

## Further Studies on the Frequency of Colorectal Cancer in Crohn's Colitis: An 11-Year Survey in the Northwest Stockholm County

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**Abstract.** *Background: The frequency of colorectal carcinomas (CRC) evolving in patients with Crohn's colitis (CC) was assessed at the Danderyds University Hospital (DUH), one of two large hospitals in Northwest Stockholm County (NWSC). Patients and Methods: A total of 121 patients with Crohn's disease (CD) were treated at this hospital between 1996 and 2006. All sections from colectomy specimens having CC and carcinoma were reviewed. Results: Of the 121 patients with CD, 79.4% (96/121) had CC. Of the 96 patients with CC, 6.3% (n=6) developed a CRC between 1996 and 2006. Discussion: Recent studies at the other large hospital in NWSC showed that during the same period (1996-2006) 7.4% (n=21) of the 282 patients with CC, developed a CRC. During this 11-year period, 7.1% (n=27) of the 378 patients with CC seen at the two hospitals that treat the vast majority of patients with CD in NWSC developed a CRC. By comparison, only 0.29% or 5,566 patients (age-adjusted) out of the 1,900,000 inhabitants in the entire Stockholm County developed a CRC during the same period. These results, obtained at a comparative time-interval in the County, substantiate several recent meta-analysis and population-based studies on the high cancer risk in patients with Crohn disease.*

It was demonstrated in the past, both in the US and in Europe (1-7), that colorectal carcinomas (CRC) evolved rather frequently in patients with ulcerative colitis (UC). Notwithstanding, Weedon *et al.* (8) postulated 35 years ago that the risk of developing a carcinoma was also valid for patients with Crohn's disease (CD).

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A recent review of the world literature (9) revealed that between 1942 and May 1996, 295 cases of CRC had evolved in patients with CD and that during the subsequent 11 years (equivalent to the time interval in the present study), 537 new cancer cases occurred. Hence, it would appear that the frequency of CRC developing in CD patients has increased worldwide in recent years, a phenomenon that was confirmed in several recent reviews, and in meta-analysis and population-based studies (10-13). In contrast, other workers (14-16) found no increased cancer risk for patients with CD.

The Danderyds University Hospital (DUH) is one of the two large hospitals serving patients with inflammatory bowel disease (IBD) in North Western Stockholm County (NWSC), the other being the Karolinska University Hospital (KUH). These two hospitals treat the vast majority of patients with CD in NWSC.

The aim of the present work was to assess the frequency of CRC in CD patients at the DUH between 1996 and 2006, a period of 11 years. The results obtained were compared with the recently reported frequency of CRC in CD patients found during the same time interval at the KUH (9) and with the frequency of CRC in the population of the entire Stockholm County during the same time interval.

### Patients and Methods

Stockholm County has a population of 1,900,000 inhabitants and NWSC of 700,000 inhabitants. In 1996, the Department of Health and Welfare sanctioned that the DUH should serve a population of 300,000 inhabitants until April 2005 and of 450,000 inhabitants thereafter (National Central Statistical Register).

Between June 1996 and May 2007, the DUH has received and treated 121 patients with CD. The diagnosis of CD was established according to the criteria suggested by Lennart-Jones (17). All colectomy specimens filed under the diagnosis of CD and a CRC during the aforementioned period were reviewed. A mean of 13 hematoxylin and eosin (H & E) stained sections (SE $\pm$ 4 sections) per colectomy specimen with a carcinoma and CD were available for study.

The Ethical Committee of the Hospital approved the study.

**Statistical analysis.** Statistical tests could not be applied in this study, as during the period of investigation, the incidence of CD dramatically increased in Stockholm County and the localization of CD has changed, with a predilection for the colon and rectum (see Discussion). Moreover, patients that ought to have attended the DUH consulted a neighbouring hospital in NWS, namely the KUH, with a differently assigned catchment population (see Discussion).

## Results

**Patients with CD treated at the DUH since June 1996.**

**Gender:** Table I show that of the 121 new patients with CD registered at the DUH, 56 were males and 65 female (ratio males/females: 0.86).

**Age at CD onset:** The mean age at CD diagnosis was 47.5 years (range 14-75 years).

**Localization of CD in the GI tract:** Table I also shows that of the 121 patients with CD, 73 or 60.3% had CC exclusively and that 23 (19.0%) with CC had, in addition, CD in the distal ileum. Thus, the total number of patients with CC with or without small bowel involvement was 79.3% (96/121).

**Cancer in patients with CC.** Between June 1996 and July 2006, 6 out of 96 patients (6.3%) with CC developed colon cancer. In Table II, the gender, age at CD diagnosis, age at cancer diagnosis, the interval between the debut of CC and cancer diagnosis in years, cancer localization, TNM staging and histological tumor type for the 6 patients, are presented.

**Gender:** Of the 6 patients with a large bowel cancer, the majority (4) were females.

**Cancer localization:** Three of the 6 carcinomas were found in the cecum, one in the right colon, one in the transverse colon and the remaining one in the sigmoid colon. No tumor evolved in the rectum or in the small intestine.

**Age at CD diagnosis:** The mean age at CD diagnosis in the 6 patients who developed cancer was 47.0 years (range 15-76 years).

**Age at cancer diagnosis:** The mean age at cancer diagnosis in the 6 patients was 60.0 years (range 37-75 years).

**Interval between the onset of CC and cancer diagnosis:** The mean interval between the onset of colitis symptoms and cancer diagnosis in the 6 cases was 13.0 years (range 0-44 years).

**TNM staging:** One of the 6 colonic adenocarcinomas was classified as T2N0, one as T4N1 and the remaining four as T3N0. None of the patients had distal metastases at the time of surgical resection.

**Histological classification:** Four out of the 6 colonic carcinomas were classified as mucus-producing moderately differentiated adenocarcinomas (in which the mucin lakes occupied >50% of the histological tumor area) and the remaining two as moderately differentiated adenocarcinomas. No case of signet ring cell carcinoma was recorded in this material.

Table I. Characteristics of patients with Crohn's disease (CD) seen at the Danderyds University Hospital between 1996 and 2006.

	No.
Patients with CD	121
Male	56
Female	65
Mean age at CD debut (years)	47.5
(range)	(14-75)
Location	
Small intestine	25
	(20.7%)
Small intestine and colon	23
	(19.0%)
Colon	73
	(60.3%)
Crohn's colitis and cancer	6

## Discussion

The results showed that during an 11-year period, 6.3% of the 96 patients with CC developed colon cancer at the DUH. During the same period, 7.4% of the 282 patients with CC treated at the KUH, developed a CRC (9). Of these, 4.9% were colon carcinomas.

A closer study of the data showed, however, that in 2 out of the 6 CC carcinoma patients treated at the DUH, and in 9 out of the 21 CC carcinoma patients treated at the KUH (9), the initial symptoms of colitis started before the period of investigation. Consequently, when only patients with CC treated within the 11 years of the study were included, 4.2% (4/96) of the DUH patients and 4.1% (12/282) of the KUH patients (9) had developed cancer. Thus, the percentage of CC patients developing cancer during the period of investigation was the same at both hospitals.

A mucinous carcinoma (with mucin lakes occupying >50% of the histological tumor area) was diagnosed in 66.7% (4/6) of the CC carcinomas seen at the DUH and in 52.4% (11/21) of the CC carcinomas seen at the KUH (9), but in only 28.8% (60/208) of the colonic carcinomas registered in the Stockholm County population between 2005 and 2007. Other authors (18-20) have previously reported a high frequency of mucin-producing carcinomas in patients with IBD. Although the cause(s) for this difference in mucin secretion between the two groups is unclear, it is conceivable that the tumor cells have evolved in a colorectal mucosa having marked goblet cell hyperplasia, often present in chronic inflammatory processes in that organ.

In 2 out of the 6 cases of cancer (33.3%) in CC seen at the DUH, the interval between first symptoms and cancer diagnosis was null, as both diagnoses were made at the time of surgery and confirmed at histology in the colectomy

Table II. Characteristics of 6 patients with cancer evolving in CC, seen at the Danderyds University Hospital between 1996 and 2006.

Case	Gender	Age at IBD diagnosis (years)	Age at cancer diagnosis (years)	Interval between CC and cancer diagnosis (years)	Cancer localization	TNM Stage	Histology
1	M	75	75	0	Sigmoid	T3N0	Moderately differentiated adenocarcinoma
2	F	51	65	10	Cecum	T3N0	Mucinous adenocarcinoma
3	M	40	40	0	Cecum	T3N0	Mucinous adenocarcinoma
4	F	74	75	1.5	Right colon	T3N0	Mucinous adenocarcinoma
5	F	15	37	22	Cecum	T4N1	Mucinous adenocarcinoma
6	F	24	68	44	Transverse colon	T2N0	Moderately differentiated adenocarcinoma

specimen. In 3 out of the 6 patients (50%) that interval was  $\leq 2$  years (Table II). At the KUH, the interval between first symptoms and cancer diagnosis was  $\leq 4$  years in 33.3% (7/21) of the CC cancer patients (9). Hence, the time interval between initial symptoms and cancer diagnosis in CC in NWSC differed from that recorded in patients with UC seen in the same area (21), in as much as in UC, the interval was 17.5 years (range 5-48 years). One of the possible explanations for the time difference in cancer development in the two inflammatory conditions of the large bowel might be that in UC the symptoms related to inflammation develop earlier, as in the majority of the cases the mucosal inflammation begins in the rectal mucosa. This localization makes the patient aware of the symptoms at an earlier stage, leading to prompt medical consultation. In contrast, in most cases of CC, the inflammation begins in the right colon.

In an exhaustive demographic study, Lapidus (22, 23) found that the annual incidence of CD in Stockholm County had increased from 1.4 cases per 100,000 inhabitants in 1959 to 1.9 cases per 100,000 inhabitants in 1989 and to 8.3 cases per 100,000 inhabitants between 1990 and 2001. This dramatic increase in the incidence of CD in Stockholm County (22, 23) is in concert with reports from other countries in Northern Europe (24, 25). Rationally, the genuinely increased frequency of CD patients since 1990 in Stockholm County as a whole should have resulted in a corresponding increased frequency of CD patients in NWSC. The increased incidence of CD in Stockholm County in later years might contribute to explaining the disparate results in the frequency of CRC evolving in the NWSC study and in other surveys. In this respect, the study on the risk of colorectal cancer in IBD carried out in Olmsted County, Minnesota, USA (26), with a catchment population of 124,277 inhabitants, showed that during a period of 61 years, 0.27% (6/223) of the patients with CC (with or without ileal extension) had developed CRC. The authors also reported that: "for the analysis of CRC risk in CD, 2 cancers diagnosed within 30 days of the IBD diagnosis were excluded" (26). The causes for excluding these 2 cases were not further elaborated, but if these 2 cases are included here for the purpose of comparing their and our results, of the

223 patients with CC (with or without ileal extension) treated in Olmsted County, 0.36% (n=8) had developed CRC during the 61 years of the study. In comparison, of the 378 patients with CC seen in NWSC with a catchment area of 550,000 inhabitants up to 2005 and of 700,000 inhabitants thereafter, 7.1% (27/378) of the patients with CC developed colorectal cancer. During the same period, 0.29% or 5,566 patients (age adjusted) in the entire Stockholm County (1,900,000 inhabitants) developed a CRC. Hence, when compared with the entire Stockholm County population during the same period, the risk in NWSC for CC patients to develop a CRC was substantially increased. Although the explanation for the disparate results obtained in Olmsted County and in the NWSC remains unclear, it should be borne in mind that in Olmsted County, the study was carried out between 1940 and 2001 (a period of 61 years), whereas the NWSC study took place more recently, between 1996 and 2006 (a period of 11 years). This is an important difference between these two surveys, considering that in later years, the localization of the CD has puzzlingly changed from being a disease preferentially localized in the small intestine to a disease mainly affecting the large bowel (9, 27). In fact, during these last 11 years, in 80% of the DUH patients (present study) and in 90% of the KUH patients (9), the CD was localized in the large bowel.

Despite the true cause for the change in localization of CD remaining elusive, it should be understood that CD, a multifactorial malady with high heritability, has a complex genetic architecture. Recently, more than 30 independent susceptible loci, conclusively associated with CD, were identified (28). Moreover, CD is associated with decreased innate immunity (29). Crohn's ileitis is associated with a reduced expression of the Wnt signalling pathway transcription factor T-cell TCF4 resulting in deficient expression of  $\alpha$ -defensins and human defensins HD 5 and HD6. CC is typically associated with an impaired induction of the  $\beta$ -human defensins HBD2 and HBD3 caused by fewer gene copy (28) numbers in the gene locus of the  $\beta$ -defensins on chromosome 8 (30). The innate defence defect mediated by a deficiency of the protective  $\alpha$ - and  $\beta$ -defensins may enable luminal microbes to invade the

mucosa and trigger the inflammation (29). It is therefore not inconceivable that the change in food habits in recent years, together with new food additives and environmental pollutants, might have changed the conditions of the mucosal microenvironment (30) and moved CD to another target organ lacking the suitable human defensin(s) which normally neutralize environmentally mutated microbes. The recent success in the treatment of CD with infliximab (31), a monoclonal antibody to tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), one of the chemical mediators of the inflammatory response, seems to substantiate these considerations.

In conclusion, during the period of this investigation, the incidence of CD has dramatically increased in Stockholm County and the localization of CD has changed, with a predilection for the colon and rectum. During the same period, the frequency of patients with CC developing cancer in the colon and rectum in NWSC was found to be substantially higher than in the population of Stockholm County as a whole.

These results have raised much concern, considering that the time interval between the first symptoms of CC and cancer diagnosis was very short in many patients. In the light of these results, it appears mandatory that patients with CC in NWSC be subjected to close colonoscopic examination, a recommendation already advanced years ago for CD patients treated at the KUH (27).

In closing, the alarming reports only a few decades ago (8) concerning the high cancer risk in patients with CD seems to be validated, not only by several recent meta-analyses and population-based studies (10-13), and by a recent review of the world literature showing a substantial increase in the number of new cancer cases reported since 1996 (9), but also by the results of the present investigation carried out between 1996 and 2006 in NWSC.

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