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Abstract: BACKGROUND Gastrointestinal and extraintestinal malignancies are long-term complications in patients with inflammatory bowel disease (IBD), likely as a result of chronic inflammation and the use of immunosuppressive medications used to control inflammation. Here, we assessed the frequency of malignancies in a large tertiary IBD centre at the University Hospital Zurich. METHODS We performed a retrospective analysis of data from 1,026 patients from our IBD clinic treated between 2007 and 2014. RESULTS Twenty-two of the 1,026 patients developed 28 cases of malignancies, 14 patients were male and 8 patients female. The median latency between IBD diagnosis and first malignancy was 13 years (range 2-27 years). Most common malignancies were non-Hodgkin lymphoma, colorectal cancer (CRC), urothelial carcinoma, cholangiocellular carcinoma (CCC) and prostate cancer. The most common tumour type in Crohn’s disease patients (13/22) was lymphoma (5 cases), in ulcerative colitis patients (9/22) CCC (2 cases) and CRC (2 cases). The observed incidence of lymphoma (32.5/100,000), bladder carcinoma (21.7/100,000) and CCC (10.8/100,000) was higher than expected and known from general population. All of the patients that developed a malignancy had received immunosuppressive therapy. Compared to a cohort of 927 IBD patients without malignancies there were no statistical differences regarding gender, antibodies targeting tumour necrosis factor and thiopurine use. CONCLUSION Our data support the assumption that a long-standing disease course and immunosuppressive therapy increase the risk for developing malignancies in IBD patients.

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Malignancies in Patients with Inflammatory Bowel Disease: A Single-Centre Experience

Mehdi Madanchi, Jonas Zeitz, Christiane Barthel, Panagiotis Samaras, Sylvie Scharl, Michael C. Sulz, Luc Biedermann, Pascal Frei, Stephan R. Vavricka, Gerhard Rogler, Michael Scharl

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Key Words
Inflammatory bowel disease - Crohn's disease - Ulcerative colitis - Malignancy - Lymphoma - Colorectal carcinoma - Cholangiocellular carcinoma - Immunosuppression

Abstract
Background: Gastrointestinal and extraintestinal malignancies are long-term complications in patients with inflammatory bowel disease (IBD), likely as a result of chronic inflammation and the use of immunosuppressive medications used to control inflammation. Here, we assessed the frequency of malignancies in a large tertiary IBD centre at the University Hospital Zurich. Methods: We performed a retrospective analysis of data from 1,026 patients from our IBD clinic treated between 2007 and 2014. Results: Twenty two of the 1,026 patients developed 28 cases of malignancies, 14 patients were male and 8 patients female. The median latency between IBD diagnosis and first malignancy was 13 years (range 2–27 years). Most common malignancies were non-Hodgkin lymphoma, colorectal cancer (CRC), urothelial carcinoma, cholangiocellular carcinoma (CCC) and prostate cancer. The most common tumour type in Crohn’s disease patients (13/22) was lymphoma (5 cases), in ulcerative colitis patients (9/22) CCC (2 cases) and CRC (2 cases). The observed incidence of lymphoma (32.5/100,000), bladder carcinoma (21.7/100,000) and CCC (10.8/100,000) was higher than expected and known from general population. All of the patients that developed a malignancy had received immunosuppressive therapy. Compared to a cohort of 927 IBD patients without malignancies there were no statistical differences regarding gender, antibodies targeting tumour necrosis factor and thiopurine use. Conclusion: Our data support the assumption that a long-standing disease course and immunosuppressive therapy increase the risk for developing malignancies in IBD patients.
Introduction

Patients suffering from inflammatory bowel disease (IBD) have an increased risk for developing intestinal and extra-intestinal neoplasia, as compared to the general population [1–3]. An important pathogenetic risk factor is considered to be the chronic ongoing inflammation resulting in tissue destruction and remodelling [4, 5]. In addition, there is good evidence that immunosuppressive drugs used to control the inflammation in IBD patients, such as purine antimetabolites (azathioprine (AZA)/6-mercaptopurine (6-MP)) or monoclonal antibodies targeting tumour necrosis factor (anti-TNF) also increase the risk for the development of certain cancers, such as non-Hodgkin lymphoma (NHL), non-melanoma skin cancer or melanoma [6, 7]. The increased risk of lymphoma and skin cancer is associated with the use of thiopurines [8]. In general, some malignancies occur more often newly or recurrently in IBD patients [9]. A recent meta-analysis showed that IBD patients taking thiopurines are at an increased risk for developing NHL [10]. A nationwide French prospective observational study (CESAME) demonstrated that patients receiving thiopurines were at an increased risk for developing lymphoproliferative disorders [11]. The increased risk of lymphoma is higher in patients with Crohn’s disease (CD), whereas patients with both ulcerative colitis (UC) and CD are at an increased risk of developing leukaemia [4, 12, 13].

With respect to the basic risk of developing malignancies in IBD, there are conflicting results. A Finnish study patients with UC were found to have an increased risk of colon, rectal, biliary tract, and thyroid cancers, and the risk of colorectal cancer (CRC) was highest among the youngest UC patients. Patients with CD had a significantly increased risk for cancers of the small intestine, anus, and biliary tract, and also for myeloma. In addition, the risk of basal cell skin cancer was increased in IBD [14]. In contrast, data from Denmark indicated that only CD patients had an increased risk of developing malignancies overall, such as small bowel cancer, lung cancer or NHL, while the general risk for developing cancer in UC patients was not increased [15]. A large population-based study from Danish health care databases found that patients with IBD, particularly CD, were at an increased risk for gastrointestinal and extraintestinal malignancies [16].

These reports indicate that there might be population-dependent differences in the risk for developing malignancies in IBD patients. Furthermore, the risk for IBD patients to develop cancer certainly also depends on individual factors, such as age, disease phenotype (CD vs. UC), IBD-related medications and disease duration. Thus, the composition of patient cohorts influences the overall outcome with respect to malignancies. Further, incidence ratios within cohorts are influenced by the recruitment location (i.e. single tertiary referral centre vs. population-based study).

As also discussed at a recent ECCO guideline conference on malignancies in IBD, more data on this topic are certainly required. Therefore, we screened the medical charts of 1,026 patients from the large IBD clinic of the University Hospital of Zurich for the incidence of malignancies after the diagnosis of IBD. A systematic clinical analysis of features and characteristics of these malignancies was performed.

Patients and Methods

We retrospectively screened the charts of 1,026 patients from the IBD clinic at the University Hospital of Zurich seen between 2007 and 2014. The study was approved by the local Ethical Committee (IRB approval number: EK-1316 by the Cantonal Ethics Committee of the Canton Zürich, Switzerland).

We reviewed patients’ medical records regarding demographics (age at diagnosis, sex), disease characteristics of their IBD, such as type and course of disease and treatment (type of IBD, complications as fistula and/or bowel stenosis, history of surgery, history of medical therapy), and data regarding any malignancies (latency between diagnosis of IBD and occurrence of malignancy, including entity, stage and its treatment). A descriptive statistical analysis was performed. Qualitative variables were expressed as percentages, whereas quantitative variables as median. For the statistical analysis, Fisher’s exact test was performed (Prism 5.04 for Windows, GraphPad Software Inc., La Jolla, Calif., USA). The tumour incidence was calculated by using the earliest tumour diagnosis year (1996) as the baseline, and then calculating the yearly incidence of tumours in the total IBD cohort in the period of time until 2014 (over a time period of 18 years). We compared our data with the data published by the National Institute for Cancer Epidemiology and Registration (NICER) collecting cancer-specific incidence ratios within cohorts are influenced by the overall outcome with respect to malignancies. Further, incidence ratios within cohorts are influenced by the recruitment location (i.e. single tertiary referral centre vs. population-based study).

As also discussed at a recent ECCO guideline conference on malignancies in IBD, more data on this topic are certainly required. Therefore, we screened the medical charts of 1,026 patients from the large IBD clinic of the University Hospital of Zurich for the incidence of malignancies after the diagnosis of IBD. A systematic clinical analysis of features and characteristics of these malignancies was performed.

Results

Demographic Aspects

Out of 1,026 patients from our IBD clinic enrolled in our data search, we identified 22 (2.1%) patients (13 (59%) with CD; 9 (41%) with UC), who developed any malignancy after diagnosis of IBD. The median age at data acquisition was 56 (range 21–85 years). The median age at the diagnosis of IBD was 30 (range 11–66 years), whereas the median latency between IBD diagnosis and......
the onset of the first malignancy was 13 years (range 2–27 years). The majority of patients were male (14, 64%, 7 with CD, 7 with UC). The median age at diagnosis of the malignancy of the male patients was 33 (range 12–66 years). Eight (36%) IBD patients who developed a malignancy were female with a median age of 30 (range 11–63 years) at diagnosis of IBD, of which 6 (75%) displayed CD and 2 (25%) UC. Further details can be found in tables 1 and 2.

In the cohort of 927 IBD patients who did not develop malignancy 540 had CD (58%), 320 UC (35%) and 67 indeterminate colitis (7%). Four hundred and forty eight were female (48%) and 479 male (52%). The median age at data acquisition was 45 years (range 19–102 years). There was no statistical difference comparing the genders (p = 0.2888) and disease types (CD vs. UC; p = 0.8240) between the patient group that developed malignancy and the cohort that did not develop malignancy.

Occurrence of Malignancies
The identified 22 patients developed 28 cases of malignancy. Table 3 shows the comprehensive list of malignancies, the distribution of tumour types and type of IBD in details. NHL was developed by 5 patients (4 CD, 1 UC, 18% of the malignancies, one of the NHL was a hepatosplenic T-cell lymphoma (HSTCL) by a CD patient), CRC by 4 patients (2 CD, 2 UC, 14% of the malignancies), urothelial carcinoma by 3 patients (2 CD, 1 UC 11% of the malignancies), cholangiocellular carcinoma (CCC) by 2 patients (2 UC, 7% of the malignancies), malignant melanoma by 1 patient (UC, 4% of the malignancies), Hodgkin’s lymphoma by 1 patient (CD, 4% of the malignancies). From the 2 UC patients who developed CCC, 1 patient had a suspected PSC (patient number 21). Out of the 6 patients who developed lymphoma (NHL including HSTCL and Hodgkin’s disease) one was treated with thiopurines alone, one was treated with a combination of thiopurines and anti-TNF antibodies, 2 were treated with anti-TNF antibodies alone, and one with steroids only. For the remaining patient, no sufficient data about his previous therapy were available. Of note the smoking status regarding the patients with urothelial carcinoma could not be retrieved.

We calculated the incidence for the most frequent tumours. For lymphoma (NHL and Hodgkin’s lymphoma combined), an incidence rate of 32.5/100,000 was calculated, for NHL alone 27/100,000, and for Hodgkin’s lymphoma 5.4/100,000. For CRC, in our patient cohort an incidence rate of 21.7/100,000 was calculated. The incidence rate of bladder carcinoma was 21.7/100,000, of CCC 10.8/100,000, and of malignant melanoma 5.4/100,000 (table 4).

IBD-Specific Medication
Two of the 22 patients received mesalazine as IBD-specific medication. Seven patients received AZA, 2 patients received 6-MP, 5 patients methotrexate, 4 patients adalimumab (ADA), 8 patients infliximab (IFX), and 1 patient certolizumab pegol (CZP). Details regarding medication are shown in table 1. Anti-TNF antibodies (ADA, IFX, CZP) were applied to 9 (41%) patients. Eight of those 9 patients (89%) with anti-TNF antibodies had a co-medication. For 4 out of 22 identified patients, no sufficient data on IBD-specific immunosuppressive therapy were available (table 1).

In the IBD population without malignancies, 220 of 927 patients received anti-TNF treatment (ADA, IFX, CZP, previous or concurrent AZA treatment included) (24%), 126 had anti-TNF treatment with no previous or concurrent AZA treatment (14%). Two hundred and fourteen had AZA treatment (37%), 120 with no previous or concurrent anti-TNF treatment (13%).

When comparing the malignoma patients with this cohort, there was no statistical difference regarding anti-TNF, with and without concurrent or past AZA treatment (p = 0.0766 and p = 0.2124, respectively), AZA treatment, with and without concurrent or past anti-TNF treatment (p = 0.3169 and p = 0.7571, respectively).

Discussion
In our IBD clinic with a large collective of 1,026 patients, 22 (2.1%) patients developed a malignancy over a time course of 7 years (2007–2014). The median latency between IBD diagnosis and occurrence of malignancy was 13 years. Of note, CCC was the earliest diagnosed tumour, with a mean latency of 13.5 years. The mean age of patients at diagnosis of malignancy was 59.5, similar to data in the literature (56.2 years [17]).

Lymphomas were the most frequent malignancies within our IBD cohort, making up 6 (21%) of all malignancies. The incidence of lymphoma in the IBD cohort was estimated to be 32.5/100,000, for NHL 27/100,000, and for Hodgkin lymphoma 5.4/100,000. The incidence rates (related to 100,000) of lymphoma in the general Swiss population, published by the Foundation NICER, were lower (Hodgkin lymphoma: 3.7 (males), 2.5 (females); NHL: 16.9 (males), 11.7 (females)) [18]. The
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<th>Thioguanine</th>
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m = Man; w = woman; y = yes; n = no; n.d. = no data. In the last column, the second number (if present) refers to a relapse/second malignancy.
CESAME study group found a similar incidence for lymphoma (related to 100,000) in French IBD patients (26/100,000 in patients discontinuing thiopurines, 20/100,000 for patients who never assumed thiopurins) [11]. Our results confirm that the incidence of lymphoma in IBD patients is higher than in the general population and is in line with other studies [10, 19]. An association between thiopurines (AZA, 6-MP, TG) and lymphoma (especially NHL) is described in the literature [11, 20]. In our cohort, 2 patients received thiopurines, 3 patients anti-TNF antibodies, and 1 patient both thiopurines and anti-TNF antibodies. Due to the small sample size of patients in our cohort, it is difficult to assess a link between medication and lymphoma. Our data suggest that lymphomas are more common in patients with CD than UC patients, in males rather than in females, and occur more frequently than in the general Swiss population. These findings are in line with available literature from other countries [21, 22].

CRC was the second most common malignancy in our IBD patients, making up 14% of all cancers. We estimated an incidence of 21.7/100,000, which is lower than the incidence in the general Swiss population (NICER, 47.7 for males, 29.5/100,000 for females). Similar results were achieved by a recent Spanish cohort study [23]. This paradoxical result is most likely caused by the fact that the median age of the investigated population was quite low and the incidence of CRC increases with age. Another reason for the low incidence may be our strict regular endoscopic screening of IBD patients, which may prevent the occurrence of CRCs [24, 25]. This decreasing trend was also confirmed by other recent studies [25, 26].

Bladder carcinoma was the third most frequent cancer. All the patients were male, with an estimated inci-

<table>
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<tr>
<th>Disease, n</th>
<th>Total numbers and type of malignancies</th>
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<tr>
<td>UC</td>
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<td>Total (n = 28), n (%)</td>
<td>1 (4)</td>
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HCC = Hepatocellular carcinoma. * The second event represents a relapse.

Table 2. Demographic characteristics of 22 IBD patients with malignancies after diagnosis of IBD, from our IBD outpatient clinic with 1,026 patients

Table 3. Summary of malignancies developed by IBD patients
The NICER data indicate an incidence of 16.7/100,000 for males. Our data are consistent with studies in other populations [4, 27, 28]. Especially, a recent publication by Beaugerie and Itzkowitz [1] pointed to the higher incidence of urothelial cancers in patients taking thiopurines, but not anti-TNF alpha antibodies. CCC occurred in our cohort only in UC patients with an estimated incidence of 10.8/100,000. Data from the general population indicate an incidence of 2.9/100,000 for males and 2.5/100,000 for females. An incidence of 21.7/100,000. The NICER data indicate an incidence of 16.7/100,000 for males. Our data are consistent with studies in other populations [4, 27, 28]. Especially, a recent publication by Beaugerie and Itzkowitz [1] pointed to the higher incidence of urothelial cancers in patients taking thiopurines, but not anti-TNF alpha antibodies. CCC occurred in our cohort only in UC patients with an estimated incidence of 10.8/100,000. Data from the general population indicate an incidence of 2.9/100,000 for males and 2.5/100,000 for females. An incidence of 21.7/100,000. The NICER data indicate an incidence of 16.7/100,000 for males. Our data are consistent with studies in other populations [4, 27, 28]. Especially, a recent publication by Beaugerie and Itzkowitz [1] pointed to the higher incidence of urothelial cancers in patients taking thiopurines, but not anti-TNF alpha antibodies. CCC occurred in our cohort only in UC patients with an estimated incidence of 10.8/100,000. Data from the general population indicate an incidence of 2.9/100,000 for males and 2.5/100,000 for females. An incidence of 21.7/100,000. The NICER data indicate an incidence of 16.7/100,000 for males. Our data are consistent with studies in other populations [4, 27, 28]. Especially, a recent publication by Beaugerie and Itzkowitz [1] pointed to the higher incidence of urothelial cancers in patients taking thiopurines, but not anti-TNF alpha antibodies. CCC occurred in our cohort only in UC patients with an estimated incidence of 10.8/100,000. Data from the general population indicate an incidence of 2.9/100,000 for males and 2.5/100,000 for females. An incidence of 21.7/100,000. The NICER data indicate an incidence of 16.7/100,000 for males. Our data are consistent with studies in other populations [4, 27, 28]. Especially, a recent publication by Beaugerie and Itzkowitz [1] pointed to the higher incidence of urothelial cancers in patients taking thiopurines, but not anti-TNF alpha antibodies. CCC occurred in our cohort only in UC patients with an estimated incidence of 10.8/100,000. Data from the general population indicate an incidence of 2.9/100,000 for males and 2.5/100,000 for females. An incidence of 21.7/100,000. The NICER data indicate an incidence of 16.7/100,000 for males. Our data are consistent with studies in other populations [4, 27, 28]. Especially, a recent publication by Beaugerie and Itzkowitz [1] pointed to the higher incidence of urothelial cancers in patients taking thiopurines, but not anti-TNF alpha antibodies. CCC occurred in our cohort only in UC patients with an estimated incidence of 10.8/100,000. Data from the general population indicate an incidence of 2.9/100,000 for males and 2.5/100,000 for females. An
incidence of 8.2/100,000 has been reported in a Danish cohort study for UC patients [17]. In our study, there is a much higher rate in UC patients, in line with literature data [4, 17]. The risk for CCC in UC patients is mainly caused by primary sclerosing cholangitis PSC [29] as confirmed in our cohort. The incidence of malignant melanoma was estimated to be 5.4/100,000, whereas NICER data suggested an incidence of 26.4 for males and 23.3/100,000 for females in Switzerland. The low incidence is in contrast with most of the population-based studies [4, 14, 30]. However, the CESAME cohort study found an incidence similar to the general population [31]. Algaba et al. [23] also confirmed this new trend. The suggested regular skin cancer screening in IBD patients may be the reason for this finding. HSTCL is a rare disorder, and only 200 cases were reported worldwide in the literature [32, 33]. Our case was consistent with literature cases [34–36], who showed the typical constellation (relatively young man (41 years)) with longstanding CD who developed HSTCL after assuming 6-MP and IFX.

Taken together, our data suggest that lymphoma (especially NHL), urothelial carcinoma and CCC are more common in IBD patients than in the general Swiss population.

Certainly this study has several limitations. We presented the data from only 1,026 IBD patients retrospectively. Patients were recruited in a tertiary referral centre for IBD. In Switzerland, patients with mild or moderate disease are usually managed by general practitioners or private practice gastroenterologists. Only patients with severe disease are usually seen at referral centers. Therefore, patients with mild disease are underrepresented in this study and the findings might therefore be biased towards more severe disease courses. Additionally, not all patients were initially diagnosed with IBD at our clinic but were seen after a major event within the course of IBD. Therefore, some data regarding medication, cancer stage and in some cases latency until occurrence of cancer are incomplete. However, more severe disease is more likely to be treated with immunosuppressive agents and may thus be more prone to the development of malignancies. This would mean that our data overestimate the risk of malignancies and their incidence as compared to a desirable Swiss population-based study. Population-based studies certainly come closer to the ‘true incidence’ of malignancies in IBD patients. However, the patients at highest risk are seen in referral centres. Therefore, we believe that our data are of value especially for those centers.

In summary, our data indicate that the onset of malignancy in IBD patients is associated with a long-standing disease course of IBD, but also with the use of immunosuppressive medication. Our data are in line with the literature. However, the incidence rates are lower than expected. Of note is the relatively high incidence of urothelial carcinoma supporting recent findings from the CESAME cohort. The risk for this tumor entity has so far been overlooked and further studies to evaluate a place for surveillance programs for urothelial cancer in IBD patients are warranted.

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**Disclosure Statement**

The authors declare no competing interests.

**Author Contributions**

M.M. and J.Z. wrote the manuscript and interpreted the data. All other authors were involved in data acquisition and data interpretation. M.S. conceived the study design and supervised the project. All authors wrote, corrected and approved the final draft of the manuscript.

**References**


