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

P Karlén, D Kornfeld, O Broström, R Löfberg, P-G Persson, A Ekblom

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 UC10 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 1966.11 The rapid evolution of the flexible fibrocolonoscope 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 six to 10 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-surveyed 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 198410 and in the Uppsala Health Care Region between 1965 and 1983,19 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></th>
<th>Cases n(%)</th>
<th>Controls n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (65)</td>
<td>52 (51)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (35)</td>
<td>50 (49)</td>
</tr>
<tr>
<td>Age at diagnosis of UC (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>9 (22.5)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>15-29</td>
<td>12 (30)</td>
<td>43 (42)</td>
</tr>
<tr>
<td>30-49</td>
<td>11 (27.5)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>50+</td>
<td>8 (20)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Extent at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>1 (2.5)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Left-sided</td>
<td>9 (22.5)</td>
<td>29 (28.4)</td>
</tr>
<tr>
<td>Total</td>
<td>23 (57.5)</td>
<td>48 (47.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (17.5)</td>
<td>18 (17.6)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

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>

ASSESSMENT OF SURVEILLANCE

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

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 included 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 colonscopy (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 colonscopies (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 colonscopic 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
surveillance and colorectal cancer mortality in ulcerative colitis

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... Register makes a non-di... population based and that links with the Swedish... performed with the intention of cancer surveillance... colonoscopies were set up. Only colonoscopies... case control status which could introduce bias...

... be enrolled in a surveillance programme, thus creating bias...

... the major strength of this study is that it is population based and that links with the Swedish Cancer Register and the Swedish Cause of Death Register makes a non-differential classification of outcome possible with both high specificity and high sensitivity. The matching criteria also eliminated some other possible confounders...

... remaining uncertainty is to what extent our results are valid if all known patients with extensive UC were enrolled in a surveillance programme, especially as there are reasons to believe that colonoscopic surveillance today is a more common procedure in these patients than in previous years. The intricate problem of external validity, which has been taken for granted in hospital based studies conducted previously, should be of lesser concern in this study, particularly due to its population based design. The colectomy rate of almost 10% (10 of 102 patients) among controls within five years prior to the cancer diagnosis of the patient is an indication of the high internal validity, which further strengthens the hypothesis of surveillance colonoscopy having a protective effect against death from CRC...

... Three major studies published in the 1990s further illustrate the problems of evaluating the effects of colonoscopy surveillance on CRC mortality.27–29 These studies are, in spite of their considerable size, difficult to interpret due to weaknesses such as different assessment of outcomes, the lack of suitable control groups and, above all, the hospital based design which does not permit generalisation of the results presented...

... 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 hint of a benefit from surveillance.30,31 This mathematical approach to the problem has however been questioned as the results depend so critically on the underlying assumptions.32

... 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 underwent only one or at most two colonoscopies before leaving the programme; similar figures were found in the study from a university hospital report from St Mark’s.27 This incomplete compliance is probably of vital importance, thus weakening the protective effect of colonoscopic surveillance and unfavourably distorting the results...

... 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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