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Abstract

Background and aims: Limited data are available on the incidence and predictors of colorectal (CRC) and small bowel adenocarcinoma (SBA) in patients with Crohn's disease (CD) from population-based cohorts. Since data are completely missing from Eastern Europe, our aim was to analyze the incidence and risk factors of CD associated CRC and SBA in the population-based, Veszprem province database, which included incident patients diagnosed between January 1, 1977 and December 31, 2008.

Methods: The data of 506 incident CD patients were analyzed (age-at-diagnosis: 31.5, SD: 13.8 years). Both hospital and outpatient records were collected and comprehensively reviewed.

Results: CRC was diagnosed in five patients (5/5758 person-year-duration) during follow-up, while no patients developed SBA in this cohort. Standardized incidence ratio (SIR) of CRC was not increased overall with five cases observed vs. 5.02 expected (SIR: 0.99, 95% CI: 0.41–2.39); however, there was a tendency for increased incidence in males (five cases observed vs. 2.56 expected; SIR: 1.95, 95% CI: 0.81–4.70). Age at onset of CD (p<0.001), male gender (p=0.022)

☆ The authors disclose: no conflicts.
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The risk of developing cancer in patients with established Crohn’s disease (CD) has been a controversial subject since the first report of colorectal carcinoma complicating CD in 1948.\(^1\) Since then several studies have addressed the association CD and the development of intestinal cancer, ascribed to malignant degeneration within inflamed areas of the small and large bowel.

An increased risk or mortality of colorectal cancer (CRC) in patients with CD has been reported in a number of studies,\(^2,4\) whereas others have found no such association.\(^5,6\) Similarly, an excess risk of small bowel cancer (SBA) has been found sometimes,\(^3,4,6,7\) but data are inconclusive and absolute risk remains small.\(^9\) The interpretation and comparison of these results is also difficult due to possible selection bias in studies from referral centers. Moreover, the discrepancy in the reported occurrence of cancer in Crohn’s disease may be due to differences in medical and surgical treatment strategies. The magnitude of risk observed in studies from referral centers\(^3,10\) generally exceeds the risk reported in population-based studies from Western Europe and North America,\(^2,4,7,8\) and in some population-based studies the overall risk for CRC is even comparable with that of the background population.\(^4,6,7\)

A recent meta-analysis summarized the available data on CRC in CD patients and showed an increasing cumulative probability of CRC during the disease course.\(^11\) However, the meta-analysis included a variety of studies with different designs, including referral center studies. The relative risk (RR) of SBA and CRC compared with the baseline population was 28.4 (95% CI: 14.46–55.66) and 2.4 (95% CI: 1.56–4.36), respectively. On subgroup analysis, patients with CD had an increased risk of colon cancer (RR: 2.59; 95% CI: 1.54–4.36) and not of rectal cancer. There was significant association between the anatomic location of the diseased bowel and the risk of cancer in that segment. The RR of developing CRC in patients whose CD only affected the small bowel was similar to the general population. In 885 patients who had CD affecting the ileocolic segment, the RR increased to 4.63 (95% CI: 2.09–10.26). In 704 patients with colonic CD, the RR was even higher at 13.36 (95% CI: 5.71–31.26). The only study that examined the CRC risk in patients with extensive CD found that this group had an even higher RR of 18.2 (95% CI: 7.8–35.6).\(^1\) In addition, higher RR was reported in males than in females (RR: 2.8; 95% CI: 1.1–5.8 vs. RR: 2.1; 95% CI: 0.7–4.8) in one Scandinavian study.\(^2\) In contrast, in a subgroup analysis of the 8 population-based studies revealed no excess risk of developing CRC in 10,258 patients (RR: 1.39; 95% CI: 0.94–2.06). Similar rates were reported in another meta-analysis.\(^12\) Meta-regression showed reduction in relative risk over the past 30 years. Subgroup analysis showed Scandinavia had significantly lower colorectal cancer relative risk than the UK and North America. Cumulative risk analysis showed 10 years following diagnosis of Crohn’s disease relative risk of colorectal cancer is 2.9% (95% CI: 1.5%–3.3%). In addition, in a case-control study from France,\(^13\) small bowel resection and prolonged salicylates use were identified as possible protective factors against SBA in CD patients.

The data available on the incidence and predictors of CRC and SBA in population-based CD cohorts are still limited. Since data are completely missing from Eastern Europe, our aim was to analyze the incidence and risk factors of CD associated CRC and SBA in the population-based, Veszprem province database, which included incident patients diagnosed between January 1, 1977 and December 31, 2008.

### 1. Patients and methods

#### 1.1. Study population

A well-characterized Hungarian cohort of 506 incident cases with Crohn’s disease (male/female: 251/255, age at diagnosis: 31.5 years, SD 13.8 years) diagnosed between January 1, 1977 and December 31, 2008 were included. Patients with indeterminate colitis at diagnosis were excluded from the analysis. The clinical data of the CD patients is summarized in Table 1. Veszprem province is located in the Western part of Hungary. The province consists of both industrial and agricultural regions. The number of permanent population was relatively stable, with a slight decrease from 376,000 to 364,500 from 1990 to 2006. The rate of Gypsies is below the Hungarian average (2.5%), while few people of Jewish ethnicity live in the province. The ratio of urban/rural residence was also relatively stable (55% urban). The source of national incidence rates of colorectal and small bowel adenocarcinoma was the National Cancer Registry (NCR)\(^14\), while source of age- and gender-specific demographic data of the province for the statistical analysis was the Hungarian Central Statistical Office (KSH).

IBD patient data were collected every year from the seven general hospitals and gastroenterology outpatient units (Internal Medicine Departments, Surgery Departments, Pediatric Departments, and Outpatient Units), each staffed by at least one gastroenterologist or internist with special interest in gastroenterology, as well as family physicians. The majority of patients (94% of CD patients) were monitored at the Csolnoky F. Province Hospital in Veszprem. This hospital also serves as a secondary referral center for IBD patients in that province. Data collection was prospective since 1985, while prior to that, data were only in Veszprem collected prospectively. In other sites throughout the province, data for this period (1977–1985) were collected.
retrospectively in 1985. Both in-patients and outpatients permanently residing in the investigated area were included in the study. Most patients were followed up regularly. Diagnoses (based on hospitalization records, out-patient visits, endoscopic, radiological and histological evidence) generated in each hospital and outpatient unit were reviewed thoroughly, using the Lennard-Jones criteria.15 The provincial IBD register data were centralized in Veszprem. The disease phenotype was assessed by a questionnaire completed by the clinician at the time of diagnosis. Both in-patients and outpatients were followed up: most patients were followed up regularly. Follow-up (years) ranged from 1 to 33. Surgical resections were performed from the early 1980s, but on a more widespread basis from the mid 1990s. Short-term oral corticosteroid treatment was used for clinical exacerbations, usually at initial doses of 40–60 mg of prednisone daily that was tapered and discontinued over 2–3 months. Methotrexate was only exceptionally used as a second-line immunosuppressive therapy beginning in the mid-1990s. Infliximab has been used for both induction and maintenance therapy in selected cases since the late 1990s. Surgical resections were performed for emergent indications (e.g., obstructive symptoms, hemorrhage), and for failure to respond to medical therapy. Moreover, due to Hungarian health authority regulations, a follow-up visit is obligatory for IBD patients at a specialized gastroenterology center every 6 months. Otherwise, the conditions of the health insurance policy change and they forfeit their ongoing subsidized therapy. Consequently, the relationship between IBD patients and specialists is a close one.

### 1.2. Treatment policy

The majority of the patients received maintenance therapy with sulfasalazine or a 5-aminosalicylic acid derivative (mesalazine or olsalazine) if tolerated, especially till the mid-1990s. Azathioprine or 6-mercaptopurine was used as maintenance therapy for steroid dependent, steroid-refractory, or fistulizing patients in selected cases, mainly after resective surgery till the late-1980s, but on a more widespread basis from the mid 1990s. Short-term oral corticosteroid treatment was used for clinical exacerbations, usually at initial doses of 40–60 mg of prednisone daily that was tapered and discontinued over 2–3 months. Methotrexate was only exceptionally used as a second-line immunosuppressive therapy beginning in the mid-1990s. Infliximab has been used for both induction and maintenance therapy in selected cases since the late 1990s. Surgical resections were performed for emergent indications (e.g., obstructive symptoms, hemorrhage), and for failure to respond to medical therapy. Moreover, due to Hungarian health authority regulations, a follow-up visit is obligatory for IBD patients at a specialized gastroenterology center every 6 months. Otherwise, the conditions of the health insurance policy change and they forfeit their ongoing subsidized therapy. Consequently, the relationship between IBD patients and specialists is a close one.

### 1.3. Statistical methods

Variables were tested for normality by Shapiro–Wilk’s W test. Wilcoxon rank sum test, $\chi^2$-test, and $\chi^2$-test with Yates correction were used to test differences in disease phenotype between subgroups of CD patients for dichotomous variables. Odds ratios (OR) were calculated. The risk for CRC and small bowel cancer relative to the general population was estimated using standardized incidence ratios (SIRs, observed/expected numbers) with 95% confidence intervals (CIs) assuming a Poisson distribution for the observed number of cancers. Expected numbers were calculated using the observed age- and sex-specific person-years at risk in the cohort combined with age- and sex-specific intestinal cancer rates from the National Cancer Registry (NCR) and Hungarian Central Statistical Office (KSH). Kaplan–Meier survival curves were plotted for analysis with LogRank and Breslow tests to determine the cumulative probability of CRC in CD. A $p$ value of <0.05 was considered as significant. Results for continuous variables are expressed as mean (standard deviation, SD) unless otherwise stated.
performed the statistical analysis. For the statistical analysis, SPSS15.0 (SPSS Inc, Chicago, IL) was used.

2. Results

2.1. Incidence of colorectal cancer and small bowel adenocarcinoma in patients with Crohn’s disease

Of the 506 patients CRC was diagnosed in five male patients during follow-up, equating an incidence rate of 5/5758 person year duration (pyd, 0–10 years: 5/1577 pyd, 11–20 years: 0/2495 pyd, >20 years: 0/1686 pyd) (see Table 2). The estimated overall annual CRC incidence was 0.09% (95% CI: 0.04–0.20%). However, in the first decade of CD, the annual CRC incidence rate was 0.32% (95% CI: 0.14–0.74%). In contrast, no SBA were diagnosed during the follow-up period. In addition, seven other malignancies were diagnosed, including one case of carcinoïd, renal cell cancer, lung cancer, gastric cancer, breast cancer, bladder cancer and one non-Hodgkin lymphoma.

Standardized incidence ratio (SIR) was not increased overall with 5 cases observed vs. 5.02 expected (SIR: 0.99, 95% CI: 0.41–2.39); however, there was a tendency for increased incidence in males (5 cases observed vs. 2.56 expected; SIR: 1.95, 95% CI: 0.81–4.70). In addition, we calculated SIRs according to the disease location (L2: 2 cases observed vs. 1.89 expected; SIRL2: 1.06, 95% CI: 0.26–4.22, L1: 2 cases observed vs. 1.67 expected; SIRL1: 1.2, 95% CI: 0.30–4.80; L3: 1 case observed vs. 1.45 expected; SIRL3: 0.69, 95% CI: 0.10–4.88). In contrast, the SIR was significantly increased in patients with stenosing disease behavior at presentation (SIR: 4.92, 9%CI: 2.05–11.81, with 5 observed cases vs. 1.02 expected) with no patients diagnosed with CRC in patients with luminal (expected: 2.60 cases) and penetrating disease (expected: 1.41 cases).

2.2. Association between clinical phenotype, surgery and risk of developing CRC in CD

In univariate analysis, age at onset of CD (pediatric (0–18 years): 0% vs. adult (19–60 years): 0.7% vs. elderly (>60 years): 9.5%, *p*<0.001), male gender (2.0% vs. 0%, *p*=0.029), disease behavior at diagnosis (stenosing: 5% vs. inflammatory and penetrating 0%, *p*<0.001), smoking status (non-smoking: 0% vs. smoking: 1.3% vs. ex-smoking 4.7%, *p* = 0.042 after Bonferroni correction) but not disease location were associated with the CRC diagnosis.

Similar results were found in a Kaplan–Meier analysis (Fig. 1). The cumulative risk for developing CRC in CD was 1.1% (95% CI: 0.6–1.7) after 10 years and 20 years. Age at onset of CD (pLogRank<0.001, pBreslow<0.001), male gender (pLogRank=0.022, pBreslow=0.023) and stenosing disease behavior (pLogRank<0.001, pBreslow<0.001) but not disease location were significantly associated with the time to developing CRC in patients with Crohn’s disease in a Kaplan–Meier analysis; however, a Cox regression analysis could not be performed due to the small number of observed cases.

The probability of surgical resection due to non-malignant disease after 5 and 10 years was overall 30.8% and 52.2% in a Kaplan–Meier analysis, while the probability of colon resection/colectomy was 18.9% and 28.5% (Fig. 2). During the follow-up 21 patients (4.2%) required subtotal colectomies/proctocolectomies.

3. Discussion

In this population-based study from Hungary, Eastern Europe, the incidence of CRC and SBA was overall not increased; however, there was a tendency for increased incidence in males. Age at onset of CD, male gender and stenosing disease behavior at diagnosis were identified as risk factors. The Veszprem province epidemiological registry served as a solid base for the prospective identification and follow-up of IBD cases from a well-defined geographic region. However, the relatively small number of patients and the low frequency of events observed in the present study may have prevented the identification of some clinically important risk factors among subsets of patients.

Although the absolute number of malignancies associated with Crohn’s disease is small, it is remarkable that the otherwise rare small bowel cancer occurred significantly more frequently than expected in population-based from

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**Table 2** Clinical characteristics of Crohn’s disease-associated colorectal cancer patients.

<table>
<thead>
<tr>
<th>No</th>
<th>Gender</th>
<th>Smoking</th>
<th>Age at symptom onset (years)</th>
<th>Age at onset of CD (years)</th>
<th>Age at diagnosis of CRC (years)</th>
<th>Duration of CD at diagnosis (years)</th>
<th>CD location at diagnosis</th>
<th>CD behavior at diagnosis</th>
<th>CRC location</th>
<th>Calendar year of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>yes</td>
<td>29</td>
<td>30</td>
<td>35</td>
<td>5</td>
<td>coecum-transverse-ascendent</td>
<td>stenosing</td>
<td>transverse colon</td>
<td>1991</td>
</tr>
<tr>
<td>2</td>
<td>male</td>
<td>yes</td>
<td>47</td>
<td>47</td>
<td>50</td>
<td>3</td>
<td>coecum-ascendent</td>
<td>stenosing</td>
<td>ascendent colon</td>
<td>2001</td>
</tr>
<tr>
<td>3</td>
<td>male</td>
<td>yes</td>
<td>55</td>
<td>56</td>
<td>59</td>
<td>3</td>
<td>terminal ileum-ascendent</td>
<td>stenosing</td>
<td>coecum</td>
<td>2005</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>ex</td>
<td>60</td>
<td>61</td>
<td>64</td>
<td>3</td>
<td>terminal ileum</td>
<td>stenosing</td>
<td>sigmoid colon</td>
<td>2006</td>
</tr>
<tr>
<td>5</td>
<td>male</td>
<td>ex</td>
<td>64</td>
<td>64</td>
<td>66</td>
<td>2</td>
<td>terminal ileum</td>
<td>stenosing</td>
<td>sigmoid colon</td>
<td>2007</td>
</tr>
</tbody>
</table>
Denmark, USA, and in a metaanalysis. The relative risk was increased by 33.2-fold to 66.7-fold. Nevertheless, the number of the patients was as low as 3 after a median follow-up of 10.8 years in 314 incident CD patients in the study from the Olmstead County. Similarly, in the Copenhagen study only four patients were diagnosed with SBA during a median follow-up of 17 years in 374 incident cases. On the contrary, after vigorous reassessment it is questionable, if there were any SBA cases in the study from the Olmstead County, since only one small bowel cancer case was SBA involving the caecum, one case of leiomyosarcoma, and a local lymphoma. In the larger present study, involving 506 incident CD cases no SBA or small bowel cancer cases were diagnosed during a median follow-up of 10.9 years.

Population-based studies from Denmark, Israel, and Sweden have reported an overall normal risk for CRC in CD, whereas studies from Canada, Sweden and the two metaanalyses including referral center data have reported an excess with relative risks of approximately 2.5. In contrast, even in the metaanalysis, authors were unable to demonstrate a significant risk increase of CRC in a subgroup analysis of the population-based studies (RR: ...
small bowel involvement alone had the highest SIR (3.0; 95% CI: 0.6–8.7) for developing CRC and those with colonic involvement only had the lowest SIR (0.8; 95% CI: 0.02–4.7). In the Copenhagen study, authors also reported an association between the age at Crohn’s disease diagnosis and age at cancer diagnosis (intestinal cancers occurred a median of 16 years after Crohn’s disease diagnosis) emphasizing the need for a longer observation. In contrast, in the present study CRC developed relatively shortly after CD diagnosis, and longer disease duration was not associated with further increased risk. In addition, Ekbom et al. reported higher RR in males (2.8; 95% CI: 1.1–5.8) then in females (2.1; 95% CI: 0.7–4.8). Similarly, a tendency of increased incidence in male patients was observed also in the present study; however, the difference was not significant. Furthermore, there was an association between a more advanced age at onset of CD and the risk of developing CRC.

Disease location was identified in some but not all previous studies. In the metaanalysis by Canavan et al., the overall pooled estimate for RR of colorectal cancer in patients with colonic disease was 4.5 (95% CI: 1.3–14.9, p < 0.015). In addition, the only study that examined the CRC risk in patients with extensive Crohn’s colitis found that this group had an extremely high RR of 18.2 (95% CI: 7.8–35.6; p < 0.01). In contrast, in the present study neither location was associated with the risk of developing CRC nor was the SIR was elevated in patients with colonic disease (colon only: 1.06; 95% CI: 0.26–4.22, ileal: 1.2; 95% CI: 0.30–4.80), on the other hand we found a significant association between disease behavior at presentation and development of subsequent CRC. Moreover, the SIR was significantly increased in patients with stenosing disease behavior at presentation (4.92; 95% CI: 2.05–11.81, with 5 observed cases vs. 1.02 expected).

In conclusion, the incidence of CRC and SBA was not increased in this population-based CD cohort from Veszprem Province, Hungary. Age at onset of CD, male gender, smoking and stenosing disease behavior at diagnosis were identified as possible risk factors.

References


