

# Prognosis of chronic ulcerative colitis in a community

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**SUMMARY** Utilising the population based data resources of the Rochester Epidemiology Project, we estimated survival and risk of subsequent colon cancer in the 182 residents of Rochester, Minnesota, initially diagnosed with chronic ulcerative colitis (CUC) between 1935 and 1979. Twenty five (13.7%) had a proctocolectomy during the course of follow up. Three patients developed colorectal adenocarcinoma after the initial diagnosis of CUC (relative risk=1.9, 95% CI 0.4-5.4). Excluding proctitis cases, the relative risk of cancer was 2.4 (95% CI 0.3-8.7). At last follow up, 37 (20.3%) were dead; only 10 patients had chronic ulcerative colitis mentioned on the death certificate. Overall survival was similar to that expected for the general population of like age and sex. Our results suggest that chronic ulcerative colitis in the community is typically a milder disease than would appear from hospital or referral centre series.

There is increasing recognition of discrepancies in the clinical spectrum and prognosis of chronic ulcerative colitis (CUC) in population based studies compared with those based on patient series.<sup>1-5</sup> The few investigations utilising the complete cohort of patients from a single community predict a lower incidence of subsequent colon cancer, for example, and a higher survival rate<sup>6-10</sup> than is evident among series of referral patients or hospital admissions.<sup>11-28</sup> The present study took advantage of the population based medical records linkage system in Rochester, Minnesota, to determine survival and the risk of subsequent colon cancer in community residents with chronic ulcerative colitis.

## Methods

### PATIENTS

Population based epidemiologic research is possible in Rochester, Minnesota, because medical care is virtually self-contained within the community and is delivered by a handful of providers. Most care is provided by the Mayo Clinic, which has maintained a common medical record system with its two large

affiliated hospitals over the past 80 years. This dossier type medical record contains both inpatient and outpatient data and is easily retrieved for review.<sup>29</sup> The diagnosis and surgical procedures entered into these records are indexed. The index includes the diagnosis made for outpatient office or clinic consultations, emergency room visits, nursing home care, inpatient hospitalisation, autopsy examination, and death certification. The records of the other medical care providers in the area who have served the local population are also indexed and can also be retrieved. Thus, the details of the medical care provided to the residents of the entire community are available for study. The potential value of this data system (the Rochester Epidemiology Project) for population based studies has been described previously.<sup>30</sup>

Using this unique data base, we identified 138 patients who were residents of Rochester when first diagnosed with chronic ulcerative colitis in the 20 year period 1960-79.<sup>31</sup> To assure complete ascertainment, we screened the charts of all Rochester residents with diagnoses of chronic ulcerative colitis; ulcerative/idiopathic/non-specific colitis, proctitis or proctosigmoiditis; inflammatory bowel disease; or chronic colitis from a variety of other presumed causes. The records of patients with Crohn's disease

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and related diagnoses were also evaluated. We discarded those who did not fulfill residence criteria and those whose diagnosis was clearly not chronic ulcerative colitis (see criteria below). In order to be considered a *bona fide* incidence case, the patient must have been a resident of Rochester for at least one year before initial diagnosis. In addition to the 138 incidence cases previously reported for 1960–79, affected residents first diagnosed between 1935 and 1959 had been identified in an earlier study.<sup>32</sup> After redefining those cases according to our diagnostic and residency criteria, 44 remained for study. Thus, 182 subjects were available for this evaluation of outcome and prognosis.

The mucosal nature and extent of disease were verified by endoscopic, radiologic, and histologic findings for each case. A positive diagnosis of chronic ulcerative colitis required typical findings – that is, diffusely granular or friable mucosa on endoscopy, with uniform involvement of the colon as observed by barium enema and/or colonoscopy. Involvement of the small intestine, with the exception of ‘backwash ileitis’, was reason for exclusion. If biopsies were taken, histologic data provided additional evidence. Cases with evidence of a specific infection or a history suggestive of antibiotic colitis, laxative abuse, or any other more obvious alternate diagnosis were not included. Exclusion of Crohn’s colitis was based on the anatomical distribution of the disease and histologic, radiologic, endoscopic, or surgical findings compatible with Crohn’s disease. The histories of patients who had inflammatory bowel disease, but in whom a clear distinction between chronic ulcerative colitis and Crohn’s colitis was lacking, were reevaluated, and their tissue specimens were retrieved for reassessment by one of our pathologists.

Cases that met the above criteria were further classified as either ‘definite’ or ‘probable’. Placement in the ‘definite’ category required radiologic or endoscopic documentation of chronic ulcerative colitis at least twice, with the observations being separated by a period of six months or more. Where there was only one observation or when observations spanned a period of less than six months, the

diagnosis was only ‘probable’. The anatomical extent of disease by radiology or colonoscopy was recorded at initial diagnosis and at the time of maximal colonic involvement. Patients were divided into five groups with regard to the maximum extent of disease: (1) proctitis (no involvement proximal to the rectum), (2) distal (no involvement proximal to the splenic flexure), (3) extensive (involvement of hepatic flexure or transverse colon and distally), and (4) pancolitis (entire colon involved). A fifth category, segmental colitis, was used for a few instances of apparent non-uniform disease which could not be designated as Crohn’s disease of the colon. In addition, four subgroups were identified based on the severity of disease. These subjective categories included: (1) transient – symptomatology and pathological features sufficient for a diagnosis of chronic ulcerative colitis but which then resolved (or were not documented) for the duration of follow up (by definition, these were all ‘probable’ cases); (2) ‘mild’ – by exclusion, those patients not in groups 1, 3, or 4; (3) ‘moderate’ – patients requiring one or more blood transfusions or more than two hospitalisations for chronic ulcerative colitis over the entire length of follow up; and (4) ‘severe’ – patients who underwent total proctocolectomy, developed toxic megacolon, or died as a result of chronic ulcerative colitis.

Each patient was followed through his or her linked medical records in the community, and those who had not been seen since 1980 were contacted by letter or telephone. Follow up was complete to death or through 1980 in 96%, with a median follow up on these subjects of 14 years. Median follow up on the remainder was 4–4 years. As an additional check for complete ascertainment of colon cancer, the chronic ulcerative colitis cases were cross checked with a listing of all diagnosed colorectal cancer cases in Rochester.<sup>33</sup>

The incidence of colorectal adenocarcinoma in this group was compared with the expected incidence (relative risk). The expected incidence was calculated using the age and sex specific person years of follow up in the cohort in conjunction with age and sex specific incidence rates of colorectal adeno-

Table 1 *Colon cancer cases found in Rochester, Minnesota, residents diagnosed with chronic ulcerative colitis (CUC), 1935–79*

Age, sex	Date of initial CUC Dx	Extent of disease	Date of CA	Case site	Status 1-1-80
Before diagnosis of CUC					
1 Male, 38 yr	25/5/79 (probable case)	Proctitis (transient)	1956	Unknown	Alive
Concurrent with diagnosis of CUC					
2 Female, 38 yr	11/6/49 (probable case)	Pancolitis	1949	Multiple	Dead
Subsequent to diagnosis of CUC					
3 Male, 88 yr	6/1/41 (definite case)	Proctitis (pancolitis elsewhere)	1962	Transverse colon	Dead
4 Male, 43 yr	30/5/60 (definite case)	Pancolitis	1969	Splenic flexure	Dead
5 Female, 49 yr	16/8/68 (probable case)	Proctitis (transient)	1984	Sigmoid	Alive

carcinoma previously determined for Rochester residents.<sup>33</sup> Assuming that the incidence follows a Poisson distribution, a 95% confidence interval for the relative risk was calculated. Statistical significance was assessed by evaluating the 95% confidence interval and noting whether or not it included the value of 1.0 (no increased risk). The cumulative Poisson distribution was also used for power calculations. Life table methods (product limit method)<sup>34</sup> were employed to estimate observed and expected survival, using as a standard the death rates of West North Central United States residents in 1970. Life table methods were also used to estimate the cumulative incidence of colorectal cancer (survival free of colon cancer). Differences between observed and expected survival and observed and expected survival free of colon cancer were assessed with the log rank test.<sup>35</sup> Statistical significance indicates  $p < 0.05$  unless otherwise noted.

## Results

Of the 182 subjects, 98 (53.8%) had definite disease and 84 (46.2%) had probable chronic ulcerative colitis, as defined. Seventy per cent of cases were mild or transient and only 30% were moderate or severe. A third of the patients had pancolitis, while distal colitis and proctitis made up most of the remainder. Unsurprisingly, patients with greater extent of disease also had more severe disease (Fig. 1). During the period of observation, the extent of disease increased in 53 (29.1%) individuals (Fig. 2). The overall course was assessed as transient in 50 (27.5%), intermittent in 119 (65.4%), and unremitting in 10 (5.5%). Clinical course could not be adequately assessed in three patients. Twenty five (13.7%) of the subjects have had a total proctocolectomy thus far, while an additional 3 (1.6%) have had a partial colectomy. All proctocolectomies were indicated for incapacitating symptoms refractory to

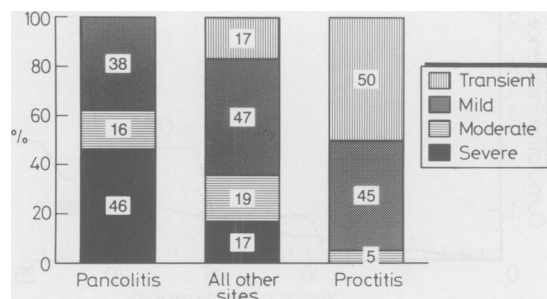


Fig. 1 Relationship of extent and severity of disease among Rochester, Minnesota, residents with chronic ulcerative colitis diagnosed, 1935-79.

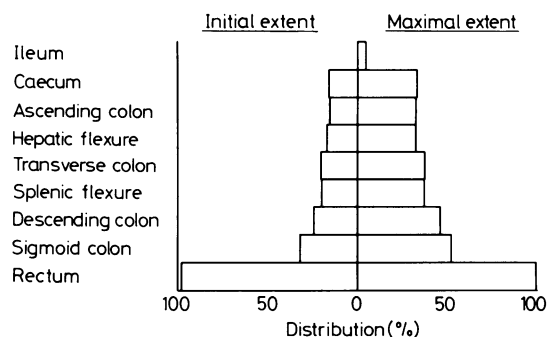


Fig. 2 Proportion of sites affected initially and maximally among Rochester, Minnesota, residents with chronic ulcerative colitis diagnosed, 1935-79. Individual patients may have involvement at more than one site.

medical management; none was done purely for cancer prophylaxis.

One man (case 1, Table 1) had colon cancer (unknown site, resected elsewhere) 23 years before the diagnosis of chronic ulcerative colitis. A second patient developed a villous adenoma of the rectum six years before endoscopic and histologic evidence of ulcerative proctitis. (At the time the villous adenoma was fulgerated, there was no evidence of inflammatory bowel disease). A third patient (case 2, Table 1) had colon cancer and chronic ulcerative colitis diagnosed simultaneously. At that time, she had endoscopic findings consistent with old chronic ulcerative colitis and had a previous history of mild recurrent, occasionally bloody, diarrhoea for 17 years; however, this had never been investigated medically.

These three individuals were deleted from the group at risk of colon cancer subsequent to the diagnosis of chronic ulcerative colitis. The remaining 179 individuals in the cohort were followed for 2535 person years for the development of colorectal cancer or until total colectomy, death, or date of last follow up. Three patients (cases 3, 4, and 5, Table 1) developed adenocarcinoma of the colon subsequent to the diagnosis of chronic ulcerative colitis. An 88 year old man with adenocarcinoma of the transverse colon first had a diagnosis of transient proctitis while a resident of Rochester. He did not have any further evaluation at Mayo Clinic because he subsequently moved from the community. Follow up revealed that he had a partial colon resection and colostomy at age 86 and was found to have cancer of the transverse colon two years afterward. He died several months later. The second patient was a 43 year old man who developed adenocarcinoma at the splenic flexure nine years after the initial chronic ulcerative colitis diagnosis, which was a pancolitis at onset. Two and a half years after the discovery of colon cancer, he died

of bowel obstruction. The third patient was a 49 year old woman who developed grade 2 adenocarcinoma of the sigmoid colon 16 years after an episode of transient proctitis. No evidence of inflammatory bowel disease was found at the time of sigmoid resection for the cancer. Because this latter individual (case 5) had findings sufficient for a 'probable' diagnosis of chronic ulcerative colitis according to our criteria, we were bound to include her; however, we recognise that the transient proctitis may have had only a coincidental relationship with the later malignancy. A fourth individual, not included here, subsequently developed squamous cell carcinoma of the anus.

The three observed cases reflect an overall incidence of adenocarcinoma of the colon in this cohort of 1.2 per 1000 person years (p-y). The expected incidence, based on colorectal cancer rates for the underlying population of Rochester, was 0.6 per 1000 p-y. The overall relative risk was thus 1.9 (2.7 for men and 1.1 for women) as shown in Table 2. Because of the small numbers involved, none of these was statistically significantly greater than the expected relative risk of 1.0. The power of this analysis to have detected a true relative risk  $\geq 3.0$  was 60% ( $\alpha=0.05$ ,

Table 2 Observed (Obs) and expected (Exp) cases and relative risk (RR) of colorectal adenocarcinoma among Rochester, Minnesota, residents with chronic ulcerative colitis (CUC) diagnosed 1935–79, followed from date of diagnosis of CUC or date of onset

	Obs	Exp	RR	95% CI
From date of diagnosis of CUC				
Men	2	0.7	2.7	0.3–9.9
Women	1	0.9	1.1	0.0–6.2
Total	3	1.6	1.9	0.4–5.4
From date of onset of CUC symptoms*				
Men	2	0.7	2.7	0.3–9.6
Women	2	0.9	2.2	0.3–8.0
Total	4	1.6	2.4	0.7–6.2

\*All Rochester incidence cases were included even if they were not Rochester residents at the time of onset of CUC symptoms.

Table 3 Observed (Obs) and expected (Exp) cases and relative risk (RR) of colorectal adenocarcinoma among Rochester, Minnesota, residents with chronic ulcerative colitis (CUC) diagnosed 1935–79, by definite or probable case and by subjective severity of disease

	Obs	Exp	RR	95% CI
Certainty of diagnosis of CUC				
Definite	2	0.9	2.3	0.3–8.2
Probable	1	0.7	1.3	0.03–7.5
Severity of symptoms of CUC				
Severe and moderate	1	0.5	2.0	0.1–11.3
Mild and transient	2	1.1	1.8	0.2–6.4

one-sided). With two observed cases, the relative risk among definite cases was 2.3 (Table 3), while the relative risk was 1.3 for probable cases based on a single case of colon cancer. Likewise, with this small number of cases no greater rate could be detected among those with moderate to severe chronic ulcerative colitis than transient or mild disease (Table 3). If the patients who only had proctitis were excluded, the relative risk for the remainder was 2.4 (95% CI 0.3–8.7). The cumulative incidence of colon cancer (2.3% at 20 years) was not significantly greater than expected either (Fig. 3). These results were not substantively altered if onset of symptoms, rather than diagnosis, were used as the inception date for initiating follow up (Table 2).

Ten individuals have developed an adenomatous polyp thus far, from 0 to 42 years after the initial diagnosis of ulcerative colitis. One patient had transient proctitis only and another had recurrent proctitis only. The other eight had more diffuse inflammatory bowel disease. One patient had the polyp diagnosed concurrently with chronic ulcerative colitis; she also had a grade 4 adenocarcinoma diagnosed at the same time, although the onset of chronic ulcerative colitis symptoms appeared to predate the cancer (case 2, Table 1), and died three months later.

Up to the time of last follow up, 145 patients were alive and 37 (20.3%) had died (Table 4). Of those who had died, chronic ulcerative colitis was the underlying cause of death in six (two definite and four probable cases). Chronic ulcerative colitis was mentioned elsewhere on the death certificate in four but not as a primary cause of death (all definite cases). Chronic ulcerative colitis was not mentioned on 26 death certificates (12 definite and 14 probable cases). The death certificate of the final patient could not be obtained. Overall survival was similar to that

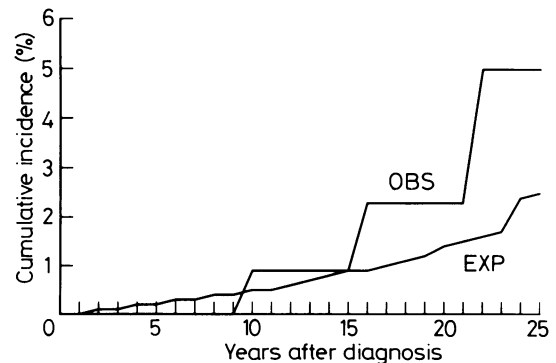


Fig. 3 Observed (Obs) and expected (Exp) cumulative incidence of colorectal cancer among Rochester, Minnesota, residents with chronic ulcerative colitis diagnosed, 1935–79.

expected for members of the general population of like age and sex (Fig. 4).

## Discussion

These data from a population based inception cohort of chronic ulcerative colitis patients corroborate a recent report from another population based study in Denmark,<sup>9</sup> in which survival did not differ significantly from that of the general population. A second population based study from Scotland<sup>8</sup> reported a good prognosis for chronic ulcerative colitis patients subsequent to the first few years after initial diagnosis. Past studies based on referral or hospital admissions have generally related much higher mortality rates.<sup>12-14 18 19 23 25 28</sup> In the present study, the best survival, relative to that expected, was among the definite chronic ulcerative colitis cases. Probable cases may have experienced somewhat worse survival because they died before a second confirmation of disease was possible (death thus producing a 'probable' diagnosis in a few instances) or because probable cases are weighted toward proctitis, which may reflect a different disease process. Indeed, we recently found that pancolitis was most closely associated with the peak in chronic ulcerative colitis incidence seen in the second and third decades, while a smaller peak in about the sixth decade of life was made up disproportionately of proctitis cases.<sup>31</sup>

The risk of subsequent colorectal cancer was examined in a variety of ways. All revealed only a moderate increase in risk relative to the general population of Rochester. It is important to note, however, that the 95% confidence intervals for all of the estimates were large, such that the upper limits might be consistent with those reports which have suggested that the relative risk of cancer is greater.<sup>15-17 23 26 35</sup> Some of the latter studies have been criticised, however, on the grounds that cancer risk estimates were artificially inflated by methodological flaws.<sup>1</sup> One might also argue that the high proportion of proctitis cases in our cohort dilutes the relative risk

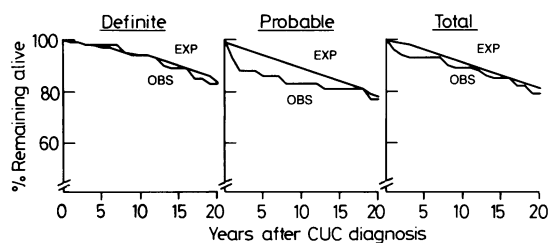


Fig. 4 Observed (Obs) and expected (Exp) survival among Rochester, Minnesota, residents with chronic ulcerative colitis diagnosed 1935-79, for definite, probable, and total cases.

Table 4 Current vital status of Rochester, Minnesota, residents with chronic ulcerative colitis diagnosed 1935-79

	Definite		Probable		Total	
	n	%	n	%	n	%
Status at last follow up						
Living	80	81.6*	65	77.4*	145	79.7*
Dead	18	18.4*	19	22.6*	37	20.3*
Death certificate						
CUC underlying cause	2	11.1†	4	21.1†	6	16.2†
CUC mentioned	4	22.2†	0	0.0†	4	10.8†
CUC not mentioned	12	66.7†	14	73.7†	26	70.3†
Unknown	0	0.0†	1	5.3†	1	2.7†

\*Percentage of total; †percentage of those who died.

of cancer for the entire group.<sup>16</sup> The relative risk for the cohort after excluding patients with proctitis, however, was still only 2.4. An alternative argument is that malignancies may have been prevented by the proctocolectomies, which were done in the most severely affected patients who might have been most at risk of subsequent malignancy.<sup>36</sup> This possibility cannot be addressed in the present analysis. Nonetheless, the absolute incidence of colorectal adenocarcinoma in the ulcerative colitis cohort was quite small. The 1.2 per 1000 person year rate reported here is little different from the 1.7 per 1000 person year figure seen in a community cohort followed with routine colonoscopy.<sup>10</sup> The cumulative incidence of 2.3% at 20 years is also less than that suggested by referral centre data.

Four additional individuals have shown evidence of mild dysplasia thus far, from six to 28 years subsequent to their initial chronic ulcerative colitis diagnosis. One patient had a proctocolectomy on the basis of symptoms (not dysplasia); the remaining three have been watched with no further sequelae. It is difficult to make conclusions with regard to dysplasia, however, because a cancer surveillance programme was only instituted within the last decade and because of the small numbers involved. So far, those showing dysplasia have had only mild evidence of such. All four cases had extensive disease of long duration, however, and close watch for progression of dysplasia is definitely warranted in the three whose colons are still intact.

Despite the presence of some severely affected individuals, our results indicate that chronic ulcerative colitis is a milder disease in community patients generally than it is in patients who are hospitalised or referred to tertiary medical centres. The risk of cancer in unselected chronic ulcerative colitis patients from the community appears to be lower than that suggested by referral centre data, and survival is relatively unimpaired. These findings are consistent with clinical spectrum data reported in a

previous paper from the same population,<sup>31</sup> in which we showed a preponderance of less severe disease than is typically quoted from referral institutions.

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