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EPIDEMIOLOGY

Increased risk of large-bowel cancer in Crohn's disease with colonic involvement

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A cohort of 1655 patients with Crohn's disease diagnosed during 1983 in the Uppsala health care region, Sweden, was followed up with respect to the occurrence of colorectal cancer to the end of 1984. 12 colorectal cancers were diagnosed, yielding an increased overall risk of 2·5. The relative risk was similar for males and females. Duration of follow-up did not affect risk. Relative risk for disease of the terminal ileum only was 1·0; for terminal ileum and parts of colon 3·2; and for colon alone 5·6. Patients in whom Crohn's disease was diagnosed before age 30 with any colonic involvement at diagnosis had a higher relative risk (20·9) than those diagnosed at older ages (2·2).

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Introduction

Until the late 1960s Crohn's disease was not thought to be associated with colorectal cancer; only 15 cases of such an association had been described in the world literature.[1] Since then three studies[2-4] have described an increased risk of colorectal cancer among patients with Crohn's disease. One[4] showed a younger mean age at diagnosis of colorectal cancer among Crohn's disease patients than among patients from the general population. Several other studies, however, have found no association between Crohn's disease and large-bowel cancer.[6-9] The risk of colorectal cancer in patients with Crohn's disease thus remains uncertain.[10]

To provide more accurate risk estimates, we investigated a population-based cohort consisting of all 1656 patients with a diagnosis of Crohn's disease up to 1983 in a strictly defined area in Sweden. We gathered information on extent of disease at diagnosis, age at diagnosis, and surgical procedures (eg, proctocolectomy) carried out during the follow-up period. We obtained virtually complete follow-up to the end of 1984, corresponding to an observation time of 1–60 years from diagnosis.

Subjects and methods

The cohort

The area chosen for study was the Uppsala health care region, which had 1·2 million inhabitants in 1965 and 1·3 million in 1983. Information about patients admitted to hospital from 1965 to 1983 was extracted from the National Board of Health and Welfare inpatient register, which recorded dates of admission and discharge and details of diagnoses and surgical procedures.

From the inpatient register we selected all patients given a discharge diagnosis compatible with Crohn's disease, by using a Swedish adaptation of ICD-7 codes 572·00, 572·09, 572·11, 572·20, and 572·21 for the period 1965–68 and of ICD-8 codes 561·04, 562·10, 563·00, 563·10, 563·99, 564·10, and 569·02 for the period 1969–83. To identify all patients with a histopathological diagnosis of Crohn's disease treated as outpatients or inpatients we also reviewed the records at the departments of clinical pathology in the region. Any patient in whom the histopathological examination of surgically removed tissues, biopsy specimens, or necropsy specimens aroused a suspicion of Crohn's disease was identified. The individual charts were retrieved and scrutinised in order to confirm or reject the diagnosis of Crohn's disease, by use of the diagnostic criteria described by Garland et al[11] for definite and probable cases. The diagnostic criteria for probable cases were made stricter by adding the prerequisite that a laparotomy report without a positive histopathological examination had to be followed by radiological confirmation.

1469 patients with Crohn's disease diagnosed in the period 1965–83 were identified (incident cases). 187 patients with Crohn's

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TABLE I—NO OF PATIENTS IN THE COHORT BY AGE AT DIAGNOSIS, EXTENT OF DISEASE, AND PERIOD OF DIAGNOSIS

Age at diagnosis	Period of diagnosis		Extent of disease				
	Before 1965	1965–83	Terminal ileum	Terminal ileum and parts of colon	Colon	Other	Total
<30 yr	120	844	343	279	239	103	964
≥30 yr	66	625	272	146	166	107	691
Total	186	1469	615	425	405	210	1655

disease diagnosed before 1965 and resident in the region on Jan 1, 1965, were also identified (prevalent cases); none had a diagnosis of colorectal cancer, but all had had at least one consultation for Crohn's disease after Dec 31, 1964. Information was inadequate in 1 case, and the remaining 1655 patients (859 females and 796 males) were included in the study. The composition of the study population is shown in table I.

The patients were assigned to one of four groups according to the extent of the disease at diagnosis: (1) disease confined to terminal ileum; (2) disease confined to terminal ileum and part of the colon; (3) disease confined to the colon; and (4) other involvement (eg, proximal to the terminal ileum with or without involvement of terminal ileum and colon). The 830 patients in groups 2 and 3 were analysed together.

Follow-up

Numbers of operations for removal of the large bowel, cases of colorectal cancer, and deaths were determined from the Swedish national record linkage system. Patients who had undergone a proctocolectomy, a colectomy, or rectal amputation in 1965–83 were identified from the inpatient register. Cases of colorectal cancer were also identified from a second source, the Swedish Cancer Registry, and deaths from the Registry of Causes of Death.

Statistical analysis

The computation of the number of person-years at risk for colorectal cancer started at the time of diagnosis of Crohn's disease or in 1958, the first year of follow-up in the Cancer Registry, for patients in whom the disease was diagnosed earlier. Each subject was followed to date of diagnosis of either malignancy (Cancer Registry), date of death (Registry of Causes of Death), date of operation, or the closing date of the study. Patients who had undergone a colectomy leaving the rectum intact were excluded from the calculation of person-years at risk for colon cancer but were included in the computation of number of person-years at risk for rectal cancer. The reverse procedure was used for patients who had undergone only rectal amputation and was thus still at risk for colon cancer.

TABLE II—STANDARDISED INCIDENCE RATIO (SIR) OF COLORECTAL CANCER IN CROHN'S DISEASE BY SEX AND EXTENT OF DISEASE AT DIAGNOSIS, AGE AT DIAGNOSIS, AND DURATION OF FOLLOW-UP

Determinant	Observed cases	Person-years	SIR (95% CI)
Sex.			
Male	7	9343	2·8 (1·1–5·8)
Females	5	9581	2·1 (0·7–4·8)
Extent of disease:			
Terminal ileum	2	7346	1·0 (0·1–3·4)
Terminal ileum + part of colon	3	4949	3·2 (0·7–9·2)
Colon only	6	4360	5·6 (2·1–12·2)
Other	1	2269	1·2 (0·0–5·9)
Any colonic involvement	9	9309	4·4 (2·0–8·4)
Age at diagnosis:			
<30 yr	5	12 025	9·5 (3·1–23·2)
≥30 yr	7	6899	1·6 (0·6–3·3)
Duration of follow-up:			
<10 yr	7	12 736	2·5 (1·0–5·1)
10–19 yr	3	5177	2·0 (0·4–6·0)
≥20 yr	2	1011	3·2 (0·4–11·4)
Total	12	18 924	2·5 (1·3–4·3)

TABLE III—COHORT STUDIES OF COLORECTAL CANCER IN PATIENTS WITH CROHN'S DISEASE

Study (area)	Observed cases	Relative risk	Patients with Crohn colitis	Relative risk Crohn colitis
Weedon et al[2] 1973 (Mayo)	8	20·0 (8·6–34·4)	80%	..
Greenstein[3] et al 1981 (New York)	7	6·9 (2·8–14·2)	22% (78% ileocolitis)	..
Gyde et al[4] 1980 (Birmingham, UK)	9	4·3 (2·0–8·2)	34%	23·8
Present study	12	2·5 (1·3–4·3)	25%	5·6

Multiplication of the number of person-years at risk by the corresponding age-specific incidence rates (from the Swedish Cancer Registry) yielded the numbers of expected cases of colorectal cancer in the cohort for successive years of observation.

The standardised incidence ratio (SIR) was used as a measure of relative risk and was defined as the ratio of observed to expected numbers of cases of colon or rectal cancer. The 95% confidence interval (95% CI) was calculated on the assumption that the observed number of cases in each class followed a poisson distribution.

The cohort was analysed by gender, age at diagnosis (<30 or ≥30 years), and extent of disease at time of diagnosis. To detect any selection bias among patients in whom a diagnosis was made before 1965, they were initially analysed separately.

A standardised mortality ratio (SMR), calculated from underlying cause of death from the Registry of Causes of Death, was used to compare morbidity and mortality from colorectal cancer.

Results

Colorectal cancer was diagnosed in 12 patients during the follow-up period 1958–84, 2·5 times the expected number of 4·9 cases (95% CI 1·3–4·3). The overall SMR was 1·7 (95% CI 0·5–3·9; observed = 5 deaths, expected = 3·0). Patients in whom the disease was diagnosed before 1965 had a relative risk of 3·1 (95% CI 0·9–8·0), compared with 2·2 (95% CI 1·0–4·3) for those in whom the diagnosis was made between 1965 and 1983. Because the excess risk was similar, the two groups were merged in further analyses. There were 9 cancers of the colon (SIR = 2·9; 95% CI 1·3–5·5) and 3 cancers of the rectum (SIR = 1·6; 95% CI 0·3–4·8).

The excess risk of colorectal cancer was similar in males and females (table II). Patients with Crohn's disease confined to the terminal ileum had the expected risk of colorectal cancer, whereas those with the disease confined to the colon had a substantially increased relative risk (SIR = 5·6; 95% CI 2·1–12·2). Those less than 30 years old at diagnosis had a higher relative risk than those diagnosed at an older age. Duration of follow-up did not significantly influence the relative risk of colorectal cancer (table II).

In those with any colonic involvement, diagnosis before the age of 30 years entailed a relative risk of 20·9 (95% CI 6·8–48·7), compared with 2·2 (95% CI 0·6–5·7) in those who were 30 years or older.

Discussion

This study confirms the increased relative risk of colorectal cancer in patients with Crohn's disease. The excess risk was not significantly different between cancer of the colon and cancer of the rectum, or between males and females. Extent

of disease at diagnosis was an important determinant of this increased risk. The relative risk was 1·0 for those with disease confined to the terminal ileum at diagnosis, 3·2 for terminal ileum and parts of the colon, and 5·6 for involvement of colon only. Patients aged under 30 at diagnosis carried a substantially higher risk than those diagnosed at older ages. Those with any colonic involvement at diagnosis before age 30 had the largest relative risk (20·9). Duration of follow-up did not seem to affect the risk estimates.

Closer surveillance of patients with diagnosed Crohn's disease may have led to a higher ascertainment of colorectal cancers in the study population than in the general population, and earlier detection would be expected to reduce mortality. However, the SMR in the two groups of subjects was not significantly different.

This study may underestimate the relative risk of colorectal cancer because patients who had colectomies after moving away from the Uppsala health care region would not have been ascertained. Conversely, the person-years at risk, and therefore the expected number of cases of colorectal cancer within the cohort, would have been overestimated among those in whom the diagnosis was made before 1965 but who had unascertained colectomies. However, the impact on our risk estimates is probably small, because emigration from the region was negligible. Date of onset of symptoms might be more appropriate than date at diagnosis to calculate duration of follow-up, but reliable information of onset of the symptoms is impossible to retreive retrospectively.

The risk of colorectal cancer and Crohn's disease varies greatly (from 4·3 to 20·0) in different studies (table III) and may depend on extent of disease, age at diagnosis, and random variation. In the study from the Mayo Clinic[2] no patient was older than 21 years at diagnosis, and 80% had colonic involvement. In the Birmingham study[4] 63% of the patients were under 30 years of age at diagnosis.

Only one previous study analysed the risk of colorectal cancer in patients with Crohn's disease by age before 30 at diagnosis.[2] The relative risk of 20·0 among those younger than 30 years in that study is almost identical to our estimate of 20·9 in those with colonic involvement. In a recent study of the risk of colorectal cancer in ulcerative colitis (unpublished), we found relative risks for the age-group 15 to 29 years at diagnosis of 14·2 for left-sided colitis and 33·1 for pancolitis. The closeness of these latter risk estimates to those for Crohn's disease with any colonic involvement suggests that there is little difference between young patients with ulcerative colitis and Crohn's disease with respect to the risk of large-bowel cancer. Longer follow-up would increase the accuracy of these risk estimates.

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REVIEW ARTICLE

What is known about the prevention of congenital toxoplasmosis?

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The French programme for the prevention of congenital toxoplasmosis consists of the diagnosis and treatment with spiramycin of acute infections during pregnancy and monthly follow-up of all identified seronegative women. The major flaw is that the efficacy of spiramycin in preventing contamination of the fetus, or at least in reducing the extent of the infection, has never been evaluated in a randomised placebo-controlled clinical trial. Its evaluation would require the follow-up of children born to mothers contaminated during pregnancy for more than 6 months, a goal that is difficult to obtain in current practice. The cost of the programme depends largely on the proportion of non-immune women of childbearing age. Since the modes of contamination are known and are linked to living habits, it should be possible to reduce the risk of infection during pregnancy by adequate health education. This approach is still to be evaluated.

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In recent years, the prevention and treatment of congenital toxoplasmosis have aroused increased interest, and national prevention programmes have been envisaged by several countries, including the United States[1] and the United Kingdom.[2]

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