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Malignancy in Crohn's disease

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SUMMARY Cancer morbidity has been evaluated in a series of 513 patients with Crohn's disease under long-term review between 1944–76. In comparison with morbidity rates for cancer in the West Midlands Region (the geographical area from which these patients were drawn) the 31 tumours that occurred represented a relative risk of 1·7 ($P < 0·01$) of cancer at all sites. For tumours at sites within the digestive system the relative risk was 3·3 ($P < 0·001$). A significant excess of tumours was found in both the upper ($P < 0·01$) and lower ($P < 0·001$) gastrointestinal tract. There was no excess of tumours at any site outside the digestive system.

The first reported case of cancer of the large intestine occurring in Crohn's disease was described by Warren and Sommers,[1] while Ginzburg and his colleagues[2] first drew attention to carcinoma of the small intestine complicating Crohn's disease.

Individual reports of cancer in Crohn's disease have been summarised.[3–7] Other examples of cancer and Crohn's disease have been described elsewhere.[8–11] Keighley and his colleagues[12] described a patient with multifocal carcinoma of the large intestine and Crohn's disease who is included in the present series.

Only two long-term studies have attempted to assess the risk of cancer complicating Crohn's disease using statistical techniques.[13 14] Weedon and his colleagues[13] identified 449 patients registered at the Mayo Clinic between 1919 and 1965 whose symptoms of Crohn's disease started before they were 21 years of age. Eight cases of carcinoma of the large intestine were observed in this selected series. This was 20 times greater than the number expected in a group drawn from the general population matched for age, sex, and years at risk. No excess was observed for cancer of the small intestine.

In an earlier study from this unit[14] the cancer risk was studied in 295 patients with Crohn's disease of whom seven had developed cancer of the digestive tract. Although the number of cases of cancer was small, the observed malignancies in the gastrointestinal tract were in excess of expectation. We have reviewed these patients as part of the present study.

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Methods

COMPOSITION OF SERIES

The series comprised 513 patients (243 males and 270 females) under long-term review in the Nutritional and Intestinal Unit between 1944 and 1976. The mean interval since diagnosis of Crohn's disease was 14·5 years (total patient years 7423·8). Nine patients were lost to follow-up, six of whom had emigrated and three of whom could not be traced. Patients lost to follow-up have been included to the end of the survey period, unless their life expectancy was less than the calculated survival. All other patients were followed to death or to the end of the survey (31 December 1976). Information concerning patients not subject to long-term review was obtained through their family practitioners, relatives, or searches of the Family Practitioners Committee records, National Health Service Central Register, and the National Deaths Register.

A number of audits[15–17] have resulted in 41 patients originally classified as having ulcerative colitis being transferred to the Crohn's disease group. In this group patient years at risk have been calculated from the date of diagnosis of their inflammatory bowel disease. Four of the patients originally classified as having ulcerative colitis and subsequently transferred to the Crohn's disease group developed carcinoma of the large intestine.

We have not been able to review all the histopathology from the patients who were treated by

Table 1 *Crohn's disease: distribution of series by sex at age of onset and diagnosis*

Group	Age (yr)	% of group	
		Onset	*Diagnosis*
Male	<30	62·6	58·4
	30+	37·4	41·6
Female	<30	64·1	55·6
	30+	35·9	44·4
Total	<30	63·3	57·0
	30+	36·7	43·0

panproctocolectomy for ulcerative colitis during the early years of the review, so that a few patients with Crohn's disease could still remain in that group. We have examined the histopathology in all patients with ulcerative colitis and Crohn's disease who developed cancer to ensure that they were categorised correctly. We have excluded one patient with Crohn's colitis from the cancer study who developed a carcinoma in a rectal polyp because there was no evidence of extension beyond the stalk. The age and sex distribution among the patients studied is summarised in Table 1 and the Figure.

STATISTICAL METHODS

As the majority of patients in this series were resident in the West Midlands Region for the duration of their illness, the cancer incidence rates for the region have been used to assess the level of the risk of cancer. Age-specific incidence rates for 52 anatomical sites in males and 53 in females were computed from notifications recorded by the Birmingham Cancer Registry for the mid-point of the study between the years 1960 to 1962 inclusive, together with the Registrar General's Census Population figures for the Region which were centred on 1961.

The survival experienced by the series was expressed as patient-years at risk grouped by sex, age at diagnosis, and interval from diagnosis. By applying the appropriate age- and sex-specific incidence rates to the patient-years at risk, the number of tumours that might be expected to occur in this series was computed. The corresponding observed number of tumours was ascertained from the clinical records of the patients with Crohn's disease corroborated by scanning the Registry files. All but three of the patients with cancer were diagnosed in this unit.

The Poisson distribution was used to test the significance of the differences between observed and expected numbers by calculating the probability of the observed number or more occurring by chance.

The analysis was carried out initially for the series as a whole and then for the group of patients with extensive colitis (disease extending proximally at least as far as the hepatic flexure). Finally, an adjustment was made to exclude years at risk among those patients who had undergone panproctocolectomy in whom the risk of developing cancer of the large intestine and rectum had been eliminated. A similar adjustment was made for those patients treated by colectomy and ileorectal

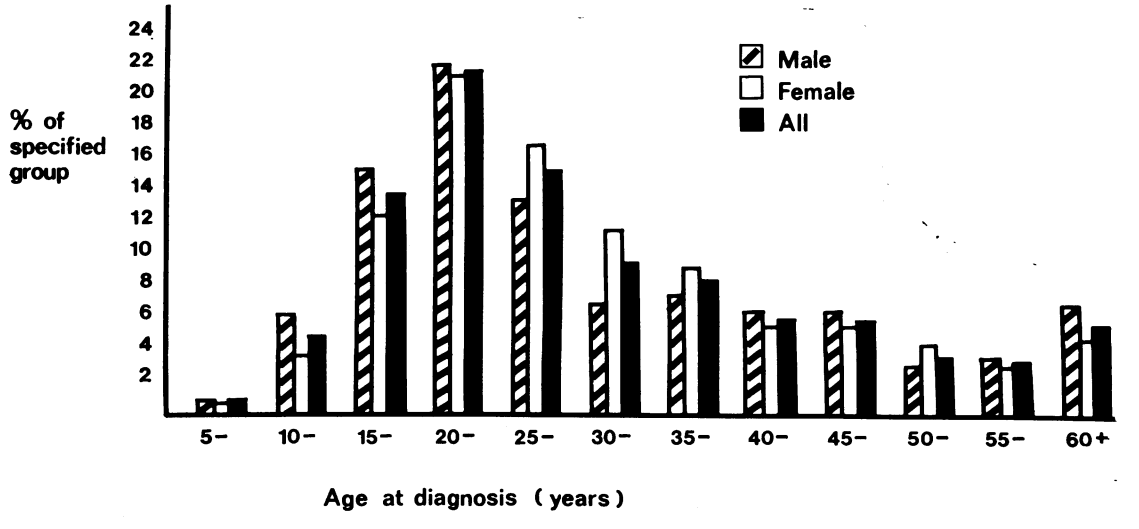

Figure *Age at diagnosis of Crohn's disease.*

Table 2 *Crohn's disease: site of disease (maximum involvement)*

Site	Cases (No.)	(%)
Stomach/duodenum	8	1·6
Distal ileum	63	12·3
Diffuse small bowel	26	5·1
Ileum + right colon	168	32·7
Ileum + extensive colon	105	20·5
Left colon	25	4·9
Right colon	14	2·7
Extensive colon	69	13·5
Other/multiple	35	6·8
Total	513	

anastomosis where the risk of developing carcinoma of the large intestine had been eliminated and the risk of developing carcinoma of the rectum remained.

Results

In this series of patients with Crohn's disease the mean age at onset of symptoms was 29·3 years with a mean duration of symptoms of 2·5 years before diagnosis. The modal age-group at diagnosis was 20–24 years for both males and females (Figure). The distribution of the maximum extent of disease is shown in Table 2. Nearly half the patients (45%) had involvement of the ileum with or without extension into the right colon, while a third had extensive involvement of the colon with or without distal ileal involvement (34%). During the period of review the cancer risk in the large intestine and rectum was eliminated by panproctocolectomy in 17·3% of patients and eliminated in the large intestine after colectomy and ileorectal anastomosis in 9·4%.

CANCER MORBIDITY

All sites

Up to the termination date of the survey (31 December 1976), 31 tumours were diagnosed in the series. These were significantly in excess ($P<0·01$) of the 18·7 tumours that might have been expected to occur during the period. Table 3 shows the distribution of tumours by anatomical systems. In males and females there was a significant excess in the digestive system as a whole.

The remaining observed numbers for all other systems were not significantly different from their expectations.

Digestive tract

In this context 'the tract' has been taken as comprising buccal cavity, throat, oesophagus, small

Table 3 *Crohn's disease: cancer morbidity—513 patients*

Site	Males E	Males O	Males P	Females E	Females O	Females P	Total E	Total O	Total P
All sites	9·46	17	*	9·21	14	—	18·67	31	†
Buccal cavity and throat	0·33	2	*	0·19	0	—	0·52	2	—
Digestive system	2·74	7	*	2·02	8	†	4·76	15	‡
Respiratory system	2·99	3	—	0·42	0	—	3·41	3	—
Breast	0·02	0	—	2·60	4	—	2·62	4	—
Reproductive system	0·72	2	—	1·92	2	—	2·64	4	—
Urinary system	0·52	0	—	0·17	0	—	0·69	0	—
Reticuloendothelial system	0·51	1	—	0·41	0	—	0·92	1	—
Skin	0·96	2	—	0·82	0	—	1·78	2	—
Remainder	0·69	0	—	0·67	0	—	1·36	0	—

E: expected number. O: observed number. P: probability. *$P<0·05$. †$P<0·01$. ‡$P<0·001$.

Table 4 *Crohn's disease: cancer morbidity—digestive system (513 patients)*

Site	Males E	Males O	Males P	Females E	Females O	Females P	Total E	Total O	Total P
All sites	9·46	17	*	9·21	14	—	18·67	31	†
Digestive system	3·13	10	†	2·26	8	†	5·39	18	‡
Upper tract	1·61	4	—	0·92	4	*	2·53	8	†
Lower tract	1·81	5	†	1·08	4	*	2·26	9	‡
Remainder—digestive system	0·34	1	—	0·26	0	—	0·60	1	—
Remainder—other sites	6·33	7	—	6·95	6	—	13·28	13	—

Upper: Buccal cavity, throat, oesophagus to distal ileum. Lower: Colon, rectum and all reticulum cell sarcomas. Remainder—digestive system: Liver, gall bladder, pancreas, appendix. O: number of cancers observed in each group. E: expected number of cancers in matched population.

and large intestine together with liver, gall bladder, and pancreas. The reticuloendothelial tumour, arising from the caecum, has also been included and is represented in the following analysis together with an expected number of reticulum-cell sarcomas at *any* site.

The excess of tumours of the tract (as defined above) was highly significant ($P<0.001$), while the observed number at remaining sites was very close to the expected number (Table 4).

The upper ($P<0.01$) and the lower tract ($P<0.001$) were at increased risk, the 'remainder' in the digestive system being one tumour of the pancreas (Table 4).

Upper tract

The significance of the excess of tumours in the upper tract ($P<0.01$) was due mainly to tumours of the stomach and oesophagus in females and in part to tumours of buccal cavity, throat, and small intestine in males.

Lower tract

Nine tumours were observed in the large intestine, which represented a highly significant excess ($P<0.001$) and a four-fold relative risk (Table 5). Adjustment of the patient-years at risk taking into account resections of the colon and rectum increased the relative risk to 4·3. The relative risk almost doubled when the analysis was restricted to patients with extensive colonic disease. The observed numbers of large bowel tumours was not significantly in excess of the expected number in patients without extensive colonic disease (shown as 'other' in Table 5).

The clinical details of patients with Crohn's disease who developed tumours of the gastrointestinal tract are summarised in Table 6.

Table 5 *Crohn's disease: cancer morbidity with particular reference to large intestine**

Patients	*Patient-years at risk*	*E*	*O*	*O/E*	*P*
Whole series (N=513)	All	2·26	9	4·0	‡
	Adjusted for colectomy/PPC	2·07	9	4·3	‡
'Extensive colonic involvement' (N=174)	All	0·39	5	12·8	‡
	Adjusted for colectomy/PPC	0·21	5	23·8	‡
Other	All	1·87	4	2·1	

*The cancer risk in patients with Crohn's disease is shown for the whole series and for those patients with extensive colitis and others separately. The patient-years at risk are shown for all patients in each group and adjusted for patients who have been treated by colectomy/PPC. The expected number of cancers in the matched population (E) are compared with the number of cancers observed in each group and the significance of ratio (O/E) is shown in the final column.
PPC: panproctocolectomy.

Discussion

This study has shown a statistically significant association between Crohn's disease and cancer of the upper and lower digestive tract. The significant increase in cancer of the upper tract was predominantly due to cancer of the oesophagus and stomach. We have been unable to confirm the earlier suggestion that there may be an increased cancer risk in the pancreas and small intestine.[11] The cancers in the upper tract, with one exception, arose remote from the site of macroscopic Crohn's disease.

The tumours of the large intestine usually occurred in the presence of extensive colonic Crohn's disease (six of nine patients) and at the site of macroscopic disease (seven of nine patients). There was histological but no macroscopic evidence of Crohn's disease at the site of cancer in one other patient (Table 6).

The cancer risk in Crohn's disease is not restricted to patients with early onset of their disease.[13] In this series all but two of the patients who subsequently developed cancer were more than 21 years of age when they first developed symptoms of Crohn's disease.

With one exception there was a long interval between the symptoms of Crohn's disease and the development of cancer of the digestive tract. We have not encountered examples of Crohn's disease and adenocarcinoma of the large intestine occurring concurrently which have been reported from Oxford.[18]

Greenstein *et al.*[7] drew attention to the frequency with which cancer and Crohn's disease occurs in bypassed intestinal loops. We have only two such examples in this series, probably because the surgical policy has been one of resection. Among the patients reported by Greenstein *et al.*[7] one group developed carcinoma many years after intestinal bypass (20 to 33 years) while the others developed carcinoma shortly after a bypass procedure (one to two years). In both groups there was a long interval between the initial symptoms of their Crohn's disease and the development of cancer irrespective of the timing of the bypass procedure. These results suggest that the duration of disease is probably a more important factor in pathogenesis than the creation of the bypassed intestinal loop itself.

The major risk of developing carcinoma of the large intestine is confined to patients with extensive long-standing colitis.[5–7] Even in this large series there are only 32 patients with extensive Crohn's colitis and an intact colon more than 10 years

Table 6 *Clinical details of patients with Crohn's disease and cancer*

No.	*Sex*	*Crohn's disease*		*Interval of symptoms to diagnosis of carcinoma (yr)*	*Maximum extent of Crohn's disease*	*Site of carcinoma*	*Histology*	*Age at death (yr)*	*Death related to carcinoma*	*Interval from diagnosis of carcinoma to death (yr)*
		Age at onset of symptoms (yr)	*Age at diagnosis (yr)*							
1	M	65	65	8	L colon	Fauces	Epithelioma	Alive	—	—
2	M	25	27	15	Total colon	Parotid	Mixed salivary adenocarcinoma	Alive	—	—
3	F	30	33	14	Distal ileum + R colon	Oesophagus (1)	Carcinoma	45	Yes	<1
4	M	53	61	13	R colon	Stomach (2)	Adenocarcinoma	67	Yes	1
5	F	48	52	24	Distal ileum + R colon	Stomach	Adenocarcinoma	75	Yes	2
6	F	27	54	44	Distal ileum	Stomach	Linitis plastica	71	Yes	<1
7	F	51	52	11	Distal ileum	Stomach	Adenocarcinoma	65	Yes	2
8	M	24	24	32	Diffuse small bowel	Pancreas	Adenocarcinoma	57	No	—
9	M	13	16	11	Diffuse small bowel	Small bowel	Adenocarcinoma	24	Yes	<1
10	F	44	44	8	Total colon	Colon + corpus uteri	Adenocarcinoma	55	Yes	3
11	M	19	19	22	Total colon	Colon	Adenocarcinoma	44	Yes	3
12	F	35	36	17	Distal ileum + R colon	Colon + ovary	Adenocarcinoma	56*	Yes	4
13	M	53	55	13	Ileum + Total colon	Colon—multiple	Adenocarcinoma	67	Yes	1
14	M	33	33	9	Total colon	Colon	Adenocarcinoma	43	Yes	<1
15	F	29	29	25	Total colon	Colon—multiple	Adenocarcinoma	Alive	—	—
16	M	31	44	31	Total colon	Colon	Adenocarcinoma	Alive	—	—
17	F	30	34	36	Distal ileum + R colon	Anal canal	Adenocarcinoma	68*	No	—
18	M	55	56	1	Distal ileum + R colon	Caecum (3)	Reticulum cell sarcoma	74	No	—

(1) Classified originally [14] as carcinoma of the pancreas.
(2) Classified originally as carcinoma of the gastro-oesophageal junction.[14]
(3) Primary arose from the caecum rather than the distal ileum [14] and reclassified as arising from the large intestine.
One cancer (case 112) [14] has not been included in this series, for we have no definite histological evidence of a carcinoma of the pancreas.
*Died after close of study (31 December 1976).

after the onset of tneir symptoms. These patients can readily be kept under close surveillance. Carcinoma of the large intestine complicating Crohn's disease tends to occur more frequently in the proximal colon when compared with the distribution in the general population,[5] so that colonoscopy may have a part to play in its early detection.

At the end of the survey only five of the nine patients developing cancer of the large intestine had died, but by December 1979 only two were still alive (two and eight years later). Four of them died from metastatic disease at intervals of one to four years after resection. One patient died in the postoperative period after resection and two others died of incidental causes nine and 18 years later (Table 6).

We found no excess deaths from cancer outside the digestive tract and the cancer risks at all other sites were closely similar to those expected in the general population.

One patient was diagnosed concurrently as having Crohn's disease and a reticulum cell sarcoma of the caecum. The timing and histological nature of the tumour were unlike any of the other cases that we have observed in this series.

The expectation of developing cancer is based on the incidence rates for the general population. It could be argued that in this clinical series under careful surveillance the cancers may have been diagnosed relatively earlier than in the general population. Earlier diagnosis could lead in itself to an apparent excess of tumours. However, this suggestion seems unlikely, for all but two of the patients presented with symptoms related to the cancer which would have merited further investigation for someone in the general population just as much as for a patient in our study.

We conclude that there is an association between Crohn's disease and cancer of the gastrointestinal tract. The whole tract may be at increased risk and the risk is not confined to areas of macroscopic Crohn's disease. The absolute numbers of patients developing cancer remains small, though since this study closed we have observed two further cancers in the upper digestive tract and three in the large intestine among patients in this series.

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References

[1]Warren S, Sommers SC. Cicatrizing enteritis (regional ileitis) as a pathologic entity. *Am J Pathol* 1948; **24:** 475–501.

[2]Ginzburg L, Schneider KM, Dreizin DH, Levinson C. Carcinoma of the jejunum occurring in a case of regional enteritis. *Surgery* 1956; **39:** 347–51.

[3]Nesbit RR Jr, Elbadawi NA, Morton JH, Cooper RA Jr. Carcinoma of the small bowel. A complication of regional enteritis. *Cancer* 1976; **37:** 2948–59.

[4]Valdes-Dapena A, Rudolph I, Hidayat A, Roth JLA, Laucks RB. Adenocarcinoma of the small bowel in association with regional enteritis. Four new cases. *Cancer* 1976; **37:** 2938–47.

[5]Darke SG, Parks AG, Grogono JL, Pollock DJ. Adenocarcinoma and Crohn's disease. A report of 2 cases and analysis of the literature. *Br J Surg* 1973; **60:** 169–75.

[6]Lightdale CJ, Sternberg SS, Posner G, Sherlock P. Carcinoma complicating Crohn's disease. Report of seven cases and review of the literature. *Am J Med* 1975; **59:** 262–8.

[7]Greenstein AJ, Sachar D, Pucillo A, *et al.* Cancer in Crohn's disease after diversionary surgery. *Am J Surg* 1978; **135:** 86–90.

[8]Savage RA, Farmer RG, Hawk WA. Carcinoma of the small intestine associated with transmural ileitis (Crohn's disease). *Am J Clin Pathol* 1975; **63:** 168–78.

[9]Gude HE. Carcinoma of the ileum in regional ileitis. *J Iowa Med Soc* 1977; **67:** 324–5.

[10]Burbidge EJ, Bedine MS, Handelsman JC. Adenocarcinoma of the small intestine in Crohn's disease involving the small bowel. *Western J Med* 1977; **127:** 43–5.

[11]Lee GB, Smith PM, Seal RME. Lymphosarcoma in Crohn's disease. Report of a case. *Dis Colon Rectum* 1977; **20:** 351–4.

[12]Keighley MRB, Thompson H, Alexander-Williams, J. Multifocal colonic carcinoma and Crohn's disease. *Surgery* 1975; **78:** 534–7.

[13]Weedon DD, Shorter RG, Ilstrup DM, Huizenga KA, Taylor WF. Crohn's disease and Cancer. *N Engl J Med* 1973; **289:** 1099–103.

[14]Fielding JF, Prior P, Waterhouse JA, Cooke WT. Malignancy in Crohn's disease. *Scand J Gastroenterol* 1972; **7:** 3–7.

[15]Daly DW. The outcome of surgery for ulcerative colitis. *Ann R Coll Surg Engl* 1968; **42:** 38–57.

[16]Eade MN, Cooke WT, Brooke BN. Liver disease in ulcerative colitis. 2. The long-term effect of colectomy. *Ann Intern Med* 1970; **72** 489–97.

[17]Allan R, Steinberg DM, Alexander-Williams J, Cooke WT. Crohn's disease involving the colon. An audit of clinical management. *Gastroenterology* 1977; **73:** 723–32.

[18]Perrett AD, Truelove SC, Massarella GR. Crohn's disease and carcinoma of the colon. *Br Med J* 1968; **2:** 466–8.