Cirrhosis as an independent risk factor for colonic adenomas

S Naveau, J C Chaput, P Bedossa, T Poynard, C Pauphilet, O Ink, C Houdayer, A Aubert

Abstract
This study aimed to determine the relation between cirrhosis and colorectal adenomatous polyps after adjustment for alcoholism and other confounding variables. Four groups of patients aged 40 years or above were studied. Group I included 100 consecutive outpatients with irritable bowel syndrome, group II 100 consecutive alcoholic inpatients without cirrhosis, group III 100 consecutive inpatients with alcoholic cirrhosis, and group IV included 36 consecutive inpatients with non-alcoholic cirrhosis. All patients underwent colonoscopy. The prevalence of adenomatous polyps was 13% in group I, 26% in group II, 58% in group III, and 22% in group IV (p<0.001). The prevalence of adenomatous polyps was greater in patients with cirrhosis than in those patients without (48.5% vs 19.5%). This difference remained significant after successive adjustment for alcoholism, sex, age, smoking, and serum cholesterol. The prevalence of adenomatous polyps was greater in alcoholic patients than in non-alcoholic patients (42% vs 15.4%) (p<0.001). This difference remained significant after successive adjustment for cirrhosis, sex, age, smoking, and serum cholesterol. These results suggest that cirrhosis is an independent risk factor for colorectal adenomatous polyps and confirm that alcoholism increases this risk.

More than one agent is involved in the causation of colorectal cancer. According to Hill et al, environmental agent A might cause adenomas to develop only in adenoma-prone people; agent B, likely to be the bacterial metabolites of the bile acids, might cause the adenomas to grow; and agent C might induce malignancy in a high proportion of large adenomas and in a small proportion of small adenomas. Studies of risk factors for colorectal adenomas may elucidate risk factors in the pathogenesis of large bowel cancer.

On one hand, though the published works give conflicting results about the relation between alcohol and colorectal cancer, suggestive evidence for a possible association has been obtained in some correlation studies. Evidence of an association has also been obtained in some case-control studies. The issue has also been examined in cohort studies, and recently a Japanese cohort study showed a close association between cancer of the sigmoid colon and alcohol consumption.

On the other hand, among 32 cases of chronic active hepatitis, four malignant tumors (12.5%), including one malignant rectal polyp, have been diagnosed. In 589 patients with alcoholic cirrhosis we have found a 12.5 fold higher incidence of colorectal cancer than the incidence observed by Faivre et al in the Côte d’Or. These results suggest: (1) a relation between alcohol consumption and colorectal cancer; (2) a possible association between chronic liver diseases and the occurrence of epithelial cancer, including colorectal cancer; and (3) a relation between alcoholic cirrhosis and colorectal cancer.

In accordance with the adenoma-carcinoma sequence theory, we conducted a study to determine the relation between cirrhosis and adenomatous polyps after adjustment for alcoholism and several other confounding variables.

Patients and methods
We studied four groups of patients aged 40 years or above. Group I included 100 consecutive outpatients considered to have irritable bowel syndrome using the criteria of Manning et al. Group II and III comprised 200 consecutive patients admitted to the hepatogastroenterology service of the Antoine Béclère hospital in Clamart, France, for alcoholism or alcoholic liver disease. Alcoholic patients had drunk at least 50 g of alcohol daily for the five years before admission or had alcoholic cirrhosis with no period of sobriety exceeding one year. Group II included 100 alcoholic patients without cirrhosis. Because of liver function test disturbances, all patients had a percutaneous liver biopsy. Liver biopsy specimens included 15 showing normal liver histology, 40 pure steatosis, 35 fibrosis with steatosis, and 10 acute alcoholic hepatitis without cirrhosis. Group III comprised 100 patients with alcoholic cirrhosis, proved histologically in 95 patients and clinically obvious in five patients in whom abnormal coagulation studies prevented percutaneous liver biopsy. These five patients had a positive computer assisted diagnosis of cirrhosis as previously presented. Group IV comprised 36 consecutive inpatients with non-alcoholic cirrhosis, 11 patients with cryptogenic cirrhosis, 10 patients with B hepatic cirrhosis, seven patients with non A-non B hepatic cirrhosis, five patients with autoimmune cirrhosis, two patients with primary biliary cirrhosis, and one patient with haemochromatosis.

The criteria of exclusion were a personal history of cancer at whatever site (n=13), personal history of adenomatous colorectal polyps (n=4), family history of colonic adenomatous polyps (n=2) or colonic cancer (n=2), rectal haemorrhage (n=2), portal systemic encephalopathy (n=2), colonoscopy refused by the patients (n=4), incomplete colonoscopy because of poor preparation (n=7), and previous colorectal surgery (n=2).

All patients underwent colonoscopy. Patients...
were advised of the aim of the study and gave informed consent before inclusion. In patients with cirrhosis, colonoscopy was performed after the resolution of ascites, and every patient had received 2 gm neomycin a day for at least three days. Colonoscopy was performed in our endoscopy suite with an Olympus CF1T10 fiberoptic colonoscope. We removed or biopsied polyps and all well defined mucosal growths whatever their size. Epithelial tumours were classified histologically as hyperplastic or adenomatous. Adenomas were classified as tubular, tubulovillous, or villous according to the criteria of the World Health Organisation. Epithelial dysplasia of adenomas was graded as mild, moderate, or severe. Histological assessment was performed by a pathologist who was unaware of the diagnosis.

Information on alcohol consumption was recorded using a specific questionnaire. The patient’s family was also interviewed, if possible. Each questionnaire was filled in by a junior (medical student) and checked by a senior (one of the authors) in the presence of the patient. Patients were asked about their drinking habits over the past five years before admission to hospital for alcoholic disorders and total duration of alcohol abuse. The average daily intake was calculated for each beverage (beer, wine, aperitifs) and expressed in grams of pure ethanol. The total daily consumption of ethanol was obtained by adding up the amounts consumed for each type of beverage. The daily consumption of each beverage was expressed as a percentage of the total daily alcohol intake.

This study was approved by the local institutional ethical committee.

**STUDY DESIGN**

The study design is that of a cross sectional prevalence study in which the prevalence for the disease (adenomatous polyps) was assessed immediately after the assessment of the exposure factors (presence of cirrhosis or alcoholism).

**STATISTICAL ANALYSIS**

We compared the prevalence of adenomatous polyps in the four groups of patients (group I: irritable bowel syndrome, group II: alcoholics without cirrhosis, group III: alcoholic cirrhosis, and group IV: non-alcoholic cirrhosis).

Search for confounding exposure factors in all 336 patients and calculation of relative risks (estimated as odds ratios) adjusted for various confounding factors in cirrhotic patients and in alcoholic patients. Because the inter-relation between one exposure factor may act to confound another, we searched for these various confounding factors – that is, factors which in an univariate analysis were both significantly different between patients with and without adenomatous polyps and between the patients of the four study groups. Previous studies have reported that age, sex, smoking, and serum cholesterol may be predisposing factors in the development of adenomas of the large bowel. Thus, in an univariate analysis we compared patients with and those without adenomatous polyps and also the patients in the four study groups with regard to the four variables. We also compared patients with and without adenomatous polyps with regard to the prevalence of alcoholicism and cirrhosis. Therefore, we compared the prevalence of adenomatous polyps in patients with cirrhosis and in patients without cirrhosis after several successive adjustments for the presence or the absence of each exposure factor which had a confounding effect in the univariate analysis. In the same way, we compared the prevalence of adenomatous polyps in alcoholic patients and in non-alcoholic patients after successive adjustment for the presence or absence of each confounding exposure factor.

**Results**

In group I (patients with irritable bowel syndrome), 15 patients had 23 polyps; 13 of these patients had 14 adenomatous polyps and two patients had only hyperplastic polyps. Three adenomatous polyps were >10 mm. In group II (alcoholic patients without cirrhosis), 31 patients had 45 polyps; 26 of these patients had 34 adenomatous polyps and five patients had only hyperplastic polyps. Four adenomatous polyps were >10 mm. In group III (patients with alcoholic cirrhosis), 64 patients had 123 polyps; 58 of these patients had 106 adenomatous polyps and six patients had only hyperplastic polyps. Nine adenomatous polyps were >10 mm. In group IV (patients with non-alcoholic cirrhosis), 10 patients had 13 polyps; eight of these patients had 10 adenomatous polyps and two patients had only hyperplastic polyps. Two adenomatous polyps were >10 mm. Characteristics of colonic polyps in the four groups are shown in Table I.

The prevalence of adenomatous polyps was 13% in patients with irritable bowel syndrome (group I), 26% in alcoholic patients without cirrhosis (group II), 58% in patients with...
alcoholic cirrhosis (group III), and 22% in patients with non-alcoholic cirrhosis (group IV) (p<0.001).

SEARCH FOR CONFOUNDING EXPOSURE FACTORS IN ALL 336 PATIENTS AND CALCULATION OF RELATIVE RISKS

Search for confounding exposure factors

Characteristics of the patients in the four groups are shown in Table II. The 105 patients with adenomatous polyps were older (p<0.005), more often male (p<0.005), alcoholic (p<0.001), and cirrhotic (p<0.001), and had a lower serum cholesterol concentration (p<0.001) than the 231 patients without adenomatous polyps. The prevalence of smokers was greater (the difference approach statistical significance p=0.06) in patients with adenomatous polyps than in patients without adenomatous polyps (Table III).

CALCULATION OF RELATIVE RISKS OF ADENOMATOUS POLYPS (ESTIMATED AS ODDS RATIOS) ADJUSTED FOR EACH CONFOUNDING FACTOR IN PATIENTS WITH CIRRHOSIS V PATIENTS WITHOUT CIRRHOSIS.

The prevalence of adenomatous polyps was greater in patients with cirrhosis than in patients without cirrhosis (48.5% v 19.5% (p<0.001). This difference remained significant after successive adjustment for each confounding factor – alcoholism, sex, age, smoking, and serum cholesterol. The relative risks of adenomatous polyps (estimated as odds ratios), adjusted for each confounding factor in cirrhotic patients, are shown in Table IV.

Calculation of relative risks of adenomatous polyps (estimated as odds ratio) adjusted for each confounding factor in alcoholic patients v non-alcoholic patients.

The prevalence of adenomatous polyps was greater in alcoholic patients than in non-alcoholic patients (42% v 15.4% (p<0.001). This difference remained significant after successive adjustment for each confounding factor – cirrhosis, sex, age, smoking, and serum cholesterol. The relative risks of adenomatous polyps (estimated as odds ratios), adjusted for each confounding factor in alcoholic patients, are shown in Table V.


**Table V Relative risks of adenomatous polyps (estimated as odds ratios) adjusted for each confounding factor in alcoholic patients vs non-alcoholic patients**

<table>
<thead>
<tr>
<th>Confounding factors</th>
<th>Odds ratio</th>
<th>95% confidence intervals</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis (yes vs no)</td>
<td>3.2</td>
<td>1.8-5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>3.6</td>
<td>2.4-6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (≤55 years vs &gt;55 years)</td>
<td>5.2</td>
<td>2.9-9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>4.1</td>
<td>2.3-7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol (≤0.76 mmol/l) (median vs &gt;0.76 mmol/l)</td>
<td>3.1</td>
<td>1.7-5.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table VII Relative risks of adenomatous polyps (estimated as odds ratios) adjusted for each confounding factor in alcoholic patients with cirrhosis vs alcoholic patients without cirrhosis**

<table>
<thead>
<tr>
<th>Confounding factors</th>
<th>Odds ratio</th>
<th>95% confidence intervals</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs female)</td>
<td>4.2</td>
<td>2.3-8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (≤55 years vs &gt;55 years)</td>
<td>3.6</td>
<td>2.6-7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>4.1</td>
<td>2.7-7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol (≤0.76 mmol/l) (median vs &gt;0.76 mmol/l)</td>
<td>3.1</td>
<td>1.6-6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The total duration of alcohol abuse (≤25 years vs &gt;25 years)</td>
<td>3.8</td>
<td>2-7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Discussion**

The question we set out to ask was: is there an association between cirrhosis and adenomatous polyps after adjustment for alcoholism and several confounding variables? The study design we chose was a cross sectional prevalence study in which the prevalence of the disease (adenomatous polyps) was assessed immediately after the assessment of the exposure factors (presence of cirrhosis and alcoholism).

We found a very important prevalence of adenomatous polyps in patients with alcoholic cirrhosis (58%). The patients with irritable bowel syndrome had the lowest prevalence (13%). This prevalence was in agreement with the results of a French cooperative study in which the prevalence of tubular or villous adenomas in patients without rectal haemorrhage or without a history of intestinal tumour was 9-7%. It is interesting to note that the localisation that characterises most polyps was the same as previously described in subjects 50-60 years old. In the four groups the adenomatous polyps occurred mostly within the rectosigmoid area.

It is important to examine the possibility that bias may explain these results. Identifying suitable control groups in epidemiological studies of adenomatous polyps is very difficult in the absence of systematic population screening. The choice of patients with irritable bowel syndrome as a control group is open to debate, but it is difficult to find a better.

To reduce the heterogeneity of the study population we carefully excluded any subject with high risk for colorectal polyps (personal or familial history of colon cancer or polycystic adenomatous polyps, or rectal haemorrhage). It is unlikely that selection factors could bias these results in this study because the adenomatous polyps were coincidental lesions that were not directly or indirectly related to the cause of admission to hospital and colonoscopy. Bias by the endoscopists and pathologists is also unlikely. Colonoscopies were performed by endoscopists who had no need to inquire about smoking or alcohol consumption. The pathologist was unaware of the diagnosis. The accuracy of data on alcohol consumption is notoriously suspect because of the unreliability of people with chronic alcoholism but the declared consumption remains the only information that can be used. Usually this information was substantiated by collateral information because the physician asked the family about the alcohol consumption of the patient. Moreover, a standard questionnaire permits comparisons of various groups of individuals interviewed in the same manner and underestimation or overestimation should be comparable.

We found that the prevalence of adenomatous polyps...
Cirrhosis as an independent risk factor for colonic adenomas

polyps was greater in patients with cirrhosis than in those without this disorder. This difference remained significant after adjustment for each confounding factor.

The mechanism by which cirrhosis might be associated with colonic adenomatous polyps is speculative. Possible mechanisms could be the effects of cirrhosis on bile acid metabolism or the effects of a genetic predisposition or an immunological disturbance. It is unlikely that cirrhosis could predispose to the development of adenomas of the large bowel by virtue of its effect on bile salt pool dynamics. Faecal concentrations of deoxycholate, a major metabolite of cholic acid, and faecal 7 dehydroxylase activity, which is responsible for deoxycholate formation, were higher in patients with cirrhotic adenomatous polyps than in controls.21 Conversely, in nine cirrhotic patients faecal bile acid analysis indicated that they had a significantly lower percentage of deoxycholic acid than 12 patients without liver disease.24 In another study a noticeable decrease in 7 dehydroxylase activity of faecal bacteria of some patients with alcoholic cirrhosis was the explanation for the lack of deoxycholate in faeces.25 Inheritance may play a role in the occurrence of adenomatous polyps.26 Because of the well established observation that not all abusers of alcohol develop cirrhosis, the presence of genetic susceptibility in the development of cirrhosis was suggested.27 28 A common genetic predisposition might have a role in the pathogenesis of colonic adenomatous polyps and alcoholic cirrhosis.29 30 The men with polyps drank more alcohol than men without polyps but the difference was not statistically significant. There was, however, an increase in the age adjusted mean number of polyps per subject with increasing levels of alcohol intake.31 Recently, Kikendall et al.,32 in a retrospective case-control study in non-alcoholic adults, found a significant association between smoking and beer consumption and adenomas. In the logistic regression, age (p<0.05) and smoking (p<0.01) were significantly associated with adenomas but beer drinking was border line (p=0.09). Furthermore, in this analysis, cumulative beer consumption was not adjusted for total cumulative alcohol consumption. Our study including alcoholic patients found a stronger association between alcohol consumption and adenomas. Ethanol may increase the risk of adenomatous polyp by direct toxicity. Recent data in rats support the theory that acetaldehyde, possibly produced by faecal bacteria from ethanol, may cause mucosal injury followed by secondary hyper-regeneration of rectal mucosa.33 Ethanol and cirrhosis may increase the risk of adenomatous polyps byinterfering with dietary habits, and the relations between alcoholism and adenomatous polyps on one hand and between cirrhosis and adenomatous polyps on the other could be the result of confounding by unspecified dietary factors. Hoff et al34 have shown increased consumption of fat and reduced consumption of fibre and cruciferous vegetables and vitamin C in the presence of polyps. Furthermore, Macquart-Moulin et al35 found that patients with colorectal polyps had a lower consumption of potassium, magnesium, and vitamin B6 than controls. The consumption of potassium,36 vitamin B6,37 magnesium,38 vitamin C,39 40 and dietary fibre41 also decreased significantly as the alcohol score increased. Though, as the alcohol intake increased, there was a decrease in percentage of energy derived from fat,42 and this study has been able to show that the mean daily fat intake apparently strongly modifies the relative risk of liver cirrhosis.43 Conversely, many impairments in absorption, digestion, or metabolism could play a part in the malnutrition of cirrhotic patients and indirectly increase the risk of colonic adenomas.

Conclusion
The most important result of this study is the greater prevalence of adenomatous polyps in patients with cirrhosis than in patients without cirrhosis after successive adjustment for each confounding factor. This result suggests that cirrhosis is an independent risk factor for colorectal adenomatous polyps. This may justify endoscopic screening in patients with compensated cirrhosis since their life expectancy is relatively long.44

Secondly, the relation between adenomatous polyps and cirrhosis may provide a new insight into the aetiology of adenomatous polyps.

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