

Crohn's disease and cancer risk (Denmark)

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Abstract

Objectives: The large number of studies of intestinal cancer among patients with Crohn's disease have provided inconsistent risk estimates in regard to risk of both colorectal and small intestinal cancer. We investigated incidence of cancer among Crohn's disease patients in comparison with the incidence in the general population of Denmark. **Methods:** From the Danish National Registry of Patients we identified 2645 patients who had been hospitalized with Crohn's disease during 1977–1989. Cancer incidence for up to 17 years was determined in the cohort and compared to an expected number derived from national cancer incidence rates.

Results: The 15 observed cases of colorectal cancer were close to the expected number of 13.1 (SIR = 1.1; 95% CI 0.6–1.9), whereas the five cases of small intestinal cancer (three adenocarcinomas and two carcinoids) observed corresponded to an 18-fold increased risk (SIR = 17.9; 95% CI 5.8–42).

Conclusions: A potential excess of colorectal cancer among subgroups of patients with Crohn's disease was not detectable in the overall risk estimate for colorectal cancer. Only for small intestinal cancer was a significantly elevated risk found among these patients hospitalized with Crohn's disease.

Introduction

Through the years the risk of cancers of the intestinal tract has been studied intensively in patients with Crohn's disease. Nevertheless, the relationship remains unclear. Several studies show an excess of cancer of the small intestine on the basis of only few cases of cancer [1–4], while others are inconclusive [5–9] (Table 1). Some studies report a clear 2 to 20-fold risk increase in the risk of colorectal cancer among patients with Crohn's disease [2, 3, 6, 8, 10], whereas other studies report no association between Crohn's disease and colorectal cancer [1, 4, 7, 9]. It has been suggested that an increased risk of colorectal cancer may be confined to the subset of Crohn's disease patients who have extensive, longstanding colitis [11, 12]. Several extraintestinal cancer types such as squamous cell skin cancer [5], non-Hodgkin's lymphoma [13], vulvar cancer [13] and bladder cancer [1] have been found to occur more

frequently among patients with Crohn's disease compared to the general population. However, none of these cancer sites has been seen in excess in more than one study. Here, we report the findings of a study on cancer risk among 2645 patients with Crohn's disease.

Materials and methods

Patients with Crohn's disease were identified in the files of the Danish National Register of Patients (NRP). This register was established in 1977 and contains information on almost all discharges from non-psychiatric hospitals in Denmark [14]. Variables registered for each discharge include the personal identification number of the patient, date of discharge, up to 20 diagnoses and all surgical procedures performed during each hospital stay. The personal identification number, unique for each inhabitant in Denmark, ensures correct linkage of information

Table 1. Summary of results in previous studies investigating cancer incidence among patients with Crohn's disease. Includes only studies in which a relative risk of cancer was calculated. In all studies the observed number of cancer cases in the cohort was compared to an expected number in the background population or in a standard population

Author and ref.	No with Crohn's disease	Years of follow-up	Colorectal cancer		Small intestinal cancer		Other cancer sites
			Obs ¹	RR ² (95% CI)	Obs	RR (95% CI)	
Weedon <i>et al.</i> [8]	449	Mean 15.8 Max 46	8	20 ($p < 0.001$)	1	Not calculated	RR not calculated
Gyde <i>et al.</i> [6]	513	Mean 14.5 Max 33	9	4.3 ($p < 0.001$)	1	Not calculated	Extradigestive, Obs = 13, RR = 1.0, 95% CI 0.5-1.7
Greenstein <i>et al.</i> [3]	579	Mean 11 Max 43	7 ³	6.9 ($p < 0.001$)	4 ⁴	85.8 ($p < 0.001$)	Extraintestinal, Obs = 13, RR = 1.1 (NS ⁵)
Greenstein <i>et al.</i> [13]	1127 ⁶	Max 43	Not investigated		Not investigated		Extraintestinal Obs = 23, RR = 0.8 (NS). Increased risk of non-Hodgkin's lymphoma, vulvar cancer and anal cancer
Gollop <i>et al.</i> [9]	103	Median 9 Max 40	1	2.0 (0.1-11.1)	1 ⁷	Not calculated	Not investigated
Fireman <i>et al.</i> [7]	365	Max 10	1	1.14 (NS)	0	-	RR not calculated
Ekbom <i>et al.</i> [10]	1655	Max 50	12	2.5 (1.3-4.3)	Not investigated		Not investigated
Ekbom <i>et al.</i> [5]	1655 ⁸	Max 50	Not investigated		1	3.4 (0.1-18.6)	Extracolonic RR = 1.1, 95% CI 0.8-1.5. Increased risk of squamous cell skin cancer
Munkholm <i>et al.</i> [4]	373	Median 8.5 Max 25	2	1.1 (0.0-5.8)	2	50 (37-66)	Not investigated
Gillen <i>et al.</i> [2]	281 ⁹	Mean 20 Max 30	8	3.4 (1.5-6.7)	2	40 (4.5-144)	Extraintestinal, Obs = 24, RR = 1.7, 95% CI 0.7-1.7
Gillen <i>et al.</i> [23]	125 ^{9,10}	-	8	18.2 (7.8-35.8)	Not investigated		Not investigated
Persson <i>et al.</i> [1]	1251	Max 35	5	0.9 (0.3-2.1)	4	15.6 (4.3-40.1)	Extraintestinal, Obs = 60, RR = 1.1, 95% CI 0.9-1.4. Increased risk of bladder cancer

¹ Number of observed cancers.

² Relative risk.

³ Cases found among patients with Crohn's colitis or ileocolitis.

⁴ Cases found among patients with regional colitis and ileocolitis.

⁵ Not significant.

⁶ Update of cohort in Greenstein *et al.* [3].

⁷ Leiomyosarcoma.

⁸ Same cohort as in Ekbom *et al.* [10].

⁹ Cohorts are partly overlapping with cohort in Gyde *et al.* [6].

¹⁰ Subcohort of cohort in Gillen *et al.* [2].

in different registers and also gives sex and date of birth of the individual. Discharge diagnoses are coded according to a Danish version of ICD-8 [15] and surgical procedures according to a Danish classification [16].

All patients with ICD-8 code 563.01 for Crohn's disease registered during 1977-1989 were extracted from the NRP, and for each of these 3360 patients all other hospitalizations before and after the index hospitalization were also obtained from the register. The hospitalization history was used to exclude 89 persons with an additional diagnosis of proctitis (ICD-8 = 569.04) and seven persons with polyposis coli (ICD-8 = 211.36). The patients were then linked to the Central Population Register in order to exclude individuals with an invalid

identification number ($n = 41$) and to obtain information on dates of death and emigration. There were 126 patients who died or emigrated within the year following the discharge with Crohn's disease; thus we ended up with 3097 persons who could be followed for more than 1 year. Of these patients, 2645 had the five-digit code for Crohn's disease (ICD-8 = 563.01) and no code for ulcerative colitis (ICD-8 = 563.19). For this group the Crohn's disease code has been shown earlier to be appropriate for identification of Crohn's patients from the NRP, since the completeness for the code was 94% and the validity was 97% [17].

The follow-up for cancer started 1 year after the first hospitalization for Crohn's disease and continued until

date of death, emigration or 31 December 1993. An additional exit date was applied, when risk of colon and rectum cancer was investigated. Accordingly, follow-up for colon cancer was discontinued at date of total colectomy (operation-code = 4506 [16]) or proctocolectomy (4508); for rectum cancer follow-up was discontinued at proctocolectomy or rectal amputation (4586, 4588). Cancer occurrence during follow-up was ascertained by linkage to the Danish Cancer Registry, which has recorded cancer incidence nationwide in Denmark since 1943. The Registry includes all malignant tumors and benign tumors of the nervous system and papillomas of the urinary tract [18]. The information from the Registry on small intestinal tumors observed during follow-up was supplemented by information from medical records, also including additional details on Crohn's disease for these cases.

The observed number of cancers in the cohort was compared to the expected number calculated from accumulated person-years and national cancer incidence rates for each sex and in 5-year age groups and calendar time periods. The standardized incidence ratio (SIR), *i.e.* the observed number of cancers divided by the expected number, was computed for all cancers and for individual cancer types with corresponding 95% confidence intervals based on the assumption that the observed number of cancer cases in a specific category follows a Poisson distribution. Exact confidence limits were calculated when the observed number was less than 10; otherwise Byar's approximation was used [19].

Results

The cohort of 2645 patients with Crohn's disease consisted of equal proportions of men and women. There were 987 (37%) persons under the age of 30 years at the first hospitalization with Crohn's disease. During the follow-up period of 1–17 years, 22,875 person-years were accumulated, yielding a mean follow-up period of 9.6 years from discharge with Crohn's disease. Of the entire cohort, 1187 (45%) patients were followed for 10 or more years. In the follow-up for colon cancer and rectum cancer, 21,335 and 21,929 person-years were accrued, respectively, so censoring observation time subsequent to surgical removal of colon or rectum reduced the total number of person-years by 4% and 7%.

A total of 143 cancers was observed among Crohn's disease patients during follow-up against 123.8 expected, which results in a slightly increased risk (SIR = 1.16; 95% CI 0.97–1.36) (Table 2). The risk of cancer of the gastrointestinal tract was slightly increased, mainly due

to an excess of small intestinal cancer (SIR = 17.9; 95% CI 5.8–42), while there was no excess of colorectal cancer (SIR = 1.1; 95% CI 0.6–1.9) on the basis of 15 observed cases. There was no significant excess of any extraintestinal cancer. The risk of breast cancer was borderline significantly reduced (SIR = 0.6; 95% CI 0.3–1.0).

Among five observed cases of cancer in the small intestine, there were three adenocarcinomas and two carcinoids (Table 3). The adenocarcinomas occurred in two women and one man. Both women had a second adenocarcinoma in the gastrointestinal tract – one in rectum (case 1) and one in cecum (case 2) – in addition to the adenocarcinoma confined to the small intestine. The age at diagnosis of the adenocarcinoma ranged from 37 to 75 years, and length from diagnosis of Crohn's disease to cancer ranged from 10 to 42 years, although length from hospitalization with Crohn's disease to cancer was much shorter (range 1.5–6 years) (Table 3). The two malignant carcinoid tumors were found in a 70-year-old woman and in a 65-year-old man. In the male patient the primary carcinoid tumor was never found, but metastases in lymph nodes of the mesenterium were incidentally found during surgery for Crohn's disease. The female patient also had lymph node metastases when the carcinoid tumor was diagnosed, but no further details on the diagnosis of the carcinoid tumor were available for this patient.

Discussion

Cancer of the small intestine was found in excess in our cohort of patients with Crohn's disease. Cancers of the small intestine occur very rarely in the general population, so even the few cases observed in the present and previous studies of Crohn's disease are enough to produce risk estimates of 16–86 [1–4], while studies with no case or one case cannot be considered as proof of no excess, but rather as inconclusive [5–9] (Table 1). Most of the positive studies provide no information on the type of small intestinal cancer. We found two malignant carcinoid tumors of a total of five small intestinal cancers, which is quite consistent with the overall distribution for small intestinal cancers in the Danish Cancer Registry. Several case reports have described the association of Crohn's disease and carcinoids both in the small and large intestine [20, 21], although a small case-control study, including cases of both adenocarcinomas and carcinoid tumors, indicated that Crohn's disease was associated only to adenocarcinomas [22]. The excess of carcinoid tumors found in the present data may be due to surveillance bias, since at least one of the

Table 2. Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIR) for cancer among 2645 patients with Crohn's disease, Denmark, 1977-1993. First year of follow-up excluded

Cancer site (ICD-7)	Obs	Exp	SIR	95% CI
All malignant neoplasms (140-205)	143	123.8	1.16	0.97-1.36
Gastrointestinal tract (140-154)	26	19.6	1.3	0.9-2.0
Buccal cavity and pharynx (140-148)	2	2.2	0.9	0.1-3.2
Esophagus (150)	1	1.0	1.0	0.0-5.6
Stomach (151)	3	3.0	1.0	0.2-2.9
Small intestine (152)	5	0.3	17.9	5.8-42
Colorectal (153-154)	15	13.1	1.1	0.6-1.9
Liver (155.0)	1	1.0	1.0	0.0-5.6
Gallbladder and bile duct (155.1)	2	1.0	2.0	0.2-7.1
Pancreas (157)	3	3.1	1.0	0.2-2.8
Lung (162)	20	14.0	1.4	0.9-2.2
Breast (170)	10	18.1	0.6	0.3-1.0
Cervix uteri (171)	5	3.9	1.3	0.4-3.0
Corpus uteri (172)	3	3.8	0.8	0.2-2.3
Ovary (175)	2	3.6	0.6	0.1-2.0
Prostate (177)	7	4.7	1.5	0.6-3.0
Testis (178)	3	1.2	2.5	0.5-7.2
Kidney (180)	5	3.1	1.6	0.5-3.8
Urinary bladder (181)	7	6.1	1.2	0.5-2.4
Melanoma (190)	3	3.8	0.8	0.2-2.4
Non-melanoma skin (191)	21	17.5	1.2	0.7-1.8
Brain and nervous system (193)	2	3.7	0.5	0.1-2.0
Lymphatic and hematopoietic (200-205)	9	7.2	1.3	0.6-2.4
Non-Hodgkin's lymphoma (200, 202, 205)	4	2.7	1.5	0.4-3.7
Hodgkin's disease (201)	0	0.6	-	0.0-5.7
Multiple myeloma (203)	2	1.1	1.7	0.2-6.3
Leukemia (204)	3	2.6	1.2	0.2-3.4
Other specified sites (156, 158-161, 162.2, 163, 164, 173, 174, 176, 179, 192, 194-197)	10	5.5	1.8	0.9-3.4
Metastases, unknown primary site and unspecified sites (198, 199)	4	3.1	1.3	0.4-3.3

tumors was found incidentally at surgery for Crohn's disease. Our detailed review of the adenocarcinomas in the small intestine found in Crohn's disease patients showed that the cancer develops in long-standing Crohn's disease, and that there seems to be a tendency for more than one intestinal cancer. The available data gave no opportunity to determine if medical treatment of Crohn's disease could be related to the development of small intestinal cancer.

The lack of information on hospitalizations prior to 1977 implies that the date of initial hospitalization with Crohn's disease does not always correspond to the date of diagnosis for Crohn's disease, as was apparent for the three Crohn's disease patients with adenocarcinomas of the small intestine who had been diagnosed with the inflammatory disease many years prior to the first discharge record in the NRP. This may lead to a selection of cancer patients into the cohort, if patients

with a well-established Crohn's disease diagnosis enter the cohort because of early symptoms of intestinal cancer, which at first are interpreted as exacerbation of the inflammatory disease. It is difficult to ascertain if such a mechanism was working to inflate the relative risk of small intestinal cancer found here and, if so, to judge the extent of overestimation, but it seems unlikely to be present only in relation to small intestinal cancer but not in relation to colorectal cancer.

Previous studies on colorectal cancer in Crohn's disease are inconsistent, as apparent from Table 1 [1-4, 6-10]. A discrepancy was even found in two regional studies from Sweden that utilized a seemingly comparable material and methodology [1, 10]. The absence of an association with colorectal cancer has previously been ascribed to short follow-up, large proportions of patients undergoing panproctocolectomy and small size of study cohorts [2]. These factors do not seem to be sufficient to explain

Table 3. Characteristics of three adenocarcinomas and two carcinoids of the small intestine observed during 1-17 years of follow-up among 2645 patients with Crohn's disease, Denmark, 1977-1993

Case no.	Histology of small intestinal tumor	Sex	Age at Crohn's diagnosis (years)	Topography of small intestinal tumor	Time between Crohn's and small intestinal cancer ¹ (years)	Age at small intestinal cancer (years)	Second gastro-intestinal cancer: topography and histology	Time between cancers (years)
1	Adenocarcinoma	Female	16	Jejunum; 1 m from Treitz's ligament	21	37	Rectum adenocarcinoma	6
2	Adenocarcinoma	Female	65	Ileum ²	10	75	Cecum ² adenocarcinoma	0
3	Adenocarcinoma	Male	22	Jejunum (blind loop)	41	63	No	
4 ³	Malignant carcinoid	Female	-	Ileum	-	70	No	
5	Malignant carcinoid	Male	48	Mesenterium	17	65	No	

¹ Time distance between diagnosis of Crohn's disease according to medical record and small intestinal cancer.

² Verified by medical record review that there were two cancers; one in ileum and one in cecum.

³ Medical record not obtainable for this case.

the lack of association in our cohort, because a considerable number of persons was followed for more than 10 years, colectomy/proctectomy only reduced the person-year count slightly, and the cohort was among the largest ever to be evaluated. Others have proposed that only a small fraction of patients with Crohn's disease - namely those with extensive, long-standing, unresected colonic disease - are actually at risk for colorectal cancer [23, 24]. From the available data we cannot identify this subset of Crohn's disease patients, but such a subset potentially at increased risk of colorectal cancer does not seem to be large enough and/or the risk of colorectal cancer does not seem high enough in this subset to have major influence on the overall result for colorectal cancer.

There was no evidence of association to any extraintestinal cancer among patients hospitalized with Crohn's disease. Since the few studies that have evaluated risk of cancers outside the gastrointestinal tract came up with non-overlapping results [1, 5, 13], the separate, significant findings in these studies are most likely due to multiple comparisons. The relative risk of small intestinal cancer was high in patients with Crohn's disease, but still only a very small fraction of patients were affected. We conclude that, with the exception of small intestinal cancer, the cancer pattern in the overall group of Danish patients hospitalized with Crohn's disease is comparable to that for the total population of Denmark. Yet a small proportion of patients with Crohn's disease may be at increased risk for colorectal cancer, but a determination hereof was beyond the scope of this study.

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