Cancer Risk in Extensive Ulcerative Colitis

J. KEWENTER, M.D., H. AHLMAN, M.D., L. HULTÉN, M.D.

Two hundred thirty-four patients with extensive ulcerative colitis from the city of Göteborg, Sweden have been followed up and the cumulative risk of development of cancer of the large bowel was estimated. These patients constitute all persons in this region who developed an extensive ulcerative colitis between 1951 and 1974. All patients were followed up until December 1975. The mean observation time was 8.5 years, median value six years. Fifteen patients developed carcinoma of the large bowel. Five of the 15 patients were still alive in December 1975. The expected number of colorectal carcinomas in a matched reference group was 0.49. The cumulative incidence of carcinoma 25 years after the onset of colitis for the whole group of patients was 34% and for those who developed the disease before 25 years of age it was 43%.

From the Department of Surgery II and III, University of Göteborg, Sahlgren's Hospital, Göteborg, Sweden

PATIENTS WITH EXTENSIVE ulcerative colitis run a greater risk of developing carcinoma of the large bowel than the general population. Opinions as to how large this risk is differ greatly between different authors.[1,2,5,6] This is hardly surprising however, as there have been differences in the method of collection of materials and the duration of the colitis has not always been taken into account, as has recently been pointed out by Devroede and Taylor.[7]

The poor prognosis in patients with UC and cancer of the large bowel makes it highly important to identify and treat patients at high risk in time.[14] Accurate knowledge of the cancer risk in this group of patients is therefore necessary. There is now convincing evidence that the colitis patients most susceptible to malignant changes are those with radiological involvement of the large bowel to at least the right flexure.[6,8,17] There are only few reports of large bowel carcinoma in which the inflammatory bowel disease has been localized exclusively to the rectum or the left side of the colon.[4,8,10,17,18] For the sake of clarity, it is therefore important to define the extension of the disease in the large bowel when the incidence of carcinoma in UC is investigated. This incidence must be quite different when all cases of UC are included in a series and when the incidence is calculated on groups of patients with the same extension of the disease.

Apart from the extension of the disease in the large bowel, the duration of the colitis in the individual patient is a most important factor for evaluating the cancer risk. Remarkably little attention has been paid to the variation in the duration of the disease between different patients when the incidence of cancer in UC has been calculated. In published reports the crude incidence has usually been used.[1,11,19] However, the use of the crude incidence to evaluate the risk of carcinoma in UC is misleading as it fails to correct for differences in duration between individual patients. The figures may thus underestimate the true incidence of carcinoma in UC. The time factor is essential and by employing the life table concept much more sophisticated and accurate results can be obtained.[6,7]

The aim of the present investigation has been to calculate the cumulative incidence of carcinoma in patients from a well-defined area of Sweden with extensive colitis *i.e.* radiological involvement of the large bowel to at least the right flexure.

Material and Methods

Hospital records for the population of Göteborg and listing of diagnosis of any type of inflammatory large bowel disease recorded during 1951–1974 were collected and examined. Only records from patients who were resident in the city of Göteborg were included in the study. Ulcerative colitis was defined by the usual clinical criteria and supported by radiological and sigmoidoscopic findings. Moreover, the diagnosis was supported by histological examination of the surgical specimen, rectal biopsy or postmortem investigation in the vast majority of patients. Patients with Crohn's colitis were excluded. Extensive colitis was defined as rectal involvement as shown by sigmoidoscopy and

Reprint requests: Jan Kewenter, M.D., Department of Surgery III, Sahlgren's Hospital, S-413 45 Göteborg, Sweden.

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TABLE 1. *Carcinoma of the Large Bowel in Association with Extensive Ulcerative Colitis According to the Length of History in the Number of Duration Years of Follow-up**

	D_i	C_i	$\lambda = C_i/D_i$	$P_i = e^{-\lambda \cdot t}$	$Q_i = 1 - P_i$	S.D.	**P**	**Q**	S.D.
1–5 years	875	0	0.000	1.000	0.000	0.000	1.000	0.000	0.000
6–10 years	523	3	0.006	0.970	0.030	0.017	0.970	0.030	0.017
11–15 years	282	4	0.014	0.932	0.068	0.032	0.904	0.096	0.035
16–20 years	147	5	0.035	0.839	0.161	0.066	0.758	0.242	0.066
21–25 years	73	2	0.027	0.874	0.126	0.083	0.663	0.337	0.086

* One patient with 44 years duration is not included in the table.

radiological evidence of large bowel involvement extending at least to the right hepatic flexure. As the majority of previous investigations have defined extensive colitis in this way,[5,6] use of this definition makes comparison with earlier studies possible.

According to this definition 234 patients had ulcerative colitis with total involvement of the large bowel, and these cases constitute the material of this study. The outcome in all patients could be followed up until December 1975. 129 patients were women. 154 patients had undergone proctocolectomy or colon resection with ileorectal anastomosis. The mean observation time was 8.5 years, median value six years.

To determine the cumulative risk of large bowel carcinoma in a patient with total involvement of the colon the concept of duration–years was used. Patients began to contribute duration–years from the year after the onset of the disease. The difference between duration–years and patient–years, *i.e.* one complete year of follow-up of an individual patient, was in our material usually small as most of the patients came to the hospital shortly after the onset of the disease. Patients then contributed to the total number of duration–years until they underwent proctocolectomy, died or until the closing date of the study, December 31, 1975. Those patients who had a large bowel resection or an ileorectal anastomosis were considered to contribute duration–years until the remaining part of the colon was removed, the patient died or until December 31, 1975.

The duration–years have been divided into five year intervals. Thus, a patient who first presented his disease in 1951 and underwent a proctocolectomy in 1963 contributed 12 duration–years, which means that he contributed 5 + 5 + 2 years in the first, second and third five year period, respectively. The number of patients (six) with a duration of more than 25 years was too small for accurate calculations. The maximum number of five year periods was therefore 5 (i = 1, 2, 3, 4, 5).

The risk of developing carcinoma of the large bowel is assumed to change with time but these changes have been considered to be small within each 5-year period.

D_i is the total sum of all duration–years within each five year period and C_i the number of carcinomas in a particular five year period. The risk (λ) of developing carcinoma within the five year period is estimated from the ratio C_i/D_i.

The probability (P_i) of a patient who lived at the beginning of an interval *not* developing a carcinoma during the interval can be calculated from $P_i = e^{-\lambda \cdot t}$, where t is the time length of the interval. Consequently, the probability of developing a carcinoma (Q_i) in the same interval is $Q_i = 1 - P_i$.

The cumulative risk after a certain period of time of a patient not developing a carcinoma can be calculated as the product of the incidences during each five year interval. $\mathbf{P} = P_1 \cdot P_2 \text{ --- } P_5$ and the cancer risk will consequently be $\mathbf{Q} = 1 - \mathbf{P}$.

Results

Fifteen patients with 17 large bowel carcinomas were found. Five in colon ascendens, five in transversum, three in sigmoid colon and four in rectum. Two of the patients with rectal carcinoma had a second cancer

TABLE 2. *Carcinomas of the Large Bowel in Association with Extensive Ulcerative Colitis According to the Length of History in the Number of Duration Years of Follow-up**

Debute ≤25 years	D_i	C_i	$\lambda = C_i/D_i$	$P_i = e^{-\lambda \cdot t}$	$Q_i = 1 - P_i$	S.D.	**P**	**Q**	S.D.
1–5 years	429	0	0.000	1.000	0.000	0.000	1.000	0.000	0.000
6–10 years	264	1	0.004	0.980	0.020	0.020	0.980	0.020	0.020
11–15 years	149	3	0.020	0.905	0.095	0.052	0.887	0.113	0.054
16–20 years	81	3	0.037	0.831	0.169	0.089	0.737	0.263	0.090
21–25 years	39	2	0.051	0.775	0.225	0.140	0.572	0.429	0.124

* Onset before 25 years of age.

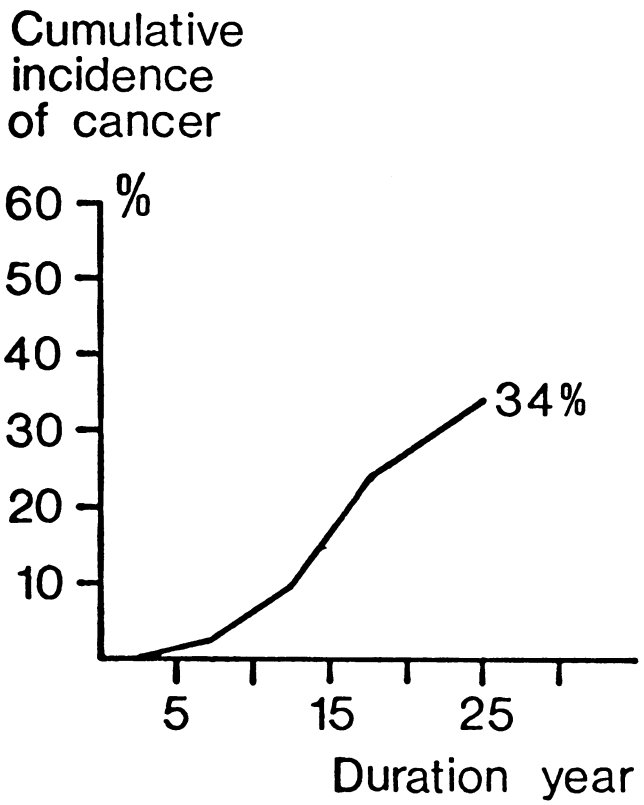

FIG. 1. Estimated cumulative probability of development of cancer in extensive ulcerative colitis.

in colon ascendens and transversum respectively. The mean age at the onset in these patients was 26 years. The duration of UC in these patients varied between seven and 44 years. The mean duration was 17 years. Five of the 15 patients were still alive in December 1975. The expected number of colorectal carcinoma in a matched reference group according to the Swedish Cancer Register is 0.49.

Table 1 shows the incidence of carcinoma in the whole group of patients. Figure 1 depicts the cumulative incidence of carcinoma in the whole group of 234 patients calculated by the actuarial material method from the data in Table 1. The cumulative incidence of developing a carcinoma 25 years after the onset of colitis symptoms was 34%. When the same calculation was performed on those patients, whose UC began before the age of 25 this figure rose to 43% (Fig. 2, Table 2). The difference in cancer incidence between the two groups after 25 years' duration was not significant.

Discussion

The results of the present study indicating that two out of five patients will eventually get a carcinoma are in accordance with those reported by deDombal[5] and Devroede et al.[6] In both these studies the incidence of carcinoma in patients suffering from extensive colitis were also studied by actuarial methods. Though the extensive colitis was carefully defined in these studies, the patients on which the result was based were not collected from a defined area but included all cases who attended the colitis clinics. Both series therefore might in fact represent a more or less selected group of patients, as compared with the present series which includes patients exclusively from the area of Göteborg. This difference is possibly the most important in explaining that the cancer incidence in these series is slightly higher than in the present investigation.

It has been suggested that the difference in incidence of carcinoma in UC might be due to geographical differences.[12] Thus, Nedbal et al.[19] reported a crude incidence of 0.5% in Czechoslovakia. Aktan et al.[1] from Turkey and Bonnevier et al.[2] from Denmark reported no large bowel carcinoma in 60 and 322 cases of UC, respectively. In the evaluation of the cancer risk none of these authors correlated the duration of the disease to the extension of the bowel involvement. As previously mentioned, it is far from satisfactory to treat

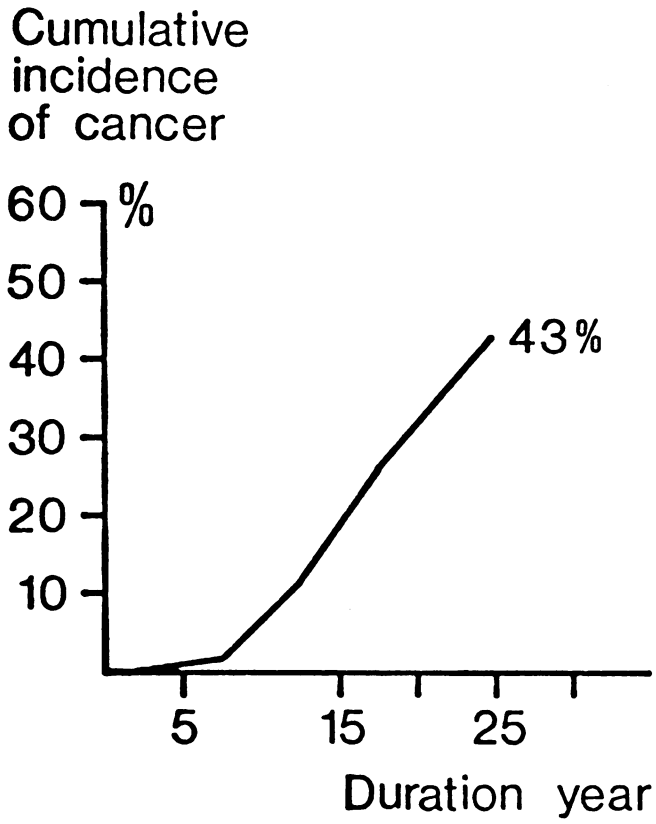

FIG. 2. Estimated cumulative probability of development of cancer in extensive ulcerative colitis. Onset before 25 years of age.

all patients with colitis of varying distribution as one big group and just calculate the crude incidence without taking into consideration the individual duration of the disease. A possible geographical difference in the incidence of carcinoma of the colon in UC still remains to be demonstrated.

Lennard-Jones et al.[16] are of the opinion that patients with quiescent extensive colitis can be managed conservatively provided that close and regular supervision can be guaranteed to the patient. This means life-long follow-up twice a year with sigmoideoscopy and rectal mucosal biopsy and a barium enema or colonoscopy if clinically indicated. They do not define this indication. If close follow-up is prevented by circumstances, they recommend elective surgery with proctocolectomy as the safest course. With a mean length of follow-up of 3.3 years they have found three patients with carcinoma of the large bowel, all alive seven, six and two years respectively after surgery. In these three cases epithelial dysplasia was observed on rectal mucosal biopsy. The future outcome of this interesting prospective investigation of patients with long-standing extensive UC will be most important. However, there seems to be accumulating evidence that rectal biopsy for precancer in ulcerative colitis is not 100% reliable.[9] In a recent group of patients with extensive UC referred to this hospital from other parts of Sweden, ten patients had the full picture of epithelial dysplasia in rectal biopsies. All these patients underwent proctocolectomy and in three of them a carcinoma was found. Another patient with carcinoma of the large bowel and UC had a negative rectal biopsy. The full picture of precancer in the rectal biopsy is to our mind an absolute indication for proctocolectomy. However, as a negative biopsy does not exclude a large bowel carcinoma, epithelial dysplasia in the rectal biopsy can so far not be regarded as the exclusive indication for surgery. Furthermore, examination of the large bowel by barium enema has in two of our cancer cases been disappointing. In one patient with UC there was a normal barium enema 16 months before a carcinoma of the large bowel was found of a later barium enema, and in another patient 14 months before the cancer was discovered. We therefore agree with the Leeds-group[5] that despite most careful follow-up of the patients, detection of a carcinoma cannot be guaranteed in patients with long-standing extensive ulcerative colitis. It is possible that regular colonoscopy of these patients with simultaneous multiple biopsies can be a useful tool for the identification of those patients who are especially prone to develop a carcinoma. However, this will only be possible in certain centres with an organized follow-up system, with a well-trained colonoscopist and with a pathologist, who is interested and skilled in interpreting large bowel biopsies. With the present-day level of knowledge, we believe that elective surgery for patients with extensive colitis of 10–15 years duration shall be carefully considered providing that the diagnosis of UC is clearly established.

The low incidence of carcinoma in the Danish series[2] was explained as a probable result of an active approach in the treatment of extensive colitis. A large number of their patients, who suffered from colitis in the entire colon as well as the majority of the patients showing a chronic continuous course of the disease were operated upon. They had no carcinoma of the large bowel in the whole material, which might be the result of a high frequency of proctocolectomy. A similar approach has been used in our hospital during the last few years. During the last five years we have had two carcinomas among the patients from the city of Göteborg. One patient presented with an ileus due to a carcinoma of the large bowel. As he was in excellent general health he had not been seen by a physician for 19 years. This patient illustrates the necessity of having complete control of *all* patients with UC. The responsibility for this control must lay with the physician. The other patient was operated upon with proctocolectomy due to a precancerous lesion in the rectal biopsy. A small carcinoma was found in the specimen. This cancer was not seen at a large bowel enema one and one-half months before surgery.

Life with an ileostomy is not so frightening that these patients should be exposed to a type of Russian roulette with about a 35% chance of getting a carcinoma after 25 years' duration of the disease. If the patient is provided with a continent ileostomy an active surgical approach to this group of patients seems to us even more justified as the quality of life for these patients is most encouraging.[15]

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References

1. Aktan, H., Paykoc, Z. and Ertan, A.: Ulcerative Colitis in Turkey. Clinical Review of Sixty Cases. Dis. Colon Rectum, 13:62, 1970.
2. Bonnevie, O., Binder, V., Anthonisen, P. et al.: The Prognosis of Ulcerative Colitis. Scand. J. Gastroenterol. 9:81, 1974.
3. Chiang, C. L.: Introduction to Stochastic Processes in Biostatistics. John Wiley & Sons, New York, 1968.
4. Cook, M. G., Path, M. R. C. and Goligher, J. C.: Carcinoma and Epithelial Dysplasia Complicating Ulcerative Colitis. Gastroenterology, 68:1127, 1975.

5. deDombal, F. T., Watts, JMcK, Watkinson, G. et al.: Local Complications of Ulcerative Colitis: Stricture, Pseudopolyposis and Carcinoma of Colon and Rectum. Br. Med. J., 1:1442, 1966.
6. Devroede, G. J., Taylor, W. F., Sauer, W. G. et al.: Cancer Risk and Life Expectancy of Children with Ulcerative Colitis. N. Engl. J. Med., 285:17, 1971.
7. Devroede, G. J. and Taylor, W. F.: On Calculating Cancer Risk and Survival of Ulcerative Colitis Patients with the Life Table Method. Gastroenterology, 71:505, 1976.
8. Edwards, F. C. and Truelove, S. C.: The Course and Prognosis of Ulcerative Colitis. IV Carcinoma of the Colon. Gut, 5:15, 1964.
9. Evans, D. J. and Pollock, D. J.: In situ and Invasive Carcinoma of the Colon in Patients with Ulcerative Colitis. Gut, 13:566, 1972.
10. Farmer, R. G., Hawk, W. A. and Turnbull Jr., R. B.: Carcinoma Associated with Mucosal Ulcerative Colitis and with Transmural Colitis and Enteritis. (Crohn's disease) Cancer, 28:289, 1971.
11. Gilat, T., Zemishlany, Z., Ribak, J. et al.: Ulcerative Colitis in the Jewish Population of Tel-Aviv Yafo. II: The Rarity of Malignant Degeneration. Gastroenterology, 67:933, 1974.
12. Gilat, T.: Geographical Differences in Diagnosis or in Clinical Course of Ulcerative Colitis? Correspondence-Replay of the Authors. Gastroenterology, 71:177, 1976.
13. Hinton, J. M.: Risk of Malignant Change in Ulcerative Colitis. Gut, 7:427, 1966.
14. Hultén, L., Kewenter, J. and Åhrén, C.: Precancer and Carcinoma in Chronic Ulcerative Colitis. A Histopathological and Clinical Investigation. Scand. J. Gastroenterol., 7:663, 1972.
15. Kock, N. G., Darle, N., Kewenter, J. et al.: The Quality of Life After Proctocolectomy and Ileostomy: A Study of Patients with Conventional Ileostomies Converted to Continent Ileostomies. Dis. Colon. Rectum, 17:287, 1974.
16. Lennard-Jones, J. E., Misiewicz, J. J., Parrish, J. A. et al.: Prospective Study of Outpatients with Extensive Colitis. Lancet, 1:1065, 1974.
17. Morson, B.: Crohn's Disease. Precancerous Changes in Colitis. Dis. Colon Rectum, 18:207, 1975.
18. MacDougall, I. P. M.: The Cancer Risk in Ulcerative Colitis. Lancet, 2:655, 1964.
19. Nedbal, J. and Maratka, Z.: Ulcerative Proctocolitis in Czechoslovakia. Am. J. Proct., 19:106, 1968.

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