenterological practitioners.

Introduction

The cause of ulcerative colitis is not known. The strongest environmental factors identified are cigarette smoking and appendectomy. Reports of a low rate of appendectomy among patients with ulcerative colitis have gained widespread attention [1]. It has been proposed that the excision of the appendix may have an immune-modulating effect that protects against ulcerative colitis. In 15 out of 18 studies, an inverse relation between appendectomy and ulcerative colitis was reported [2]. Case-control studies have shown that, when performed before UC development, appendectomy is associated with a: lower incidence of UC, with an odds ratio of 0.23; higher age of UC development; less active disease; a lower need for corticosteroids or azathioprine; lower relapse rate and colectomy risk [3-5].
Cohort studies however, have yielded conflicting results regarding the relationship between appendectomy and the subsequent risk of ulcerative colitis [6, 7]. A cohort of over 424,000 Swedish appendectomy patients and of age-, gender-, and location-matched controls [6] were followed for over 5 million person-years for a subsequent hospital diagnosis of ulcerative colitis. Those having undergone appendectomy had an incidence of ulcerative colitis approximately three quarters that of controls [6]. Important factors associated with a lower incidence of ulcerative colitis included appendectomy before the age of 20 years and appendectomy for appendicitis or mesenteric lymphadenitis (vs abdominal pain or other reasons) [6]. A Danish cohort of over 154,000 appendectomy patients was followed for over 1 million person-years for a subsequent hospital diagnosis of IBD [7]. The appendectomy cohort was only 13% less likely than expected to be diagnosed with ulcerative colitis, which was not statistically significant [7].

Reports of a low or no consumption of cigarette smoking among patients with ulcerative colitis also abound [1]. The odds ratio for developing ulcerative colitis among current smokers is consistently less than 1. A meta-analysis noted that current smokers are 40% as likely as those who have never smoked to develop ulcerative colitis [8]. French smokers with ulcerative colitis who quit smoking had more active disease, more hospitalizations, and greater need for corticosteroids or azathioprine compared with those who continued to smoke [9].

Why the case-control studies and the 2 large cohort studies yielded conflicting results remains unclear. All of them have been performed in the setting of tertiary care centers, and data from patients seen by first-line, community gastroenterologists are lacking. Therefore, it appeared worthwhile to specifically study these patients, usually suffering from less severe disease, in order to see whether the observations performed in referral centers would be confirmed. The purpose of the study was to compare the history of previous appendectomy and smoking habits in a group of patients with UC and a control group followed by gastroenterological practitioners.

**Material and methods**

**Patient population**

Five hundred gastroenterologists from metropolitan France were randomly selected with CEGEDIM (a data provider of medical information), using the quota method, based on gender and administrative area of residence. The recruitment procedure was terminated when 100 physicians had agreed to participate in the study.

Pairs of case and control patients were recruited as follows. Each physician was asked to include the first 3 consecutive patients seen in consultation for UC, whatever the reason for the consultation. This population constituted the case-patients (UC-patients). For each UC-patient, the physician was asked to include the next available age- (±5 yrs) and gender-matched patient seen in consultation, provided that there was no personal history of IBD.

Patients were diagnosed as having UC according to the Lennard-Jones [10] definition. The protocol was declared to the “Comité Consultatif sur le traitement de l’information en Matière de Recherche dans le Domaine de la Santé” and the “Commission Nationale de l’Informatique et des Libertés” (CNIL), French agencies that serve as institutional review boards for such studies.

Data were collected during a single visit. For UC-patients, the questionnaire included sections on: a) demographic details; b) previous history of appendectomy; c) topography of lesions as evidenced by the macroscopical extent of lesions in the previous colonoscopy; d) current and previous medical and surgical treatments for UC; e) previous history of appendectomy; f) current and previous smoking habits; and g) family history of inflammatory bowel disease. For controls, the questionnaire included sections on: a) demographic details; b) previous history of appendectomy; c) current and previous smoking habits; d) family history of IBD.

Based on this questionnaire, UC patients and controls were divided into never-or-former, and current smokers, and into subjects with or without a previous history of appendectomy.

**Statistical analysis**

Statistical analyses were performed using SAS package 8.2 (SAS Institute, Cary, NC, USA). Polytomous variables are described as effective percentages. Descriptive statistics are provided as mean, standard deviation, range and median. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in a pairwise-matched analysis. Smoking was controlled by logistic regression analysis. In both groups, a trend test was used to compare intervals between appendectomy and UC diagnosis. All tests of significance were two-sided. A P value of less than 0.05 was considered to indicate statistical significance.

**Results**

A total number of 396 patients was recruited and available for final analysis between June and December 2003, as 198 pairs of UC patients and controls, matched for sex- and age (±5 years). The mean age (SD) was 43.7 (14.3) and 43.9 (14.2) yrs in UC-patients and controls, respectively (NS). The disease profile of UC-patients is presented in the table I, and the results are summarized in the table II.

**Appendectomy**

Twenty four UC-patients (12%) and 92 controls (46%) had undergone appendectomy (P<0.0001). The appendectomy had been performed before the age of 20 in 15 UC-patients (63%) and 73 controls (79%) (P=0.04). In UC, the pairwise-matched OR of previous appendectomy in patients compared with controls was 0.10 (95% CI, 0.05-0.21) (P<0.0001). Age of UC development was not associated with previous appendectomy (P=0.95).

**Smoking habits**

The proportion of current smokers was higher in controls (22%) than in UC-patients (11%) (P=0.0002). A total of 176 UC-patients (89%) and 155 controls (78%) were never or former smokers. The resultant pairwise-matched OR was 2.40 (95% CI 1.31-4.38) for former and never smokers versus current smokers (P=0.004). Tobacco consumption was similar in the two groups (P=0.16) as was the past consumption in subjects who stopped their smoking habit (P=0.23).

**Family history of IBD**

Eleven percent of UC-patients and 3.5% of controls had at least one familial case of inflammatory bowel disease (P=0.006). However, this difference was not significant when only family history of UC (P=0.43) or Crohn’s disease (P=0.22) was considered. In multivariate analysis, the OR of family history of UC in UC-patients compared with controls was 2.80 (95% CI, 1.01-7.77) (P=0.04). The OR of family history of Crohn’s disease was 1.83 (95% CI, 0.70-5.32).

**Discussion**

In this case-control study based on outpatients seen by French private practice gastroenterologists, we have observed a strong negative correlation between appendectomy and ulcerative colitis, with an odds of developing UC of about 0.1 in...
patients who underwent appendectomy. Our observation thus parallels and confirms similar reports emanating from international and referral centers [2-7, 11, 12].

In the present study, we found a particularly strong negative association between appendectomy and UC, and this resulted from a marked difference of appendectomy rates between the case and controls groups. This difference may be attributable to a surprisingly high prevalence in the control group. Indeed, whereas the prevalence of appendectomy in our UC group (12%) is slightly higher than the 0.5-8% prevalence reported in other similar studies, a 46% rate in the control group is strikingly above the 5.7-24% reported in earlier reports [2]. The causes underlying this observation are uncertain. The fact that our control patients were recruited not from healthy subjects but from non-UC outpatients seen by gastroenterologists, may have biased the group towards a health-seeking behavior, thus resulting in an unexpectedly high prevalence of previous appendectomy. Interestingly, similarly high prevalent appendectomy rates have already been observed in both the UC and control groups (8% and 30.6%, respectively), in a previous French study from a referral center [12], which suggests that appendectomy rates in France may be higher than in other countries. Further studies are needed to confirm this hypothesis.

Our patients probably suffered from a less severe disease profile than inpatients reported in other series. This can be inferred from their lower rates of pancolitis (21% in our patients compared to 33% to 37% previously reported [13, 14]) and intestinal surgery (1% in our patients versus 14% to 44% reported [13-16]).

The inverse association between appendectomy and the development of ulcerative colitis has been observed in a number of case-control studies. A critical review of 17 studies involving almost 3600 cases and over 4600 controls showed that appendectomy was associated with a 69% reduction in the subsequent risk of ulcerative colitis [2]. When multivariate analysis was used to control other important factors such as cigarette smoking, the apparent protective effect of appendectomy remained significant.

Since the first widely published report of an inverse association between ulcerative colitis and cigarette smoking [17] many

### Table 1

<table>
<thead>
<tr>
<th>Duration of disease (y) [mean (SD)]</th>
<th>8.0 (9.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic extent of disease (last colonoscopy)</td>
<td></td>
</tr>
<tr>
<td>Left-sided colitis or below</td>
<td>79%</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>21%</td>
</tr>
<tr>
<td>Nb of relapses during the first 5 y after diagnosis</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4%</td>
</tr>
<tr>
<td>1</td>
<td>21%</td>
</tr>
<tr>
<td>From 2 to 3</td>
<td>48%</td>
</tr>
<tr>
<td>≥4</td>
<td>27%</td>
</tr>
<tr>
<td>Patients having required oral glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>47%</td>
</tr>
<tr>
<td>1</td>
<td>23%</td>
</tr>
<tr>
<td>2 to 3</td>
<td>22%</td>
</tr>
<tr>
<td>≥4</td>
<td>8%</td>
</tr>
<tr>
<td>Patients having required immunosuppressors</td>
<td>18%</td>
</tr>
<tr>
<td>Patients having required surgery</td>
<td>1%</td>
</tr>
<tr>
<td>Extra-intestinal manifestations</td>
<td>11%</td>
</tr>
<tr>
<td>Current treatment on inclusion</td>
<td></td>
</tr>
<tr>
<td>5-asa</td>
<td></td>
</tr>
<tr>
<td>— Oral</td>
<td>59%</td>
</tr>
<tr>
<td>— Topical</td>
<td>34%</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>— Oral</td>
<td>12%</td>
</tr>
<tr>
<td>— Topical</td>
<td>13%</td>
</tr>
<tr>
<td>Immunosuppressors</td>
<td>11%</td>
</tr>
</tbody>
</table>
studies have confirmed this finding [8]. In many studies, former cigarette smokers were noted to have an increased risk of ulcerative colitis relative to those who never smoked [18-25]. When these results are pooled, it appears that ex-smokers are 70% more likely than those who never smoked to develop ulcerative colitis [8]. Cigarette smoking may also influence the course of ulcerative colitis. In one study, active smokers were half as likely to be hospitalized for ulcerative colitis as nonsmokers, whereas ex-smokers were 50% more likely to be hospitalized and twice as likely as current smokers or those who never smoked to undergo colectomy [26]. In another study, approximately 45% of ulcerative colitis patients who resumed smoking reported symptom improvement, and those who improved smoked an average twice as many cigarettes daily as those who did not [27]. French smokers with ulcerative colitis who quit smoking had more active disease, more hospitalizations, and greater need for corticosteroids or azathioprine compared with those who continued to smoke [9].

In our patients, we confirmed that current smoking decreased the risk for UC development by a factor of 2.4. Interestingly, a similar inverse association with cigarette smoking and illness has been noted for related conditions such as primary sclerosing cholangitis, with or without associated IBD [28-30] and pouchitis [31]. The protective effect against primary sclerosing cholangitis suggests a systemic protective effect rather than a local effect in the colon.

In population-based studies, approximately 5% to 10% of all affected individuals with IBD report a positive family history, indicating that the greatest risk factor for developing IBD is having other family members with the disease [32, 33]. The relative risk for IBD among first-degree relatives can be estimated by using either a cohort or a case-control design. In a cohort study, Orholm et al. showed a population relative risk of 10 for relatives of patients with UC [34]. Similar relative risk estimates (14- to 15-fold increased risk) for first-degree relatives in two case-control studies have been reported [35, 36]. In ulcerative colitis, phenotypic differences between family and sporadic cases appear to be limited, but little data are available for analysis [37]. In our study, we showed that family history of UC, but not Crohn’s disease, was associated with UC.

In summary, this study confirms a strong negative correlation between both appendectomy and tobacco smoking and the development of UC, in a general practice-based population suffering from a mild disease profile.

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REFERENCES


