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.**

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

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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[10] 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 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 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 1984[19] 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

	Cases n(%)	*Controls n(%)*
Sex		
Male	26 (65)	52 (51)
Female	14 (35)	50 (49)
Age at diagnosis of UC (y)		
<15	9 (22.5)	14 (14)
15–29	12 (30)	43 (42)
30–49	11 (27.5)	31 (30)
50+	8 (20)	14 (14)
Extent at diagnosis		
Proctitis	1 (2.5)	7 (6.9)
Left-sided	9 (22.5)	29 (28.4)
Total	23 (57.5)	48 (47.1)
Unknown	7 (17.5)	18 (17.6)

Table 2 Colonoscopy surveillance in patients and controls

Surveillance colonoscopy	*No of patients*	*No of controls*	*Relative risk*	*95% CI*
Never	38	84	1.0	Reference
Ever	2	18	0.29	0.06 to 1.31
Never	38	84	1.0	Reference
1	1	6	0.43	0.05 to 3.76
2+	1	12	0.22	0.03 to 1.74

CI, confidence interval.

cluded all patients in the health care region being hospitalised. In order to identify outpatients with a diagnosis of UC the records at the departments of clinical pathology were reviewed. The medical records of all the patients with a possible diagnosis of UL were scrutinised to confirm or reject the diagnosis.[20]

The colonoscopies were performed in several different hospitals and follow up routines were not completely uniform. Most hospitals, however, had the routine of performing surveillance colonoscopies every first or every second year and biopsy specimens were taken from 6–10 different locations in the colon 8–10 years after diagnosis.

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.

CONTROLS

For each patient the aim was to select three controls matched individually by age at diagnosis (plus or minus five years), duration of disease, extent of disease at diagnosis, and sex. Furthermore, the controls had to be alive at the time of death of the patient and to have some part of the colon intact five years prior to the diagnosis of the cancer of the patient; this gives colonoscopic surveillance the opportunity to exert a possible protective effect. Due to these strict criteria, the control group was confined to 102 of 120 individuals. Table 1 shows the characteristics of the patients and controls.

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]

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

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 were included, thus excluding index colonoscopies and those being made due to clinical symptoms or signs.

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.

One 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 benefit of 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 undergo only one or at most two colonoscopies before leaving the programme; similar figures were found in the study from Leeds[28] and to some extent by the 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.

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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