Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study

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Abstract

Background—Colonoscopic surveillance is a standard procedure in many patients with long standing, extensive ulcerative colitis (UC), in order to avoid death from colorectal cancer. No conclusive proof of its benefits has been presented however.

Aims—To evaluate the association between colonoscopic surveillance and colorectal cancer mortality in patients with UC.

Patients—A population based, nested case control study comprising 142 patients with a definite UC diagnosis, derived from a study population of 4664 patients with UC, was conducted.

Methods—Colonoscopic surveillance in all patients with UC who had died from colorectal cancer after 1975 was compared with that in controls matched for age, sex, extent, and duration of the disease. Information on colonoscopic surveillance was obtained from the medical records.

Results—Two of 40 patients with UC and 18 of 102 controls had undergone at least one surveillance colonoscopy (relative risk (RR) 0.29, 95% confidence interval 0.06 to 1.31). Twelve controls but only one patient with UC had undergone two or more surveillance colonoscopies (RR 0.22, 95% confidence interval 0.03 to 1.74), indicating a protective dose response relation.

Conclusion—Colonoscopic surveillance may be associated with a decreased risk of death from colorectal cancer in patients with long standing UC.

Keywords: colonoscopic surveillance; colorectal cancer; ulcerative colitis; epidemiology

Death from colorectal carcinoma is the single most important factor for long term mortality in patients with ulcerative colitis (UC).1–9 Until the beginning of the 1970s prophylactic proctocolectomy was the only available option to avoid this outcome. However, the recognition that mucosal precancerous lesions, later referred to as dysplasia, are associated with the development of colorectal cancer in patients with UC has provided an alternative approach for this group of patients. A prospective endoscopic follow up programme at St Mark’s Hospital in London was initiated in 1966.10 The rapid evolution of the flexible fibrecolonoscope led to the initiation of endoscopic surveillance programmes at centres in the UK, USA, Sweden, and Israel in the 1970s.12–15 Most surveillance programmes have included a total colonoscopic examination at regular intervals combined with multiple biopsy sampling from different locations in the large bowel. Such programmes are now widely used in clinical practice and offered to many patients with long standing extensive UC.

The primary aim of these programmes has been to reduce the overall mortality due to colorectal cancer. However, the value of colonoscopic surveillance in this respect has never been evaluated by a randomised controlled trial. For both practical and ethical reasons, it is unlikely that such a trial will ever be carried out.

Previous reports on this subject have mainly been longitudinal descriptive studies without a valid non-survayed control group. Hence the benefits of colonoscopic surveillance in patients with UC have been questioned.16–18 In order to evaluate the impact of colonoscopic surveillance on colorectal cancer (CRC) mortality in patients with UC, a nested case control study was performed using observational data from a large population based cohort of patients with UC.

Materials and methods

STUDY POPULATION

The study population consisted of all patients with UC diagnosed in Stockholm County between 1955 and 198419 and in the Uppsala Health Care Region between 1965 and 1983,20 who were 10 years of age or more at the time of UC diagnosis and had at least five years duration of disease since diagnosis. A total of 4664 individuals with a definite diagnosis of UC were derived from a background population comprising approximately three million people living in Stockholm County and in the Uppsala Health Care Region.

The identification of UC patients in both Stockholm County (n=1547) and in Uppsala Health Care Region (n=3117) has been described in detail previously.19–21 In short, the identification of patients in Stockholm County was performed manually or partly manually between 1955 and 1969. Since 1969, a computerised register including all hospital admissions in Stockholm County has been used. The medical records of all departments of internal medicine, surgery, paediatrics, and infectious diseases were searched for possible patients with ulcerative colitis using diagnostic criteria in accordance with earlier studies.

In Uppsala the patients with UC were selected from an inpatient register that in-
Table 1  Characteristics of controls and patients with ulcerative colitis who died from colorectal cancer

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cases n(%)</th>
<th>Controls n(%)</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26 (65)</td>
<td>52 (51)</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>14 (35)</td>
<td>50 (49)</td>
<td>0.7</td>
<td>0.4 to 1.2</td>
</tr>
</tbody>
</table>

Table 2  Colonoscopy surveillance in patients and controls

<table>
<thead>
<tr>
<th>Surveillance colonoscopy</th>
<th>No of patients</th>
<th>No of controls</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>38</td>
<td>84</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever</td>
<td>2</td>
<td>18</td>
<td>0.29</td>
<td>0.06 to 1.31</td>
</tr>
<tr>
<td>Never</td>
<td>38</td>
<td>84</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>0.43</td>
<td>0.05 to 3.76</td>
</tr>
<tr>
<td>2+</td>
<td>1</td>
<td>12</td>
<td>0.22</td>
<td>0.03 to 1.74</td>
</tr>
</tbody>
</table>

CI, confidence interval.

PATIENTS
All Swedish citizens are exclusively identifiable by a 10 digit national registration number.22 The patients in the study population are recorded on computer registers by this individual number. Through computerised links to the Swedish Cancer Register and the Swedish Cause of Death Register all patients in the cohort were followed up for occurrence of colorectal cancer, date of death, and the underlying cause of death up until 1988. The Swedish National Cancer Register has been in operation since 1958. All diagnosed malignant tumours must be reported to this register by both the physician and the pathologist or cytologist, making the register almost complete.23 The Swedish Cause of Death Register includes the date of death for all individuals in Sweden from 1952 as well as the underlying cause of death.

All patients in the study population that had died from colorectal cancer after 1975 were identified and none had had a diagnosis of colorectal cancer before the time of the UC diagnosis. The end points in the study were the end of follow up (31 December 1988) or date of death if this occurred earlier.

RESULTS
Forty patients who died from colorectal cancer and 102 matched controls were analysed. All were diagnosed as having total or extensive (inflammation reaching at least proximal to the hepatic flexure) colitis.

Two of 40 patients and 18 of 102 controls had undergone at least one surveillance colonoscopy (relative risk (RR) 0.29, 95% confidence interval 0.06 to 1.31) (table 2). Twelve controls but only one patient had undergone two or more surveillance colonoscopies (RR 0.22, 95% confidence interval 0.03 to 1.74), indicating a protective dose response relation (table 2). Ten of 102 controls (10%) underwent colectomy within five years prior to diagnosis of the cancer of the patient.

DISCUSSION
The optimal study design to show the effect of colonoscopic surveillance on CRC mortality is a prospective trial. Such a trial would include randomisation, and have death from colorectal cancer as the end point. However, practical problems, as noted above, together with ethical considerations, the need for large number of patients, and the substantial length of follow up required indicate the difficulties involved in

ASSESSMENT OF SURVEILLANCE
The medical records for the patients and controls were scrutinised in a uniform manner. Specific information about exposure to colonoscopic surveillance was collected until the date of cancer diagnosis. Only colonoscopies with multiple biopsy specimens from all parts of the colon, performed within the frame of a surveillance programme, were taken into account. Index colonoscopies or colonoscopies performed due to any clinical signs or symptoms were excluded. If the medical records did not clearly indicate that the colonoscopy was conducted as a cancer prophylactic measure the procedure was excluded.

STATISTICAL METHODS
The association between colonoscopic surveillance and CRC mortality was analysed by the relative risk obtained by the odds ratio. Matched analyses were performed using conditional logistic regression analyses. The estimated standard deviations of the regression coefficient estimates were used to assess 95% confidence limits.24
such a study. Thus, any evaluation has to be done through analytical observation studies using retrospective data.

This is the first study to implement established case control methodology in order to assess the benefit of surveillance with colonoscopy in patients with UC. The main finding, although not statistically significant, indicates that colonoscopic surveillance may have a protective effect against death from colorectal cancer. This protective effect is even more pronounced if the patients underwent two or more surveillance colonoscopies, indicating a protective dose response relation. In spite of the fact that the study is derived from a large cohort of 4664 patients with UC within a population of three million people, there is a lack of statistical power as only 40 patients died from CRC. Furthermore, less than 20% of the controls had a history of colonoscopic surveillance, a proportion most likely reflecting the clinical practice in Sweden in the 1970s and the early 1980s.

The lack of information in patients and controls of potential confounding factors is another concern. Pharmacological treatment— that is, sulphasalazine, which has been shown to decrease the risk of CRC, 25–26 constitutes such a potential confounding factor. Patients with active disease are likely to be more frequently in contact with the health care system and thus undergo more frequent pharmacotherapy, but could also be more likely to be enrolled in a surveillance programme, thus creating bias.

The assessment of exposure to surveillance in this study was made without blinding for case control status which could introduce differential misclassification of exposure. In order to control for this possible bias, strict criteria for what could be considered surveillance colonoscopies were set up. Only colonoscopies performed with the intention of cancer surveillance and unfavourably distorting the results. The problems associated with surveillance programmes do not only concern the enrolment of patients but also the difficulties of keeping those patients on the programmes. Our study indicates that the majority of patients under surveillance undergo only one or at most two colonoscopies before leaving the programme; similar figures were found in the study from Sweden. 32 This mathematical approach to the problem has however been questioned as the results depend so critically on the underlying assumptions. 32

In an alternative approach, analytical survival models trying to maximise the basis for decision making for cancer risk in UC have been used. The results indicated a benefit of surveillance. 30–31 This mathematical approach of patients under surveillance having a protective effect against death from CRC.

In conclusion, this case control study indicates that colonoscopic surveillance may be associated with a decreased risk of death from colorectal cancer.

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