# Complications of Inflammatory Bowel Disease Revisited

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**Colofon**



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# Een herziene benadering van complicaties van inflammatoire darmziekten

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*Opgedragen aan mijn lieve vader*

## CONTENT

# Chapter I

## General introduction and thesis-outline

## INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease (IBD) encompasses two major chronic gastrointestinal diseases of unknown origin: ulcerative colitis (UC) and Crohn's disease (CD). UC solely affects the colon, whereas CD can involve any component of the gastrointestinal tract from the oral cavity to the anus. In 2004, an estimated 1.4 million persons in the United States and 2.2 million persons in Europe suffered from these diseases.[1] The incidence of IBD has been increasing over the years, which for UC varies greatly between 0.5 and 24.5/$10^5$ inhabitants, and for CD varies between 0.1 and 16/$10^5$ inhabitants worldwide.[2,3] The prevalence rates of IBD reach up to 396/$10^5$ inhabitants.[3]

## COMPLICATIONS OF IBD

IBD patients have a diminished quality of life, both as a consequence of the disease and its treatment.[4,5] Several therapeutic strategies, including the wide use of immunomodulatory agents, have been advocated in the treatment of these chronic diseases, each with its own risks and benefits.[6] Besides the treatment-associated risks, IBD itself is also associated with several complications, including haemorrhage, intestinal perforation or stricturing, development of fistulas (in CD patients) and abscess formation and the development of colorectal carcinoma (CRC). These complications have a large impact on patients' quality of life. Clinical practice is evolving rapidly, with increasing understanding of the pathogenesis of IBD and its complications. Consequently, patients are also confronted with these new insights into their disease, the treatment and the prevention of complications, including intense CRC screening programs, and medications with often unknown side-effects. Research in this patient group is therefore in need of a multidisciplinary approach. Adherence to treatment is an important aspect in preventing the relapsing course of disease and the development of complications. Patients' perceptions of their disease, effect of medication and the associated risks are increasingly recognized as important determinants of disease outcome. The clear understanding of determinants of adherence is likely an important factor that could contribute towards improving the outcome of complications of IBD.

This thesis addresses several aspects of complications in IBD from a multidisciplinary perspective. This thesis will in the first place address the risks of malignancy in IBD including the role of CRC surveillance colonoscopy. Secondly, we will address the patients' perceptions of their disease and the associated risks.

## PART 1: (PRE) MALIGNANT COMPLICATIONS OF IBD

### Cancer in fistulas

Fistulas result from full-thickness disease of an hollow organ rupturing into an adjacent hollow viscus or through the abdominal wall and are a common manifestation of CD. Two major types of fistulas in CD patients are perianal- and enterocutaneous fistulas. Perianal fistulas are abnormal communications between rectum and skin. The specific pathogenesis of perianal fistulas is unknown. They occur in up to 43% of CD patients and can result in substantial morbidity, like fecal incontinence, scarring and continuous seepage.[7] Enterocutaneous fistulas are abnormal communications between bowel and skin. **Chapter II** describes a CD patient who presented with a persistent enterocutaneous fistula. Although colonoscopy did not show any abnormalities, the resection specimen surprisingly revealed a well-differentiated adenocarcinoma, originating from the fistulous tract. This case report raised the question of how often cancer does in fact complicate fistulas. In **chapter III** we present the results from a retrospective cohort study in which we assessed the prevalence of cancer in enterocutaneous or perianal fistulas in nine large hospitals in The Netherlands.

### Small bowel cancer

IBD patients carry an increased risk of developing CRC.[8-10] CD patients also appear to have an increased risk of small bowel cancer.[10] **Chapter IV** elaborates in this issue in greater detail with a case series of three CD patients who developed an adenocarcinoma in the small bowel.

### IBD-related CRC

#### *Epidemiology*

CRC is among the most feared long-term complications of IBD and accounts for approximately 10-15% of all deaths in IBD patients.[8] The exact magnitude of the CRC risk has remained controversial in the past due to various biases and methodological errors in published studies. A well-cited meta-analysis from 2001 estimated the cumulative incidence of CRC in UC patients at 2% after 10 years of disease, 8% after 20 years and 18% after 30 years of disease.[8] Recent population-based studies indicate a much lower risk ranging from 1/500 to 1/1600 patients annually.[11] **Chapter V** will give an overview and critical appraisal of the current knowledge about the epidemiology of IBD-related CRC.

#### *Risk factors*

Several risk factors for CRC have been identified, including long disease duration, extent of disease beyond the hepatic flexure, co-presence of primary sclerosing cholangitis (PSC), the presence of pseudopolyps and a family history of sporadic CRC.[12-17] The risk also varies with geography: incidence rates for CRC are higher in the USA and the UK compared to Scandinavia and other countries.[8] However, it is unknown whether these risk factors solely apply

to patients in tertiary referral centers and data on CRC characteristics of IBD patients from non-referral centers are limited. Moreover, many studies are small, making it difficult to study several variables simultaneously and to adjust for potential confounders.

*Risk analyses*

Data on the IBD-related CRC risk and the associated risk factors are inconclusive and it remains therefore uncertain whether we are over-, or underestimating the actual IBD-related CRC risk. In **chapter VI** we report the results of a nationwide nested case-control study to assess the risk of developing IBD-related CRC in patients seen in general, non-academic hospitals. Moreover, we studied the characteristics of IBD-related CRC to assess risk-factors for developing CRC in general hospitals using time-dependent analyses.

## Surveillance

Surveillance colonoscopies are an important strategy to detect CRC and dysplasia at an early stage and thereby decrease CRC-related morbidity and mortality.[18, 19] Current recommendation is to take at least 33 biopsies from the colon at various levels to have a 90% sensitivity for the detection of dysplasia.[20] A reasonable way to do this is to take at least 4 random biopsies at 10 cm distances apart along the entire colon; in addition all suspicious, raised or strictured areas should be biopsied. The most recent surveillance guideline recommends pancolonic dye spraying with targeted biopsy of abnormal areas as the technique of choice.[23]

Guidelines recommend to initiate surveillance in those patients who have had extensive colitis for 8-10 years and in those who have had left-sided colitis for 15-20 years.[21, 22] More recent guidelines suggest to perform a screening colonoscopy after 8-10 years of disease in *all* IBD patients irrespective of disease extent.[23, 24] For those with concomitant PSC, at risk for both CRC, cholangiocarcinoma and hepatocellular carcinoma, annual colonoscopy is indicated. Of note, a recent study in the Dutch academic medical centers suggested that IBD patients developed CRC even before the recommended start of surveillance.[25] However, data on clinical characteristics of IBD-related CRC cohorts, including factors that lead to earlier development of CRC, are scarce and mainly originate from tertiary centers.[25-27] Data on both patient-, and disease characteristics of patients with IBD-related CRC from non-tertiary community care centres are lacking. It is therefore unknown whether the clinical characteristics of high-risk tertiary referrals differ from the average IBD population in general hospitals. To implement evidence based surveillance strategies in the total IBD population, characteristics of patients with IBD-related CRC in general hospitals are needed. Moreover, parameters which may predispose to early development of CRC in general hospitals need to be determined to identify subgroups of patients in need of earlier start of surveillance. **Chapter VII** reports on our studies to identify patient-, and disease characteristics of IBD-related CRC in patients from general hospitals in The Netherlands.

*The burden of CRC surveillance*

CRC surveillance for all IBD patients is associated with major burden and costs that may not be of benefit for many patients. An individually tailored CRC surveillance program in IBD patients would be of major benefit. In **chapter VIII** we processed the data from the nested case-control study presented in Chapter VI. We propose a model that can be applied in daily clinical practice allowing for an individualized approach to CRC surveillance needs in IBD patients in general hospitals.

*Mucosal inflammation while the patient is clinically in remission*

Mucosal healing in IBD may be an important sign of efficacy of treatment and a prognostic marker of long-term disease. Endoscopic examination of asymptomatic IBD patients often reveals ulcers, erosions, or strictures. However, data are lacking on whether it is necessary to interfere with the therapeutic strategy when a patient in clinical remission shows endoscopic inflammation. Furthermore, it is unknown if interference is needed for those with histological inflammation only. In **chapter IX** we report on our studies of the prevalence of mucosal inflammation in patients in clinical remission, the therapeutic decisions that are consequently made in clinical practice, and the impact on the disease course. Moreover, we distinguish between endoscopic and histological inflammation to assess any disparities with regard to the treatment strategy and course of disease.

*Asymptomatic inflammation as a pitfall for surveillance colonoscopy*

Active inflammation is one of the pitfalls during surveillance. The specificity of dysplasia as a marker of pre-cancer or cancer is controversial. Low-grade dysplasia is difficult to distinguish histologically from regenerative changes as a result of inflammation.[28] Therefore surveillance biopsies cannot be accurately assessed when active mucosal inflammation is present. For these reasons, surveillance colonoscopies may need to be repeated or rescheduled in patients with active inflammation. This is a burden for both patients as well as the endoscopy unit. **Chapter X** describes a prospective randomized controlled study that addresses the issue as to whether corticosteroid pretreatment may enhance a more reliable assessment of dysplasia severity by decreasing active mucosal inflammation.

## PART 2: PATIENTS' PERCEPTIONS OF DISEASE AND ASSOCIATED RISKS

### Patient empowerment

Patients' perceptions as a part of patient empowerment and shared decision-making are becoming increasingly important in therapeutic strategies for chronic diseases like IBD.[29] Patient empowerment includes that patients are responsible for their choices and the consequences of their choices. As a result of empowerment, patients may develop a greater sense

of self-efficacy regarding various disease and treatment-related behaviors, and may express changes in life priorities and values. Due to empowerment, patients are also expected to better self-manage not only their disease, but also their lives.[30]

### Shared decision-making

Shared decision-making is increasingly advocated as an ideal model of treatment decision-making.[31-33] In this model the physician has the responsibility to inform the patients and to give them advice, whereas the actual decisions on how to act on this information are made in collaboration between the patient and physician.[34] It has been suggested that patients show better adherence when they are actively involved in the decision-making process.[35, 36] Non-adherence is an important reason for relapsing disease in IBD.[37] Shared decision-making can be used to educate patients about the utmost importance of adherence to medication and the necessity to commit and follow-through on their treatment. A systematic review of the effects of shared decision-making suggested that shared decision-making is especially suitable for long-term decisions and/or in case of a chronic disease.[36] However, further data on the preferences of patients with IBD are lacking. **Chapter XI** therefore describes a large patient empowerment study assessing IBD patients' preferences with regard to their involvement in the decision of treatment choices.

### Patients' knowledge of disease and associate risks

Patients' perceptions and their accurate knowledge of their disease are of utmost importance to make appropriate decisions regarding the management of their disease. However, limited data are available about IBD patients' knowledge of disease and the associated risks. In **chapter XII** we therefore map out IBD patients' knowledge of disease, perceived risks of CRC and colonoscopy, and their perspectives on the current recommendations for colectomy when low-grade dysplasia is found. Moreover, in **chapter XIII** we assessed IBD patients' perspectives of the treatment-associated risks and benefits of anti-Tumor Necrosis Factor (anti-TNF) treatment.

### Therapy adherence and disease- related functional status

Adherence to treatment is an important aspect in preventing the relapsing course of disease and the development of complications. However, the available data on adherence in IBD patients are contradictory and stimulating adherence might therefore be a challenge. To elucidate further on the impact of IBD on daily life and to assess IBD patients' perceptions of therapy adherence we describe in **chapter XIV** the results from a nationwide patient empowerment study on therapy adherence and functional status in IBD patients.

### Conclusions and future directions

Finally, **chapter XV** will present an overview and general discussion of the results presented in this dissertation. Moreover, it will discuss the impact of our results on clinical practice and future research.

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# Chapter II

## Surgery is indicated for persistent enterocutaneous fistulizing Crohn's disease

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## ABSTRACT

We describe a patient with Crohn's disease who presented with a persistent enterocutaneous fistula. Colonoscopy showed no abnormalities in the terminal ileum and cecum. The patient was treated with corticosteroids and azathioprine for Crohn's disease. The fistula responded partially to therapy. Surgery was performed and revealed a well-differentiated adenocarcinoma, originating from the fistula tract. In persistent enterocutaneous fistulas surgery is indicated and could keep us from shocking surprises.

## CASE REPORT

A 41-year old male with a five-year history of Crohn's disease presented to our hospital with a persistent enterocutaneous fistula in the right lower quadrant of the abdomen. Five years earlier, he had been admitted to the hospital because of a fistula in the right lower part of the abdomen. Colonoscopy and small bowel follow through demonstrated no abnormalities, however an ultrasound revealed thickening of the wall of the ileum, and an abscess in the right lower abdomen. The abscess was drained by a CT-guided drain, however, a draining fistula persisted. Due to the abnormalities on the small bowel follow through and the persisting fistula the diagnosis of Crohn's disease was made. Therefore the patient was treated with prednisolon, azathioprine and mesalazine. The patient showed partial responds to this therapy. He was then, five years after initial presentation with Crohn's disease, referred to our outpatient clinic. On physical examination a draining enterocutaneous fistula was observed, no other abnormalities were found. Biochemistry revealed an increased CRP of 27 mg/l (n= < 3 mg/l). Colonoscopy demonstrated no abnormalities. An ultrasound revealed an infiltrate around the ileum. Due to this persistent fistula he was referred for surgery.

One week before the planned surgery the patient was admitted due to a rise in temperature. An ultrasound showed an inflammatory infiltrate in Douglas, but no signs of an abscess. The patient was treated with oral prednisolon 30 mg daily, amoxicillin-clavulanate 625 mg daily, and azathioprine 200 mg daily. Because of increased swelling and pain, and a temperature rise during treatment of prednisolon, another ultrasound was performed five days later. This ultrasound showed an active fistulous tract without any trace of an encapsulated abscess, nor of free fluid in Douglas (Figure 1).

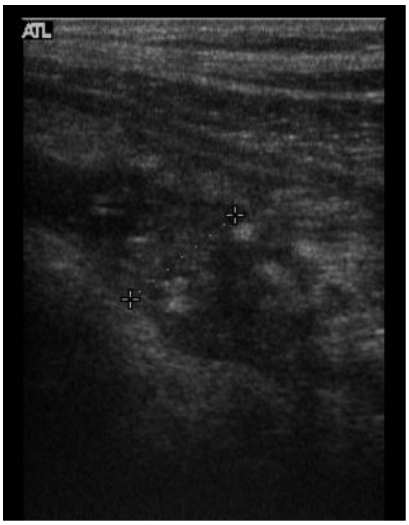


**Figure 1.** Fistula in the abdomen with heterogeneous polypous structure inside the lumen, suspect for malignancy (diameter 1.42 cm).

The patient was therefore referred for surgery. By means of a laparatomy an ileocecal resection was performed with creation of an ileo-stoma. Histopathology of the resection specimen revealed a perforation of the ascending colon with localization of a well-differentiated adenocarcinoma, originating from the fistulous tract (Figure 2). The mucosa of the resection specimen demonstrated an inactive inflammation. One of the four lymph nodes was positive. A CT scan was performed and did not reveal any metastases. Decided was to start on adjuvant chemotherapy. The tumor was staged as pT2 N1 M0.

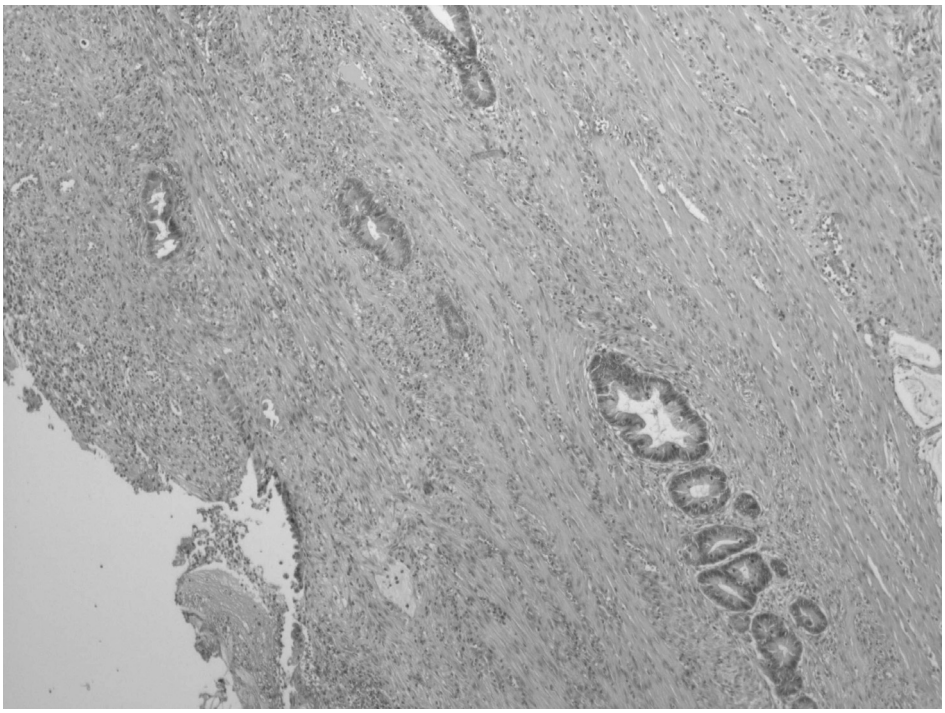

**Figure 2.** H&E section demonstrating adenocarcinoma infiltrating the muscular layer of the colon (right side) and covering part of the fistulous tract (left side; 10x objective).

## DISCUSSION

Enterocutaneous fistulas are abnormal communications between bowel and skin. The majority of enterocutaneous fistulas (75-85%) arise postoperatively, most commonly after surgery performed for a malignancy, inflammatory bowel disease, or adhesiolysis. Around 20% of all enterocutaneous fistulas occur spontaneously. These fistulas develop in the presence of cancer or inflammatory bowel disease. Enterocutaneous fistulas also occur in the presence of previous radiation therapy, diverticular disease, appendicitis, perforated ulcer disease or ischemic bowel.[1]

Our patient was diagnosed with Crohn's disease. He had developed an enterocutaneous fistula without antecedent surgery, radiotherapy or cancer. He was therefore treated for Crohn's disease with prednisolon and azathioprine, but he responded only partially to this therapy.

Known is that treatment of enterocutaneous fistulas may be difficult and long-term. Possible therapies are operative management and conservative management. Adequate nutritional support is an essential factor in reducing the mortality rate of both treatments.[2] Surgical treatment consists primarily of the resection of the diseased intestinal segment, extirpation of the fistula, and debridement of the fistulous tract through the abdominal wall and subcutaneous tissue.[3] Prior to the development of Infliximab, patients with fistulas often required surgery, since medical management was rarely successful. The response to Infliximab in Crohn's patients is associated with the type of fistulas. Present *et al.* stated that Infliximab is efficacious in the treatment of enterocutaneous fistulas complicating Crohn's disease.[4] Evenson *et al.* on the other hand, concluded in their article that the role of Infliximab in the management of enterocutaneous fistulas remains to be resolved.[1] Since medical therapy was not successful in our patient and a draining enterocutaneous fistula persisted, decided was not to give Infliximab and the fistula was removed surgically.

Enterocutaneous fistulas have been associated with a high risk of morbidity and death. The mortality of enterocutaneous fistulas is 10 to 30% and is related to sepsis, malnutrition, and fluid, electrolyte or metabolic disturbances. Early diagnosis of the fistula and resuscitation of the patient, early recognition and control of sepsis with imaging-guided drainage and antibiotic therapy, fluid and electrolyte balance and meticulous wound care may further limit the morbidity and mortality.[1, 2]

Because of the longstanding existing fistula our patient was admitted for surgery and surprisingly a primary adenocarcinoma within the fistula tract was found. There is sparse literature on the occurrence of cancer in enterocutaneous fistulas. A study with 17 year's follow-up after surgical management of enterocutaneous fistulas in Crohn's disease did not report the occurrence of cancer.[5]

However, a few case reports have described the development of adenocarcinoma in perianal fistulas complicating Crohn's disease.[6] A review of the literature demonstrates that 15 of 33 cases (45 percent) of anorectal carcinoma in Crohn's disease were associated with fistulas.[7] The causative relationship between anorectal fistulas and cancer is unknown as well as the pathogenesis of carcinoma in enterocutaneous fistulas. Traube *et al.* stated that adenocarcinoma in the fistula tract may develop because of chronic stimulus to mucosal regeneration, known as "scar-tissue carcinoma".[8] Church *et al.* suggested that in some cases the carcinoma may be the cause of the fistula.[9] The diagnosis of adenocarcinoma in chronic fistulas is difficult and

may be delayed further since symptoms usually are attributed to the fistula and therefore adenocarcinoma may not be suspected and biopsy examination is usually performed late.[10] Based on this present case report we can conclude that in persisting enterocutaneous fistulas earlier surgery is indicated.

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# Chapter III

## Malignant transformation of perianal- and enterocutaneous fistulas occurs rarely: Results of 17 years of follow-up from The Netherlands

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## ABSTRACT

**Background and aims:** Malignant transformation of fistulas has been observed, in particular in perianal fistulas in Crohn's disease (CD) patients. The prevalence of adenocarcinoma in enterocutaneous fistulas and non-CD related fistulas, however, is unknown. We investigated adenocarcinoma originating from perianal and enterocutaneous fistulas in both CD patients and non-CD patients from nine large, mostly tertiary referral, hospitals in The Netherlands.
**Methods:** Patients suffering from fistulizing disease and either dysplasia or adenocarcinoma between January 1990 and January 2007, were identified using the nationwide automated pathology database (PALGA). Clinical and histopathological data were collected and verified using hospital patient charts and reported by descriptive statistics. The total CD population comprised 6058 patients.
**Results:** In a study-period of 17 years, 2324 patients with any fistula were reported in PALGA. In 542 patients also dysplasia or adenocarcinoma was mentioned. After initial review and additional detailed chart review, 538 patients were excluded, mainly because the adenocarcinoma was not related to the fistula. In the remaining four patients, all suffering from CD, adenocarcinoma originating from the fistula tract was confirmed. The malignancies developed 25 years (IQR 10-38) after CD diagnosis, and 10 years (IQR 6-22) after fistula diagnosis. Median age at time of adenocarcinoma diagnosis was 48.3 years (IQR 43-58). Only one patient had clinical symptoms indicative for adenocarcinoma. In three other patients, the adenocarcinoma was found coincidently.
**Conclusions:** Adenocarcinoma complicating perianal or enterocutaneous fistula tracts is a rare finding. Only 4 out of 6058 CD patients developed a fistula-associated adenocarcinoma. We could not identify any malignant transformations in non-CD related fistulas in our 17 years study-period.

## INTRODUCTION

Fistulas constitute a common complication of Crohn's disease (CD) and occur in 30-50% of CD patients at some time during the course of their illness.[1, 2] They result from full-thickness disease rupturing into an adjacent hollow viscus or through the abdominal wall; however the exact pathogenesis still remains unclear. Fistulas are classified according to their location and their connection with contiguous organs.[3] They can be external (e.g. perianal or enterocutanous fistulas) or internal (e.g. enteroenteric, enterovesical, enterouterine, or enterovaginal fistulas connecting the intestine with various organs or anatomic structures).

In a few case reports, the development of adenocarcinoma in perianal fistulas complicating CD has been described.[4] A recent systematic review of literature on cancer in perianal fistulas in CD patients revealed 61 published cases.[5] The causal relation between anorectal fistulas and cancer is unknown. The diagnosis of adenocarcinoma in chronic fistulas is difficult and may be delayed further since symptoms are usually attributed to the fistula and may therefore postpone suspicion for development of adenocarcinoma.[6]

Prior studies mainly focused on perianal fistulas as a complication of CD and little is known about adenocarcinoma in enterocutaneous fistulas and in non-CD related fistulas. A study with 17 years of follow-up after surgical management of enterocutaneous fistulas in CD did not report the occurrence of adenocarcinoma.[7] In a recent case report we described the development of adenocarcinoma in a CD patient with a longstanding enterocutaneous fistula.[8]

We hypothesized that patients with CD-related fistulas are at increased risk for malignant transformation of perianal or enterocutaneous fistulas, whereas this risk is probably not increased in patients with non-CD-related fistulas. If so, screening is probably necessary. Hence, we aimed to identify all adenocarcinomas originating from perianal and enterocutaneous fistulas in nine large hospitals (eight academic and one third-line referral hospital) in The Netherlands. Secondly, we assessed the clinical characteristics of those subjects with an adenocarcinoma originating from a fistula.

## MATERIALS & METHODS

### Study population

Patients with dysplasia or adenocarcinoma in a perianal fistula or enterocutaneous fistula in The Netherlands were identified using the nationwide network and registry of histology and cytopathology (PALGA).[9] The PALGA database contains all pathology reports generated in the Netherlands from 1990 until the present, and are concluded with diagnostic terms in line with

SNOMED® terminology. Each subject in the database has a unique identifier which allows tracking of individual patients over time and throughout the country. The following search criteria were used for the time period January 1st, 1990 until January 1st, 2007: (colon OR rectum OR anus) AND fistula AND (all primary carcinoma AND/OR atypia AND/OR all epithelial dysplasia AND/OR all carcinoma in situ AND/OR all micro invasive tumors). Additionally, in a second search The PALGA system was searched for the word "fistula" mentioned in free text of all pathology reports from the nine participating hospitals. The participating hospitals were the Erasmus Medical Center, Rotterdam, VU University Medical Center Amsterdam, University Medical Center Groningen, Leiden University Medical Center, Radboud University Medical Center Nijmegen, Academic Medical Center Amsterdam, University Medical Center Utrecht, Maastricht University Medical Center and Rijnstate Hospital, Arnhem.

### Outcome parameters

The primary outcome measure was the presence of adenocarcinoma in perianal or enterocutaneous fistulas. The secondary outcome variable was the presence of adenocarcinoma in CD related perianal or enterocutaneous fistulas.

To delineate the definition of fistula-tract-associated adenocarcinoma, the PALGA-report had to fulfill the following criteria: the fistula had to be present > 6 months prior to diagnosis of adenocarcinoma, and the fistula and the adenocarcinoma had to occur in the same histology-specimen. Exclusion criteria were the following: occurrence of adenocarcinoma at an anatomical localization apart from the fistula, fistula formation due to adenocarcinoma or fistulizing inflammation along with an adenocarcinoma. If there was any doubt about the origin of the adenocarcinoma in relation to the fistula, the patient was not excluded at this stage. Of the selected patients, clinical charts and pathology reports were reviewed to confirm the diagnosis of adenocarcinoma and fistulas.

If the diagnosis was confirmed, additional data concerning gender, age, type and cause of the fistula, disease characteristics of adenocarcinoma/dysplasia and fistula, date of onset of the fistula and date of adenocarcinoma, history of colonic surgery, and presence of CD were collected. The complete medical history was assessed, including prior colonoscopies and pathology reports. If CD was present the following data were additionally collected: date of diagnosis, date of onset symptoms attributable to CD, duration of disease, and disease characteristics including extent of disease, severity of disease, surveillance-details, and CD-behavior. Extent of disease was subdivided in four categories based on type and extension of inflammation: limited CD, extensive CD, ileitis terminalis only, and ileocecal CD. Limited CD was defined as <50% segmental CD in the colon and extensive CD was defined as >50% segmental CD in the colon. Severity of disease was graded as mild, moderate or severe colitis based on both histological and endoscopic features. Duration of medication use before ad-

enocarcinoma diagnosis was subdivided into four categories (0-25%, 25-50%, 50-75%, >75% of duration of follow-up).

### CD population in participating centers

The size of the CD population per hospital was assessed using local hospital registries at the departments of Gastroenterology and Hepatology in each hospital. All participating hospitals have a specialized IBD clinic with a database including all their IBD patients. The total CD population consisted of 6058 patients.

### Statistical Considerations

Descriptive statistics, including medians with interquartile ranges (IQR), are reported. Statistical analysis was performed with SPSS for Windows software (version 15.0).

## RESULTS

In the nine participating hospitals, 2324 patients (1193 males, 1021 females) had the diagnostic term fistula in the PALGA system (Figure 1). The primary search revealed 237 patients with both a fistula and dysplasia or adenocarcinoma (105 males, 121 females). An initial review of the excerpts excluded 112 patients. Main reasons for exclusion were: adenocarcinoma and fistula in different specimen, fistula caused by an adenocarcinoma or fistulizing inflammation along with an adenocarcinoma. In total, 125 out of 237 patients (41%) were included for detailed chart review to confirm diagnosis and collect clinical data.

The second PALGA search revealed 1136 pathology-excerpts from 305 patients (146 males, 159 females) from the nine hospitals. After initial review 61 patients remained eligible.

Summing up, 186 patients (125 patients from the first PALGA-search + 61 patients from the second search) were eligible for detailed chart review.

### Adenocarcinoma originating from perianal or enterocutaneous fistulas

Of the 186 cases that were included for detailed chart review, four patients had a confirmed diagnosis of an adenocarcinoma in direct association with chronic perianal or enterocutaneous fistulizing disease. Main reasons for exclusion were: fistula formation due to adenocarcinoma, or the adenocarcinoma occurred at an anatomical localization apart from the fistula.

The four patients, selected out of 2324 histopathological reports, suffered all from CD, and thus, none of the patients with non-CD related fistulas were found to have developed an

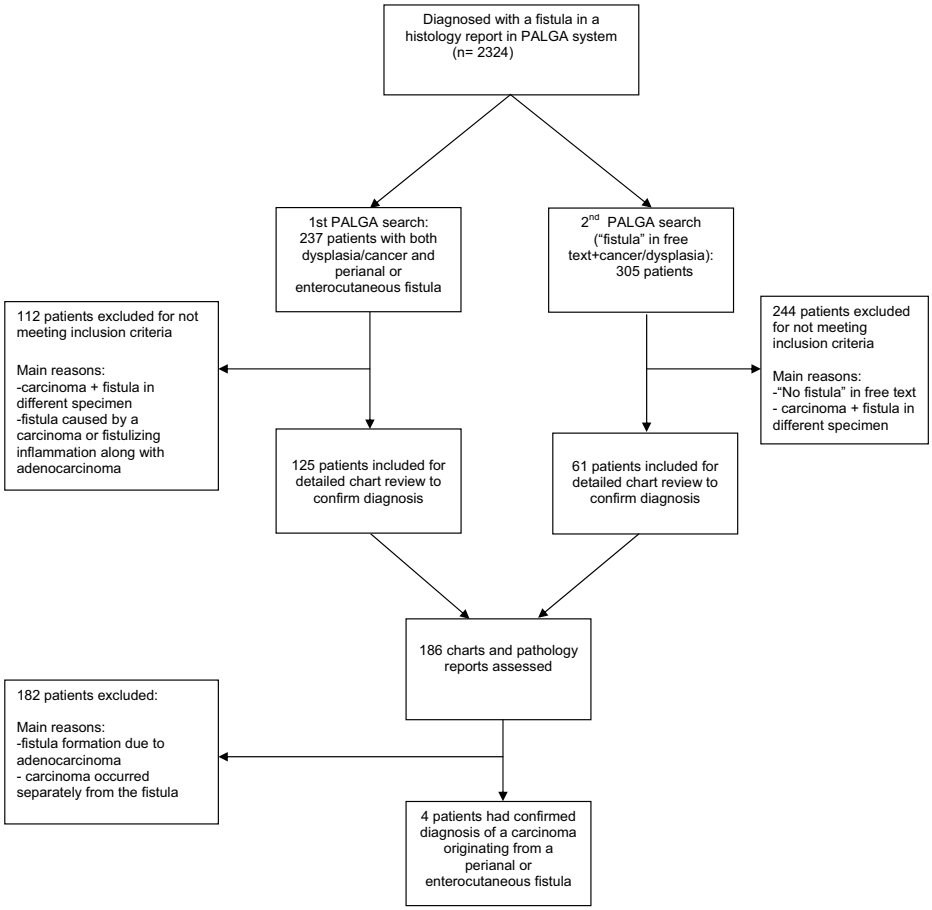


**Figure 1.** Flow chart study population

adenocarcinoma in relation with the fistula tract. Four out of 6058 CD patients developed an adenocarcinoma originating from the fistula tract.

### Patient characteristics

Clinical data for the four patients with adenocarcinoma are summarized in Table 1. All patients had persistent fistulas, which responded only partial to therapy. The median age at time of adenocarcinoma diagnosis was 46.2 years (IQR 41-58). CD disease characteristics of the four fistula-carcinoma patients are listed in Table 2. The adenocarcinoma developed on average 22 years (IQR 9-38) after establishment of CD and 9 years (IQR 4-22) after the diagnosis of a fistula tract as a complication of CD. In case of perianal fistula formation, the fistula was complex. Patient 4 was lost to follow-up at four years after adenocarcinoma diagnosis. All other patients were still alive at the end of the follow-up period (August 1st, 2008). Median follow-up time after adenocarcinoma-diagnosis was 3.5 years (IQR 2-6).

**Table 1.** Patient characteristics

| Patient No. | Gender | Age at diagnosis Carcinoma (yrs) | Duration CD (yrs) | Symptoms | Duration fistula (yrs) | Type of fistula | Cause of fistula | Type of carcinoma | Therapy carcinoma |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 41.6 | 20.7 | None | 3.8 | Perianal | IBD | Adenocarcinoma | Rectum extirpation + local radiotherapy |
| 2 | M | 41.5 | 5.4 | None | 5.4 | Entero-cutaneous | IBD | Adenocarcinoma | Right-sided hemicolectomy + chemotherapy |
| 3 | F | 50.7 | 42 | None | 25 | Perianal | IBD | Adenocarcinoma | Proctectomy + adjuvant radiotherapy |
| 4 | M | 60.2 | 24.3 | purulence resulting from fistula | 12.3 | Perianal | IBD | adenocarcinoma | Rectum amputation + chemotherapy |

**Table 2.** IBD disease characteristics

| Patient No. | Age at CD-diagnosis (years) | Extent of CD | Maximum severity of CD | Medication-use during follow-up* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 5-ASA | immunosuppressives | corticosteroids | Methotrexate | Anti-TNF |
| 1 | 20.9 | >50% segmental CD | Severe | <25% | >75% | 50-75% | <25% | - |
| 2 | 36.1 | Ileocoecal CD | Severe | >75% | 50-75% | >75% | - | - |
| 3 | 8.7 | Ileocoecal CD | Severe | - | 25-50% | <25% | <25% | <25% |
| 4 | 35.9 | <50% segmental CD | Unknown | >75% | <25% | <25% | - | - |

*between onset of CD and carcinoma diagnosis

*Medical history before adenocarcinoma diagnosis*

None of the patients had major co-morbidity in their medical history or during follow-up. In two patients several surgical procedures had been performed, all because of CD-related indications. Patient 1 underwent an ileocecal resection and reresection 13 and 8 years before diagnosis of the adenocarcinoma, respectively, and followed by drainage of peri-anal abscesses one year before adenocarcinoma diagnosis. Patient 3 underwent a subtotal colectomy 10 years prior to adenocarcinoma diagnosis.

*Diagnosis of the adenocarcinoma*

In patient 1, abdominoperineal rectum extirpation was performed because of a persistent fistula tract. No malignancies were found at this time. Four years after the surgery adenocarcinoma was found in biopsies that were taking during inspection of the area because of a persistent fistula. Revision of the initial biopsies from the resection specimen demonstrated that the tumor was already present at time of the rectum extirpation.

In patient 2, the adenocarcinoma was found coincidently during surgery for his persistent enterocutaneous fistula. Histopathology of the resection specimen revealed a perforation of the ascending colon with localization of a well-differentiated adenocarcinoma, originating from the fistula tract

In patient 3, a large perianal defect was found during physical examination in the out-patient clinic. Biopsies were taken by the dermatologist and these biopsies revealed adenocarcinoma originating from the fistula tract, consistent with an anal duct carcinoma.

Patient 4 was the only patient who had symptoms indicative, but not pathognomonic, for concurrent adenocarcinoma. This patient had a draining fistula with extensive (bloody) purulence.

## DISCUSSION

In this large retrospective cohort study in nine large hospitals from The Netherlands we confirm that adenocarcinoma is a rare complication of longstanding fistula formation. In our study-period of 17 years, in only four CD patients out of at least 2324 fistula patients, an adenocarcinoma originating from the fistula tract could be confirmed, whereas no adenocarcinoma were observed in non-CD related fistulas. The total CD cohort in these hospitals comprised 6058 CD patients.

The diagnosis of adenocarcinoma in chronic fistulas is difficult and is presumably delayed since symptoms usually are attributed to the fistula. Subsequently, adenocarcinoma may not be suspected and biopsy examination is usually performed only in a late stage of disease.[5] In our cohort, only one patient had symptoms that raised suspicion of concurrent adenocarcinoma. All other adenocarcinomas were diagnosed coincidently. In patients with longstanding complex fistulas, performance of a thorough anorectal examination is hampered, due to various reasons, such as pain, anal stricturing, and limited endoscopic view. This is in line with a systematic review of literature demonstrating that on initial examination, adenocarcinoma was suspected and proven in only 20% of cases.[6]

Previous reports have mainly focused on CD-related fistulas, in particular perianal fistulas. In a 14-year follow-up of more than 1,000 patients, only seven patients were found to have adenocarcinoma associated with anorectal fistulas.[10] The prevalence was estimated to be only 0.7% in CD patients. Additional review of 33 other cases of anorectal adenocarcinoma demonstrated that 45% were clearly associated with fistulas.[10] Connell *et al.* reported four cases of adenocarcinoma in anorectal fistulas out of 1,250 CD patients, which equals a prevalence of 0.3%.[11] Another systematic review of case series and reports published between 1950 and 2008 revealed 61 cases of adenocarcinoma arising in perianal fistulas in CD.[6] Contrary to previous studies, we did not restrict our cohort to CD patients, complicated by perianal fistulas. Although we combined both perianal and enterocutaneous fistulas and assessed also non-CD related fistulas, our results imply that the prevalence is lower than was previously reported. Out of 6058 CD patients, only four patients developed an adenocarcinoma in a longstanding fistula, which is by approximation calculated to be a prevalence of 0.004%.

This is to our knowledge the first multicenter study that aimed to specifically assess the prevalence of adenocarcinoma originating from an established fistula tract. In contrast with previous single center experiences, this study population of nine participating hospitals included all patients with an established fistula in a histopathology report. These results suggest that patients with non-CD related fistulas are not at increased risk for developing an adenocarcinoma in the fistula tract. On the other hand, inclusion of non-CD related fistulas might partly explain the low by approximation calculated prevalence for the development of malignancies in fistula tracts.

This study is limited by the fact that no exact prevalence or incidence can be given. Although we are confident to have found all the fistula-associated adenocarcinoma during our study-period, we cannot give an exact number of the baseline cohort because of the following two reasons: Firstly, biopsy specimens are only harvested by exception from 'regular' fistulas (i.e. fistulas ascribed to a complicated course of CD), and therefore no histological data are available of the majority of this type of fistulas. As the data were gathered from a histopathological

database, these series are obviously biased by having only samples from those patients from whom specimens were available following endoscopic or surgical biopsy, or from a resection specimen. Secondly, the total CD population cannot be extracted from the PALGA database. In stead, local hospital registries were used to estimate the magnitude of the baseline cohort of CD patients. Although each IBD-clinic accurately records their patient cohort and these registries are assumed to be adequately maintained, only an estimation by approximation of the prevalence of fistula-associated adenocarcinoma in CD patients can be calculated. Nevertheless, in this cohort comprising as many as 2324 patients with any fistula and an observation-period of 17 years, only four subjects developed a malignant transformation of the fistula. This implies that the estimated prevalence is unlikely to exceed 0.17% in case of patients with any manifestation of a fistula. Moreover, we estimate that the prevalence of fistula-associated adenocarcinoma in any CD patient is approximately 0.004%.

The causative relationship between anorectal fistulas and adenocarcinoma is unknown. There are two hypotheses: one suggesting that fistulas might lead to malignant transformation because of chronic inflammation of mucosa, known as "scar-tissue adenocarcinoma" [12] and another suggesting that cancer may be the cause of the fistula.[13] The latter is not supported by our study because all of our patients had a clinically established fistula for at least five years.

In conclusion, we demonstrated that adenocarcinoma complicating perianal or enterocutaneous fistulas is a rare phenomenon. Out of 2324 patients with a fistula, only four patients developed an adenocarcinoma in the fistula tract during an observation-period of 17 years. Only four out of 6058 CD patients developed a fistula-associated adenocarcinoma. We could not identify any malignant transformations in non-CD related fistulas. Although it remains a rare complication, caution is needed since the diagnosis of concomitant adenocarcinoma formation in already established fistulas is difficult to make.

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# Chapter IV

## Small bowel carcinoma mimicking Crohn's disease: a case series

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## ABSTRACT

We describe three patients diagnosed and treated for presumed Crohn's disease, but who were subsequently diagnosed with a small bowel carcinoma. This case series underlines the necessity of performing a full work up in the diagnosis of CD and to consider small bowel carcinoma in patients with small bowel CD failing medical therapy.

## CASE SERIES

### Patient 1

A 57-year old male with a 9.5-year history of Crohn's disease (CD) presented at the outpatient clinic with abdominal pain localized in the right lower quadrant of his abdomen. Because of a suspected relapse he used budenoside 9 mg and mesalazine 3000 mg daily. Small bowel follow throughs at 10 and 7 years prior to this current relapse demonstrated an extensive stenosis of the terminal ileum. During ileocolonoscopy, the terminal ileum was not intubated but erosions with edema of the mucosa were seen through the ileocecal valve. Due to the difficulty of the procedure no biopsies were taken. Colonoscopies during follow-up showed no abnormalities, but the terminal ileum was never intubated. Biopsies taken from the colon showed by histology a mild chronic, non-specific colitis with a slightly elevated number of inflammatory cells. No granulomas could be identified.

At the current presentation physical examination was normal. Biochemistry revealed a slightly increased ESR of 21 mm/hour (n= < 15) and a CRP of 24 mg/l (n= < 11 mg/l) with a normal blood count. Because of the previous difficulties with ileocolonoscopy it was decided to perform an abdominal Computed Tomography (CT)-scan which showed a thickened ileocecal valve with minor induration of the surrounding fat tissue. A colonoscopy, performed afterwards, showed a thickening of the ileocecal valve, which could not be passed. Histopathological biopsy samples from the valve revealed a mucineous adenocarcinoma.

An abdomincal Magnetic Resonance Imaging (MRI) demonstrated a pathologic terminal ileum over a distance of at least 30-35 cm (Figure 1). Furthermore, there was infiltration of the surrounding fat tissues with enlarged mesenterial glands without metastasis. The patient underwent an extended ileocecal resection. Peroperatively a peritoneal carcinomatosis was seen which was confirmed by histology. The patient was treated with three courses of chemotherapy (Oxaplatin, Avastin and Xeloda). Unfortunately; the patient died five months later.

### Patient 2

A 50-year old female presented with severe abdominal pain accompanied with vomiting. She had a two-year history of CD diagnosed by abdominal CT-scan. However, she had symptoms, possibly attributable to CD for 20 years. During the CT-scan a thickened terminal ileum over a length of at least 30 cm with extension of the inflammation in the adjoining mesenterial fat tissue was seen. Also the right-sided colon seemed involved in this process and these findings were suggestive for CD (Figure 2). A previously performed colonoscopy was without abnormalities in the colon. One year before the CD diagnosis the patient was evaluated for upper abdominal pains and was diagnosed with cholecystolithiasis and reflux esophagitis and the patient underwent a laparoscopic cholecystectomy with no further abnormalities found during laparoscopy.

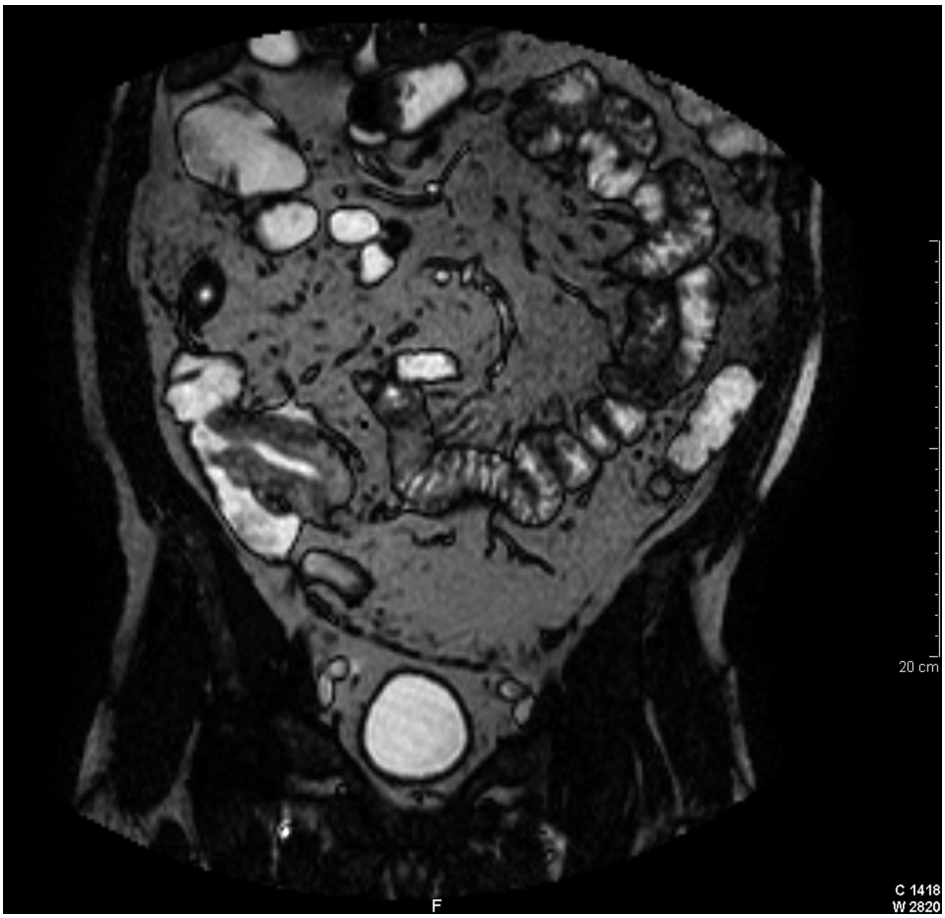


**Figure 1.** Magnetic Resonance Imaging before cancer diagnosis in patient 1. This figure demonstrates a pathologic terminal ileum with increased colouring and a wall-thickness of > 1.7 cm. Furthermore, there is infiltration of the surrounding fat tissues with enlarged mesenterial glands. There are no metastases. The pathologic segment comprises at least 30-35 cm.

After diagnosis the patient was treated with 5-ASA 3000 mg daily and prednisolon 20 mg daily, with a good initial response, and the prednisolon was tapered. However, as symptoms recurred one year before this current admission azathioprine 150 mg was added. Nevertheless, the patient's abdominal complaints deteriorated despite the use of immunosuppressives. Ileocolonoscopy showed no abnormalities but an abdominal CT-scan showed an inflamed terminal ileum with fistula tracts. She was diagnosed with relapse of CD during azathioprine and remission was induced with three times anti-TNF and for maintenance azathioprine was switched to methotrexate subcutaneously 25 mg weekly.

At current presentation, 8 months after anti-TNF induction therapy, she presented at the emergency room. Physical examination revealed signs of intestinal obstruction. A CT-scan

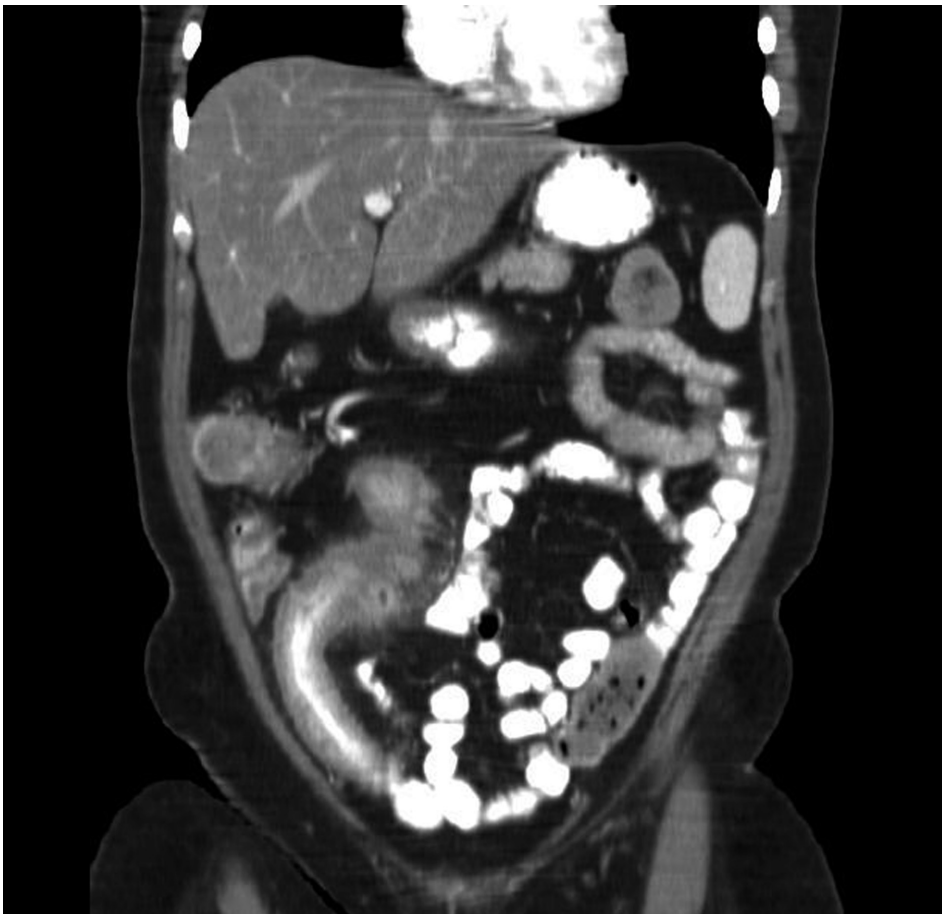

**Figure 2.** A CT-scan of patient 2 suggestive for CD. This figure demonstrates a thickened terminal ileum of at least 30 cm with extension of the inflammation in the adjoining mesenteric fat. Moreover, the right-sided colon seems to be involved in this process.

was performed and showed stenosis of the terminal ileum. The patient was referred for an immediate ileocecal resection, at which 30-50 cm of the small bowel was resected with construction of an ileocolonic anastomosis. Histological examination of the resected specimen revealed extensive inflammation with a highly differentiated adenocarcinoma, growing into the tunica propria. The tumor was staged as pT2N0Mx. The patient recovered well and is still under control for her CD, which is momentarily in remission. Five years after surgery there are still no signs of tumor recurrence.

### Patient 3

The 3rd patient is a 48-year old female who was admitted because of vomiting, diarrhoea, abdominal pain and weight loss since 7 months. Her past medical history consisted of fibromyalgia and congenital deafness. Her symptoms deteriorated two weeks before presentation

with severe abdominal cramps that were located in the left abdomen, and were related to food intake. Physical examination demonstrated signs of an acute abdomen. Biochemistry revealed an elevated CRP of 35 mg/l (normal < 11mg/l). An abdominal CT-scan showed a stenosis in the terminal ileum with prestenotic dilatation of the entire small intestine. Furthermore, moderate abdominal lymphadenopathy was seen. She was diagnosed having probable CD (Figure 3).

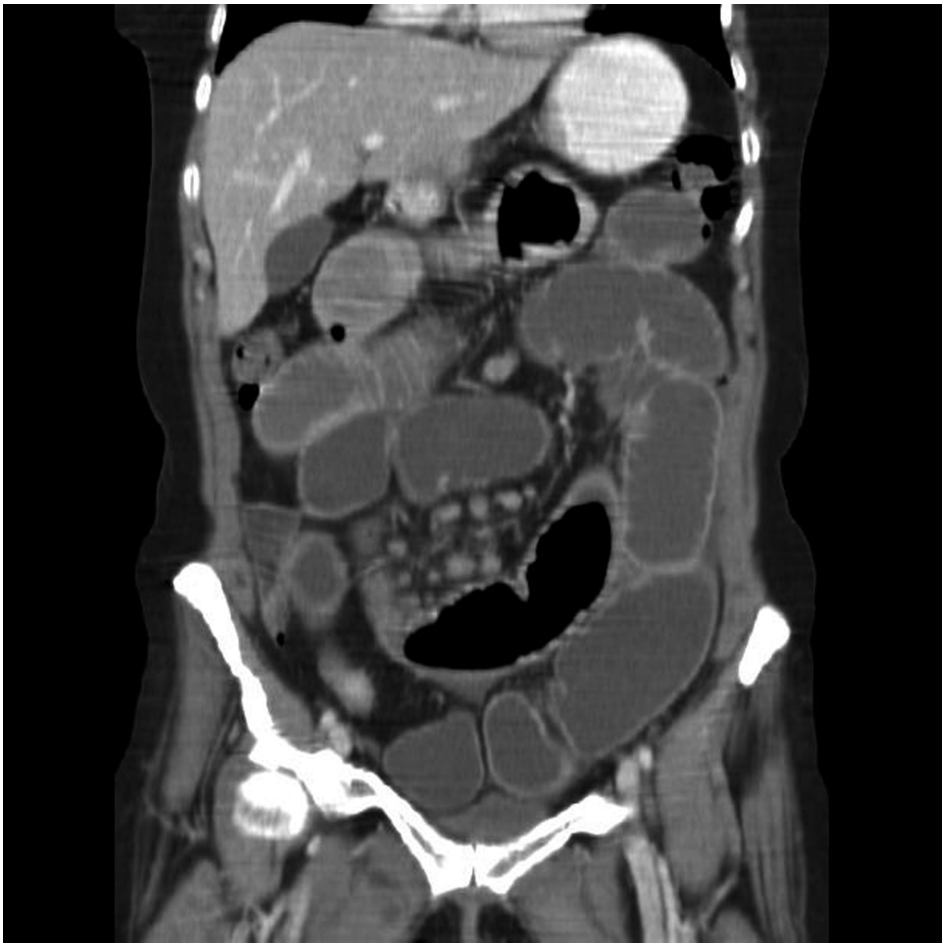

**Figure 3.** An abdominal CT-scan of patient 3 showing a stenosis in the terminal ileum with prestenotic dilatation of the entire small intestine. Furthermore, moderate abdominal lymphadenopathy is seen.

The patient was admitted and initially symptoms improved under starvation. As resumption of food intake immediately led to recurrent ileus, an ileocecal resection was performed. Histology confirmed the diagnosis of CD. The resected specimen, however, also contained an adenocarcinoma. There were no lymph node metastases (pT3N0M0). She received no adjuvant therapy and during follow-up colonoscopies showed no abnormalities. Follow-up of

**Table 1.** Patient characteristics

| Patient No. | Gender | Age at diagnosis Carcinoma (yrs) | How was CD-diagnosis made ? | Duration CD (yrs) | Medication use during fu* |
|---|---|---|---|---|---|
| 1 | M | 57 | Small bowel follow- through:<br>extensive stenosis of the terminal ileum and a severe ileitits with cobblestones and ulcerations conform CD<br><br>Abdominal CT-scan:<br>thickened ileocecal valve in the right lower abdomen with minor induration of the fat tissue.<br><br>Colonoscopy:<br>no abnormalities (terminal ileum not always reached) Once, in terminal ileum possible erosions and edema. | 9.5 | Budenoside + Mesalazine |
| 2 | F | 50 | Abdominal CT-scan:<br>a strongly thickened terminal ileum of at least 30 cm with extension of the colitis in the adjoining mesenterial fat tissue + fistula tracts<br><br>Ileocolonoscopy:<br>no signs of CD<br><br>2nd Abdominal CT-scan:<br>inflamed terminal ileum + fistula tracts | 2 | 5-ASA + prednisolon + immunisuppressives + Anti-TNF |
| 3 | F | 48 | CT-scan:<br>compatible with CD<br><br>Resection specimen:<br>active inflammation in the terminal ileum with mucosal erosions and transmural inflammation with fibrosis. | 0 | none |

*between onset of CD and carcinoma diagnosis

mesenteric lymph node showed no progression. Eighteen months later the patient relapsed with CD lesions in the neoterminal ileum, for which she was treated with azathioprine 150 mg daily. No malignancy or metastases have been demonstrated during a 6-year follow-up.

**Table 2.** Tumor characteristics

| Patient No. | Symptoms prior to cancer-diagnosis | Imaging leading to cancer-diagnosis | Diagnosis carcinoma | Type of carcinoma | Tumor characteristics |
|---|---|---|---|---|---|
| 1 | Abdominal pain in right lower quadrant + persistent stenosis in terminal ileum | Colonoscopy: no CD activity, thickening of the wall of the ileocecal valve<br><br>MRI: pathologic terminal ileum + infiltration of surrounding fat tissues with enlarged mesenterial glands | Histopathological analysis of biopsies taken during colonoscopy | Mucineus adenocarcinoma | pT4N2M1 |
| 2 | Abdominal pain with severe vomiting + thickened terminal ileum at CT-scan | CT-scan: thinkened terminal ileum | In resection specimen after ileocecal resection because of persistent stenosis in terminal ileum | adenocarcinoma | pT2N0Mx |
| 3 | Persistent vominting, diarrhea, abdominal pain and weight loss | CT-scan: dilatated jejunum + ileum + lymphadenopathy with local stenosis+prestenotic dilatation | In resection specimen after ileocecal resetion for an ileus | adenocarcinoma | pT3N0M0 |

## DISCUSSION

This case series describes three patients with suspected Crohn's disease (CD) who were diagnosed with small bowel adenocarcinoma (SBA). In all of these cases the initial work-up of the patient with radiologic imaging failed to diagnose the malignancy. Furthermore, a solid diagnosis of a (relapsing) CD in all these cases was lacking.

Guidelines for diagnosing CD state that for suspected CD, ileocolonoscopy and biopsies from the terminal ileum as well as each colonic segment to look for microscopic evidence of CD are first line procedures to establish the diagnosis.[1] Irrespective of the findings at ileocolonoscopy, further investigation is recommended to examine the location and extent of any CD in the small bowel (SB). Unfortunately, in none of our patients the diagnosis of CD could be confirmed endocopically or histologically before tumor-diagnosis. Only one patient

underwent an ileocolonoscopy, which was not conclusive for the diagnosis of CD. A recently published prospective study demonstrated that a high percentage of patients with known CD and persistent symptoms show SB lesions on double-balloon enteroscopy, despite a conventional ileocolonoscopy.[2] This underscores the importance of imaging the small bowel in these cases with a high suspicion of CD.

Small bowel adenocarcinoma (SBA) is uncommon and represents only 1% to 5% of all gastrointestinal tract malignancies. CD is a risk factor for the development of SBA.[3-6] A study comparing CD related SBA to de novo SBA, reported a cumulative risk in CD patients with SB involvement of 0.2% (95% CI, 0–0.8) at 10 year and 2.2% (95% CI, 0.7–6.4) at 25 years.[7] The diagnosis is difficult due to nonspecific presenting symptoms which frequently mimic CD. Radiographic imaging of obstruction due to adenocarcinoma may not differ in appearance from fibrotic of inflammatory strictures in CD.[8] As such, the diagnosis can be delayed, and is often detected at a late stage, leading to a poor prognosis. The mortality at one and two years ranges from 30%-60% depending on the tumor stage.[9] In our patients, radiographic imaging identified a thickening or stenosis of the terminal ileum, however, CT-scans were unable to diagnose the SBA. Although CT and MRI are the current standards for assessing the small intestine with regard to intestinal involvement and penetrating lesions in CD [1], radiologic imaging may therefore not be the optimal diagnostic tool to identify SBA.

A review of the literature from 1956-1999, has demonstrated 131 published cases with SBA in CD patients. These patients were predominantly male with a mean age at cancer diagnosis of 49 years old and a mean duration of CD of 18 years.[8] A study comparing SBA in CD patients with SBA de novo, demonstrated that SBA present after a median time of 15 year after CD diagnosis.[7] However, in our cases it presented already in the first decade after CD diagnosis. Our experience emphasizes the unpredictability of SBA as a complication of CD.

In conclusion, we underline the necessity of performing full work-up in the diagnosis of CD and considering small bowel carcinoma in patients with small bowel CD failing medical therapy. SBA in CD is a rare, but dreaded complication of CD and early (preoperative) diagnosis remains a challenge. Based on this case series we can conclude that in a patient followed for ileal CD with unusual symptoms, especially with sub occlusive syndrome, SBA should be suspected. CT-scans are insufficiently sensitive to differentiate SBA from small-bowel CD. Therefore, in patients with a suspicious lesion, endoscopy with histological biopsies or even explorative surgery should be considered to rule out SBA.

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# Chapter V

## Are colorectal cancer rates in IBD lower than we think?

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## ABSTRACT

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC). It accounts for 10-15% of all deaths in IBD patients. Although many years of research have addressed issues surrounding IBD-related CRC, there are still many unanswered questions. One unsolved aspect is the incidence of IBD-related CRC, since recent studies indicate a much lower risk of IBD-related CRC than was reported previously. Furthermore, identification of patients at risk, and thereby prevention and management of CRC, needs to be improved.

## COLORECTAL CANCER IN IBD REMAINS AN UNSOLVED ISSUE

Inflammatory bowel disease (IBD) patients are at an increased risk of developing colorectal cancer (CRC): CRC causes 10-15% of all deaths in IBD patients. Due to this risk, surveillance colonoscopy with multiple biopsies is currently recommended for detection of dysplasia or asymptomatic early CRC.[1] Because recent studies indicate a much lower risk of CRC than was previously reported, it is debatable whether this invasive strategy is necessary for all IBD patients. This chapter will give an overview and critical appraisal of current knowledge about the epidemiology of IBD-related CRC.



## WHAT DO WE KNOW?

### Epidemiology

A frequently cited meta-analysis from 2001 estimated the cumulative incidence of CRC in ulcerative colitis (UC) patients to be 2% after 10 years of disease, 8% after 20 years and 18% after 30 years of disease.[2] The relative CRC risk in Crohn's disease (CD) patients has been estimated at approximately 5.6 and should therefore raise the same concerns as in UC.[3, 4] More recent population-based studies suggest that the data from 2001 overestimate the actual IBD-related CRC risk and lean towards more conservative risk estimates ranging from 1/500 to 1/1600 patients annually.[5]

### Risk factors

The CRC risk is increased in patients with extensive and longstanding colitis. Additional risk-factors include the presence of primary sclerosing cholangitis (PSC), pseudopolyps, chronic mucosal inflammation, and a family history of sporadic CRC.[3, 6] The risk also varies with geography, incidence rates for CRC being higher in the USA and the UK compared to Scandinavia and other countries.[2]

## HAVE WE BEEN OVERESTIMATING THE TRUE RISK OF IBD-RELATED CRC?

### Controversies in published data

The exact magnitude of the CRC risk has remained controversial due to various biases and methodological differences in published studies. Initial reports were mainly based on data from referral centers during an era with different medical and surgical options than are available today for IBD. Therefore, the high risk reported may have been a consequence of referral bias and over-interpretation due to the high percentage of extensive and chronically active cases in these cohorts. Nowadays, better methods of surveillance, and more widespread use of medicines that control

**Table 1.** The risk of colorectal cancer in recent (population-based) studies

| Study | Location | Observed period | Cohort size | | |
|---|---|---|---|---|---|
| | | | Total IBD | UC | CD |
| *Winther et al.*[7]*+ Jess et all.*[8] | Copenhagen Denmark | 1962-1987 | 1,534 | 1,160 | 374 |
| *Bernstein et al.*[9] | Manitoba, Canada | 1984-1997 | 5,529 | 2,672 | 2,857 |
| *Palli et al.*[10] | Florence, Italy | 1978-1992 | 920 | 689 | 231 |
| *Jess et al.*[11] | Olmsted, MN, USA | 1940-2001 | 692 | 378 | 314 |
| *Lakatos et al.*[13] | Veszprem, Hungary | 1974-2004 | - | 723 | 0 |
| *Goldacre et al.*[12] | Oxford,UK | 1963-1999 | 12,117 | 6,990 | 5,127 |
| *Terdiman et al****[14] | USA | 2001-2003 | 1,172 | 696 | 476 |

SMR: standardized mortality ratio; IRR: incidence rate ratio; RR rate ratio; OR: Odds ratio
* cases that occurred within the first year of IBD admission were excluded. When including these cases, the SIR for colon would be (UCcolon 3.2 (95% CI 2.6-3.6) / CDcolon (2.8 (95% CI 2.1-3.6)/UCrectum 2.3 (95% CI 1.7-3.1)/ CDrectum 2.0 (95% CI 1.2-3.1)
** the cumulative incidence in the study from olmested, MN was reported at 5 years (0% for UC, 0.3% for CD), at 15 years (0.4 % for UC,1.6% for CD) and at 25 years (2% for UC and 2.4% for CD)
*** not a population-based study. The cohort consisted of CRC-cases from 2 large administrative claims databases

inflammation are likely to influence the CRC risk in IBD patients. Recent population-based studies have demonstrated a much lower risk (Table 1). Although this could be an effect of improved medical and surgical therapies, these population-based studies probably included more patients with limited and less severe disease, and therefore may have underestimated the CRC risk.

## A critical appraisal of recent studies

Of the recent population-based studies, the largest originate from Copenhagen, Denmark and Manitoba, Canada.[7-9] The Danish study reported a standardized morbidity ratio of 1.05

| Follow-up Person-years | | # Cases | | Crude incidence per year (%) | | Risk expressed in relative terms (95% CI) | | | Cumulative incidence UC (%) ** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| UC | CD | UC | CD | UC | CD | Term | UC | CD | 10 yrs | 20 yrs | 30 yrs |
| 22,290 | 6,569 | 13 | 4 | 0.06 | 0.06 | SMR | 1.05 (0.6-1.8) | 1.64 (0.2-5.9) | 0.4 | 1.1 | 2.1 |
| 19,665 | 21,340 | 36 | 24 | 0.18 | 0.11 | IRR Colon | 2.75 (1.9-4.0) | 2.6 (1.7-4.1) | - | - | - |
| | | 13 | 5 | 0.07 | 0.02 | IRR Rectum | 1.90 (1.1-3.4) | 1.08 (0.4-2.7) | - | - | - |
| 7,877 | 2,716 | 10 | 2 | 0.13 | 0.07 | SIR | 1.79 (0.9-3.3) | 1.43 (0.2–5.3) | - | - | - |
| 5,567 | 4,908 | 6 | 6 | 0.11 | 0.12 | SIR | 1.1 (0.4-2.4) | 1.9 (0.7-4.1) | -** | -** | -** |
| 8,564 | - | 13 | - | 0.15 | - | - | - | - | 0.6 | 5.4 | 7.5 |
| 59,415 | 51,270 | 68 | 28 | 0.11 | 0.06 | RR Colon | 2.2 (1.7-2.8)* | 1.6 (1.1-2.4)* | - | - | - |
| | | 35 | 11 | 0.06 | 0.02 | RR Rectum | 1.8 (1.3-2.6)* | 1.2 (0.6-2.15)* | - | - | - |
| - | - | 231 | 177 | - | - | Crude OR | 6.72 (5.8-7.0) | 6.6 (5.6-7.8) | - | - | - |

(95% CI 0.6-1.8) and a cumulative probability of CRC of only 2.1% at 30 years of disease. However, there was a high rate of surgery and long-term use of 5-ASA maintenance therapy in this cohort which could explain the low CRC incidence rates. In the Canadian study, a somewhat higher incidence rate ratio (RR) of 2.75 (95% CI 1.9-4.0) for colon cancer and 1.9 (95% CI 1.1-3.4) for rectal cancer was reported. Despite the large population-based cohort there was a relatively short follow-up period, so the authors suspect that in time there will be higher rates of CRC in these patients.

Two smaller studies from Italy and Olmsted county with only 12 cases each revealed no significantly increased CRC risk.[10, 11] However, Minnesota is comparable to Denmark with a high surgery rate and also advocates maintenance-treatment with 5-ASA. Surprisingly, CD patients with small bowel involvement only were at higher risk for developing CRC than those with colonic involvement only.[11] The relatively small number of patients and low frequencies of events observed may have masked differences in risk between subsets of patients.

The most recent population-based study originates from the UK and also demonstrated a low RR for CRC in UC patients (RR-colon 2.2; 95% CI 1.7-2.8).[12] Although this was a relatively large study, the mean follow-up time per patient was only 8.5 years. To avoid short-term misdiagnosis or ascertainment bias this report excluded cancer cases that occurred within one year of the first recorded IBD-admission, which accounted for 39% of all UC cases and 48% of CD cases. Calculated cancer rates may therefore have been artefactually lower than they really were. The existence of asymptomatic colitis may have put a patient at risk without the patient or physician being aware: in our opinion these patients should have been included, with a resultant estimated increase in RRs of 0.5-1.2 points.

A recent Hungarian population-based study revealed a relatively high cumulative incidence (7.5% at 30 years of disease), despite the fact that most patients in this cohort received sulfasalazine or 5-ASA for maintenance treatment and that colonoscopic surveillance was performed in all compliant patients.[13] However, the percentage of patients with non-CRC related colectomies was below that reported in Western European countries. Fewer colectomies likely results in longer standing refractory inflammatory disease, which may have contributed to the relatively high CRC risk reported.[13]

An increased CRC risk is also demonstrated in an American case-control study [14]. In this study, IBD diagnosis was associated with a six- to seven-fold increase in CRC risk. However, this study analyzed administrative claims data only, and the IBD diagnostic codes were not verified by independent investigators. Therefore, the strong association found between CRC and IBD may have been secondary to diagnostic misclassification. Moreover, there was the potential for confounding, especially by variables not captured using medical claims data such as family history of CRC and duration, extent and severity of colonic involvement with IBD.

## Conclusion

In conclusion, it remains unclear whether we are over- or underestimating the actual IBD-related CRC risk. Geographical differences as well as differences in local treatment policies and methodological differences compromise interpretation of published studies. Moreover, the recently reported lower incidence rates might result from successful treatment strategies, including 5-ASA maintenance therapy and dysplasia surveillance programs. The latter is supported by a 30-year analysis of a colonoscopic surveillance-program in a British referral center which suggests that the CRC-rate in IBD patients is approximately half of what had initially been reported in 2001.[15]

## A GLANCE INTO THE FUTURE

CRC is among the most feared long-term complications of IBD. Therefore, a sound knowledge of the overall epidemiology of CRC in IBD patients is important if we are to improve clinical practice and strengthen the basis of surveillance guidelines to decrease CRC-related morbidity and mortality. Surveillance colonoscopy is used as the foundation of a prevention strategy, with colectomy being reserved for patients in whom dysplasia or CRC are discovered. However, if the IBD-related CRC risk is indeed low, we should question whether we should continue performing surveillance in all IBD patients, bearing in mind its invasive nature and cost. Factors which influence time to CRC in both referral and non-referral centres need to be determined to identify patients in need of an earlier start of surveillance. Consequently, a risk-prediction tool should be developed for individually tailored CRC surveillance. To facilitate such an approach, further research on the epidemiology of IBD-related CRC is essential.

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# Chapter VI

## The risk of inflammatory bowel disease related colorectal carcinoma is limited: results from a nationwide nested case-control study

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## ABSTRACT

**Background and aims:** The risk of inflammatory bowel disease (IBD)-related colorectal cancer (CRC) remains a matter of debate. Initial reports mainly originate from tertiary referral centers, and conflict with more recent studies. Overall epidemiology of IBD-related CRC is relevant to strengthen the basis of surveillance-guidelines. We performed a nationwide nested case-control study to assess the risk of IBD-related CRC and associated prognostic factors in general hospitals.

**Methods:** IBD patients diagnosed with CRC between January 1990 and July 2006 in 78 Dutch general hospitals were identified as cases using a nationwide automated pathology database. Control IBD patients without CRC were randomly selected. Clinical data were collected from detailed chart review. Poisson regression analysis was used for univariable and multivariable analyses.

**Results:** Hundred-seventy-three cases were identified through pathology and chart review and compared to 393 controls. The incidence rate of IBD-related CRC was 0.04%. Risk factors for IBD-related CRC were older age, concomitant primary sclerosing cholangitis (RR per year duration 1.05; 95% CI 1.01-1.10), pseudopolyps (RR 1.92; 95%CI 1.28-2.88), and duration of IBD (RR per year 1.04; 95%CI 1.02-1.05). Using immunosuppressive therapy (OR 0.3; 95% CI 0.16-0.56, p<0.001) or anti-TNF (OR 0.09; 95% CI 0.01-0.68, p 0.02) was protective.

**Conclusions**: We found a limited risk for developing IBD-related CRC in The Netherlands. Age, duration of PSC and IBD, concomitant pseudopolyps and use immunosuppressives or anti-TNF were strong prognostic factors in general hospitals.

## INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at increased risk for developing colorectal cancer (CRC). CRC accounts for approximately one sixth of all deaths in IBD patients.[1] The exact magnitude of the CRC risk has remained controversial in the past due to various biases and methodological errors in published studies. A well-cited meta-analysis from 2001 estimated the cumulative incidence of CRC in ulcerative colitis (UC) patients at 2% after 10 years of disease, 8% after 20 years and 18% after 30 years of disease.[1] The relative CRC risk in Crohn's disease (CD) patients has been estimated at approximately 5.6 and should therefore raise the same concerns as in UC.[2, 3] However, initial reports were mainly based on data from referral centers during an era with quite different medical and surgical therapies for IBD. More recent population-based studies suggest that the data from 2001 overestimate the actual IBD-related CRC risk and lean towards more conservative risk estimates ranging from 1/500 to 1/1600 patients annually.[4] However, geographical differences as well as differences in local treatment policies and methodological errors complicate a correct interpretation of published studies. Moreover, the recently reported lower incidence rates might be a result from successful treatment-strategies, including 5-ASA maintenance-therapy and dysplasia surveillance programs. Data on the IBD-related CRC risk is therefore inconclusive and it remains unsure whether we are over-, or underestimating the actual IBD-related CRC risk.

Several risk factors for CRC have been identified, including long duration of disease, extent of disease to the hepatic flexure, co-presence of primary sclerosing cholangitis (PSC), the presence of pseudopolyps and a family history of sporadic CRC.[5-10] However, it is unknown whether these risk factors solely apply to patients in tertiary referral centers and data is limited on CRC-characteristics of IBD patients from non-referral centers. Moreover, many studies are small, making it difficult to study several variables simultaneously and to adjust for potential confounders. By enhancing the knowledge of prognostic factors, clinicians might be able to identify subgroups of patients who need closer surveillance and to apply protective strategies to existing treatment policies.

We performed a nationwide nested case-control study to assess the risk of developing IBD-related CRC in general hospitals. Moreover, we studied the characteristics of IBD-related CRC to assess risk factors for developing CRC in this cohort of general hospitals using time-dependent analyses.

## MATERIALS & METHODS

### Histopathology database

This study has been approved by the Institutional review board of the Erasmus Medical Center, Rotterdam, The Netherlands. We identified all IBD patients diagnosed with CRC in all 93 general hospitals in The Netherlands in the period from January 1st, 1990 until July 1st, 2006. We hereto used the nationwide network and registry of histo- and cytopathology (PALGA).[11] The PALGA database contains all pathology reports generated in the Netherlands from 1990, which are concluded with diagnostic terms in line with SNOMED® terminology. Each subject in the database has a unique identifier, which allows tracking of individual patients over time and throughout the country regardless of whether treatment is received at the same or different institute. Every record in the database contains a summary of the original pathology report and diagnostic codes similar to the Systematized Nomenclature of Medicine classification of the College of American Pathologists that are given by the pathologist who made the diagnosis. The diagnostic code contains a term indicating the anatomical location, type of sample, and a morphological term describing the finding (e.g., "colon*biopsy*carcinoma").

### Cases and controls

The following search criteria were used to identify cases in the PALGA system: (colon AND/OR all primary carcinoma, colon AND/OR all carcinoma in situ, colon AND/OR all micro invasive tumors, rectum AND/OR all primary carcinoma, rectum AND/OR all carcinoma in situ, rectum AND/OR all micro invasive tumors) AND (colitis AND/OR UC AND/OR indeterminate colitis AND/OR idiopathic colitis AND/ OR CD). Cases were defined as those with histological confirmed IBD and meta- or synchronously CRC. All IBD patients diagnosed with colorectal cancer in a general hospital were included, irrespective of where they were treated afterwards. Patients who were initially treated and diagnosed with cancer in an academic hospital and referred to a general hospital after cancer diagnosis were excluded. A control group was formed by IBD patients from these general hospitals in The Netherlands. Control patients were defined as histological confirmed IBD patients who had not developed CRC in the same time-period. To acquire a control group which was representative for the total IBD population in general hospitals, controls were randomly selected and solely matched with cases for the time period for being at risk for CRC.

### Further data extraction

Detailed clinical data from cases and controls were collected from the charts, endoscopy reports and pathology reports. The clinical data included: type of IBD, gender, time of diagnosis of IBD and CRC, extent and severity of disease, history of colonic surgery, concomitant PSC, time of diagnosis of PSC, use of medication (ever used) and surveillance details. Extent of disease was subdivided in five categories based on type and extent of inflammation: left-sided

UC, extensive UC, limited CD, extensive CD or unclassified colitis. Limited CD was defined as <50% segmental CD including those with ileitis terminalis or ileocoecal inflammation. Extensive CD was defined as >50% segmental CD. Severity of disease was graded as mild, moderate or severe colitis based on both histological and endoscopic features.

### IBD population in participating centers

The size of the total IBD population cannot be extracted from the PALGA database, without verification of each diagnosis in the patient charts. This is not feasible for identifying all IBD patients on such a large scale. The size of the IBD population per hospital was therefore assessed from centralized systems for registration of diagnosis and treatment. Each hospital in The Netherlands scores the number of IBD patients for registration of diagnosis and treatment for both admitted patients and outpatients. These registries are used for billing and data reporting and therefore the coverage and adequacy of these codes is high.[12-15] All diagnostic codes are based on the International Classification of Diseases, 10th edition (ICD 10). Medical experts were involved in the determination of these diagnostic codes, which are defined as the whole set of activities (diagnostic and therapeutic interventions) of the hospitals and medical specialist. Each diagnostic code is characterized by a code combining information on diagnosis (based on ICD 10) and treatment. This system facilitates negotiation between health insurers and hospitals on prices and at the same time provides a catalogue of medical services. Moreover, an appropriate diagnostic code is required for medical insurance companies before they are prepared to cover medical therapy for IBD. Concerning the diagnostic codes for IBD: there are two codes, one for CD, and one for UC. The diagnosis of IBD has to be verified by endoscopy, histology or radiology before a patient can be registered as IBD patient. All diagnostic codes are linked to patients' social security numbers and each patient can therefore only be counted once. Validity of these registration codes is verified in several ways:

First, internal validation of the diagnostic codes is performed in a standard way in each hospital.[16] This is a requirement of the coordinating organization and is performed by comparing the diagnostic codes to the medical examinations that are performed in this patient; e.g., without endoscopy, radiology or pathology, no diagnostic code for IBD can be given.

Secondly, the law requires that each hospital annually carries out a random sample survey. [17] In this sample they have to check 10-20% of all their diagnostic codes. In this sample, each diagnosis has to be verified by pathology-, radiology-, and endoscopy-data. These data are thereafter checked by the Ministry of health.

Thirdly, to further improve the validity of our study, we randomly checked the correct diagnostic codes of 1851 patients. An external expert verified the diagnosis and the associated

diagnostic codes, based on and pathology-, radiology-, and endoscopy reports and the entire clinical charts from the various hospitals. In total, 14 patients appeared not to have IBD based on the above mentioned criteria. In two hospitals an IBD database was available. When combining the data from the registry of diagnostic codes and this IBD database, forty additional patients were diagnosed with IBD (classified by the above mentioned parameters), but were not coded with a diagnostic code for IBD. The misdiagnosis in the 14 patients with a false diagnostic code for IBD could be related to missing data, since not all data could be verified.

### Statistical analysis

Statistical analysis was performed using Poisson regression of time to CRC with time-dependent covariates. The total follow-up of all patients was split up in years from start of follow-up (1-1-1990) or diagnosis of IBD until end of follow-up (01-07-2006) or incidence of CRC. For every year, baseline predictors were noted (such as gender and characteristics of the disease at onset) and time-dependent predictors were calculated (such as age, duration of disease, duration of primary sclerosing cholangitis). All cases were included to assess the incidence of IBD-related CRC. For the analyses of prognostic factors for CRC development, cases with a synchronous diagnosis of IBD and CRC were excluded, as well as patients with an unknown date of diagnosis of IBD.

Both univariable and multivariable analyses were performed. Variables with <5% positive or negative values were excluded (i.e. prior colonic surgery and family history of sporadic CRC). Predictors with a p-value below 0.10 were included, provided they had a plausible sign.[18] Age and sex were retained in the multivariate model irrespective of statistical significance. Continuous predictors (age and duration of IBD and PSC) were tested for non-linearity; if a predictor had a significantly non-linear effect we used a restricted cubic spline function for a flexible fit to the data.[19] Missing values for extent of IBD and pseudopolyps were multiply imputed using the nearest neighbour method.[20]

Medication use could not be analyzed using time-dependent analysis, since duration of medication use could not be split up per year due to the retrospective design of this study. Medication use was therefore analyzed using logistic-regression analysis. First, univariate analysis was performed. Secondly, multivariate analysis was performed using backward stepwise regression analysis. The model included possible confounders like gender, location and type of IBD, concomitant PSC, pseudopolyps, and colonic surgery prior to diagnosis of IBD and poly-medication usage. Poisson regression analyses were performed using R software (version 2.7.1, R Foundation for Statistical Computing, Vienna, Austria). Logistic regression analyses were performed using SPSS for Windows software (version 15.0).

## RESULTS

The initial PALGA search identified 3738 patients with a potential IBD-related CRC (1797 females, 1941 males). Of these, 1672 patients were aged ≤ 65 years (708 females, 964 males). In our PALGA search we identified a limited group of 59 patients with a suggestive IBD and CRC above 65 years at the initial search. These patients were excluded to minimize the interaction with sporadic CRC. Further analysis of the pathology excerpts within the PALGA search left 468 patients ≤ 65 years old with a possible IBD-related CRC. The main reason for exclusion was no evidence of IBD before CRC. This included inflammation other than colonic (e.g. peritonitis), colonic inflammation diagnosed years after the diagnosis of CRC, ulceration merely due to CRC, "no indication for IBD" in all pathology reports, or no defined diagnosis of CRC or colitis due to other causes of inflammation than IBD (e.g. ischemia). Pathology excerpts that showed no certain determination or cause of the colitis were not excluded at this stage. Additional hospital data were used to make a definite diagnosis.



### Cases

In total, 78 out of all 93 Dutch general hospitals were willing to participate for detailed chart review to confirm the diagnosis of IBD-related CRC (see list of participants at end of manuscript). A total of 430 of the 468 patients identified by the PALGA search could hence be further assessed. In each hospital the responsible physicians verified the results from the search. If there was any doubt or recall was insufficient, the search was checked in the local pathology databases.

This strategy yielded 197 pts ≤ 65 years old in whom the diagnosis of IBD-related CRC could be confirmed. Three patients were excluded because the duration of their IBD was unknown. In 21 patients IBD and CRC were diagnosed simultaneously. Of the remaining 173 patients, 65 were female (38%), 113 had UC (65%), 58 had CD (34%) and 2 patients had unclassified colitis (1%). The mean age of these patients at diagnosis of IBD was 33 years (Table 1). Twenty-four patients (12%) had been included in a dysplasia surveillance program prior to CRC diagnosis (data on surveillance was missing in 9 patients (5%)). On average, patients were included in a dysplasia surveillance program after a median of 9 years of disease (interquartile range (IQR) 1-23 years) with an interval between each surveillance colonoscopy of 2 years (IQR 1-2.5). In total, four cases (2%) were lost to follow-up directly at cancer diagnosis and another eight patients (4%) were lost to follow-up within a half year after cancer diagnosis. In total, 94% of cases remained under treatment at the same general hospital for their cancer-treatment.

### Controls

In 22 randomly selected hospitals 392 control patients were identified. Of these controls, 234 were female (60%), 175 had UC (45%), 207 had CD (53%) and 10 patients had unclassified

**Table 1.** Results of the univariate Poisson regression analysis

| | At start† | End of virtual follow-up | | Rate Ratio (95% CI) | p-value |
|---|---|---|---|---|---|
| | | Cases | Controls | | |
| **Nr of patients** | | 173 | 392 | - | |
| **Disease** | | | | | **p<0.001*** |
| Ulcerative colitis | | 113 | 175 | 1.0 | |
| Crohn's disease | | 58 | 207 | 0.49 (0.36-0.68) | |
| Unclassified colitis | | 2 | 10 | 0.48 (0.12-1.95) | |
| **Sex** | | | | | **p<0.001*** |
| Female | | 65 | 234 | 1.0 | |
| Male | | 108 | 158 | 1.99 (1.46-2.71) | |
| **Age** | | | | | **p<0.001*** |
| <20 | 50 | 0 | 18 | 0 NA | |
| 20-30 | 172 | 7 | 65 | 0.40 (0.18-0.91) | |
| 30-40 | 149 | 32 | 123 | 1.0 | |
| 40-50 | 120 | 48 | 92 | 1.80 (1.15-2.82) | |
| 50-60 | 61 | 50 | 70 | 2.64( 1.69-4.11) | |
| 60-65 | 13 | 36 | 24 | 11.49 (7.13-18.49) | |
| **Duration of IBD** | | | | | **p<0.001*** |
| <10 | 474 | 52 | 259 | 1.0 | |
| 10-20 | 60 | 56 | 87 | 2.26 (1.55-3.29) | |
| >20 | 31 | 65 | 46 | 4.42 (3.07-6.36) | |
| **Extent IBD at onset IBD††** | | | | | **p<0.001*** |
| Left-sided UC | | 36 | 109 | 1.0 | |
| Extensive UC | | 24 | 51 | 1.34 (0.80-2.24) | |
| Unknown UC | | 53 | 15 | 2.68 (1.76-4.10) | |
| < 50% segmental CD | | 16 | 120 | 0.43 (0.24-0.77) | |
| > 50% segmental CD | | 16 | 63 | 0.82 (0.46-1.49) | |
| Unknown CD | | 26 | 24 | 1.33 (0.88-2.20) | |
| Left-sided CU | | 0 | 7 | 0 NA | |
| Extensive CU | | 0 | 2 | 0 NA | |
| Unknown CU | | 2 | 1 | 2.16 (0.52-8.96) | |
| **Degree of inflammation at onset** | | | | | **p<0.001*** |
| Mild | | 23 | 108 | 1.0 | |
| Moderate | | 30 | 131 | 1.19 (0.69-2.05) | |
| Severe | | 26 | 105 | 1.10 (0.62-1.92) | |
| Unknown | | 94 | 48 | 2.80 (1.77-4.41) | |
| **Concomitant pseudopolyps** | | | | | **p<0.001*** |
| No | | 68 | 298 | 1.0 | |
| Yes | | 71 | 76 | 2.25 (1.61-3.14) | |
| Unknown | | 34 | 18 | 3.86 (2.56-5.83) | |
| **Duration of PSC** | | | | | **p<0.001*** |
| 0 | 555 | 156 | 387 | 1.0 | |
| 0-5 | 3 | 5 | 1 | 2.36 (0.97-5.75) | |
| 5-10 | 3 | 7 | 1 | 5.03 (2.36-10.72) | |
| >10 | 4 | 5 | 3 | 3.05 (1.25-7.43) | |

**Table 1.** Continued

| | At start† | End of virtual follow-up Cases | Controls | Rate Ratio (95% CI) | p-value |
|---|---|---|---|---|---|
| **Rectal sparing at onset IBD** | | | | | **p<0.001*** |
| Negative | | 122 | 360 | 1.0 | |
| Positive | | 3 | 17 | 0.69 (0.22-2.16) | |
| Unknown | | 48 | 15 | 2.85 (2.04-3.98) | |
| **Positive family history CRC** | | | | | **p<0.001*** |
| Negative | | 72 | 260 | 1.0 | |
| Positive 1st degree | | 7 | 12 | 1.90 (0.88-4.13) | |
| 2nd degree | | 4 | 11 | 1.11 (0.40-3.03) | |
| Unknown | | 90 | 109 | 1.72 (1.27-2.35) | |
| **Colon surgery prior to onset IBD** | | | | | **p<0.001*** |
| No | | 148 | 384 | 1.0 | |
| Yes | | 7 | 5 | 3.19 (1.50-6.80) | |
| Unknown | | 18 | 3 | 3.45 (2.11-5.62) | |

† only shown for time dependent predictors

†† Onset IBD defined as date of diagnosis of IBD

UC: ulcerative colitis, CD: Crohn's disease, CU: unclassified colitis, IBD: inflammatory bowel disease, PSC: primary sclerosing cholangitis, CRC: colorectal carcinoma



colitis (3%). Mean age of patients at diagnosis of IBD was 31 years (Table 1). Twenty-nine patients (7%) had been included in a dysplasia surveillance program prior to CRC diagnosis. This was significantly less than the cases (p=0.02). On average, patients in the control group were included in a dysplasia surveillance program after a median of 9 years of disease (IQR 2-16 years) with an interval between each surveillance colonoscopy of 2 years (IQR 0-2).

### Incidence rate IBD-related CRC

The size of the IBD population could be assessed in 58 hospitals, with a total of 26,855 patients. In these 58 hospitals, 163 patients aged ≤ 65 years, developed an IBD-associated CRC between January 1st, 1990 and July 1st, 2006. Assuming an at-risk period of 15.5 years, the incidence rate is 0.04% (149/(26,855*15.5)*100=0.04%).

### Prognostic factors for development of CRC

Results from univariate Poisson regression analysis are demonstrated in Table 1. After correcting for possible confounders, age at IBD diagnosis (p<0.001), duration of PSC (p=0.02), duration of IBD (p<0.001), and concomitant pseudopolyps (p=0.002) were significantly associated with the development of CRC (Table 2). Age was modeled with a spline function. The increase of risk with age was small up to 55 years, and increased strongly thereafter. We used multiple imputation to complete missing data for the extent of IBD, and concomitant pseudopolyps.

**Table 2.** Results of the multivariable Poisson regression analysis

| Variable category | Rate ratio (95% CI) | p-value |
|---|---|---|
| **Age** | NA | **p<0.001*** |
| **Sex** | | |
| Female | 1.0 | **p=0.17** |
| Male | 1.25 (0.91-1.73) | |
| **Duration of PSC (per year)** | 1.05 (1.01-1.10) | **p=0.02*** |
| **Duration of IBD (per year)** | 1.04 (1.02-1.05) | **p<0.001*** |
| **Extend of IBD at onset** | | |
| Left-sided UC | 1.00 | |
| Extensive UC | 1.18 (0.71-1.97) | **p=0.07** |
| <50% segmental CD | 0.64 (0.41-1.00) | |
| >50% segmental CD | 0.84 (0.49-1.44) | |
| Unclassified colitis | 1.02 (0.28-3.74) | |
| **Concomitant pseudopolyps** | 1.92 (1.28-2.88) | **p=0.002*** |

NA: not applicable, PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease.
†The effect of age was modeled by a restricted cubic spline, therefore no effect-size can be given.

### Influence of medication use

Data on medication use could not be retrieved in 14 patients. These patients were therefore excluded for the analysis of the influence of medication use on the development of IBD-related CRC. In 159 cases data was available on their medication use. In total, 148 out of 159 cases (93.1%), and 388 out of 392 controls (99%) used any kind of medication to treat their IBD (p=0.004). Eight-six percent of the cases was treated with 5-ASA compared with 89% of the controls (p>0.05). The use of 5-ASA was not related to less diagnosis of CRC. Patients treated with thiopurines were less often diagnosed with CRC compared to those never treated with thiopurines (p<0.001, Table 3). A protective effect was also seen for corticosteroids (p<0.001), MTX (p=0.03), anti-TNF (p<0.001), and calcium (p <0.001). Patients treated with ursodeoxycholic acid (p<0.001) and ferrofumerate (p=0.03) were more frequently diagnosed with CRC .

The use of thiopurines (OR 0.3; 95% CI 0.16-0.56, p<0.001), the use of anti-TNF (OR 0.09; 95% CI 0.01-0.68, p=0.02), remained significantly predictive for the development of CRC after correcting for possible confounding factors, including gender, location and type of IBD, concomitant primary sclerosing cholangitis, pseudopolyps, and colonic surgery prior to diagnosis of IBD .

## DISCUSSION

In this large nationwide nested case-control study we identified a low incidence rate of IBD-related CRC in general hospitals. Secondly, we identified several strong prognostic factors

**Table 3.** Results of univariate cox regression analysis for medication use

| | Cases | Controls | Rate ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Nr of patients** | 159 (%)† | 392 (%) | - | |
| **5-ASA** | | | | **p=0.03*** |
| Yes | 137 (86) | 351 (89) | 0.61 (0.39-0.95) | |
| No | 22 (14) | 41 (11) | 1.0 | |
| **Thiopurines** | | | | **p<0.001*** |
| Yes | 36 (23) | 216 (55) | 0.45(0.31-0.66) | |
| No | 123 (77) | 176 (45) | 1.0 | |
| **Corticosteroids** | | | | **p=0.001*** |
| Yes | 102 (64) | 326 (83) | 0.56 (0.41-0.78) | |
| No | 57 (36) | 66 (17) | 1.0 | |
| **MTX††** | | | | n.s. |
| Yes | 2 (1) | 23 (6) | 0.32 (0.08-1.23) | |
| No | 157 (99) | 369 (94) | 1.0 | |
| **Anti-TNF** | | | | |
| Yes | 4 (3) | 75 (19) | 0.21 (0.08-0.56) | **p=0.002*** |
| No | 155 (97) | 317 (81) | 1.0 | |
| **Ascal** | | | | n.s. |
| Yes | 5 (3) | 7 (2) | 0.95 (0.39-2.25) | |
| No | 154 (97) | 385 (98) | 1.0 | |
| **NSAIDS††** | | | | n.s. |
| Yes | 7 (4) | 9 (2) | 1.2 (0.57-2.59) | |
| No | 152 (96) | 383 (98) | 1.0 | |
| **Folic acid** | | | | n.s. |
| Yes | 16 (10) | 42 (11) | 0.66 (0.39-1.11) | |
| No | 143 (90) | 350 (89) | 1.0 | |
| **Calcium** | | | | **p=0.025*** |
| Yes | 10 (6) | 74 (19) | 0.48 (0.25-0.91) | |
| No | 149 (94) | 318 (81) | 1.0 | |
| **Ursodeoxy acid** | | | | **p=0.039*** |
| Yes | 13 (8) | 4 (1) | 1.83 (1.0-3.24) | |
| No | 146 (92) | 388 (99) | 1.0 | |
| **Ferrofumerate** | | | | n.s. |
| Yes | 47 (30) | 81 (21) | 0.85 (0.60-1.21) | |
| No | 112 (70) | 311 (79) | 1.0 | |

† In 14 cases data on medication use was not retrievable.

†† MTX: methotrexate, NSAIDS: non-steroidal anti-inflammatory drugs , Anti-TNF: Anti tumor necrosis factor

for developing IBD-related CRC for patients in general hospitals, including older age, longer duration of IBD, longer duration of PSC, and co-presence of pseudopolyps. We found a protective role for thiopurines and anti-TNF.

The incidence rate of IBD-related CRC risk in our cohort of general hospitals was estimated at 0.04%, which is limited and in contrast with previous studies.[1, 3, 5, 6] However, initial reports were mainly based on data from referral centers. Therefore, the high detected risk might have been a consequence of referral bias and over-interpretation due to the high percentage of

extensive and chronically active cases in these cohorts. More recent population-based studies already suggest a more conservative risk ranging from 1/500 – 1/6000 patients annually.[4] Although this could be an effect of improved medical and surgical therapies, these data are difficult to interpret due to methodological errors and geographical differences as well as differences in local treatment policies. Some studies were limited by a small sample size or short follow-up [21, 22], or high surgery rates and the local advocate of 5-ASA maintenance therapy.[22-24] Other studies were limited by the lack of clinical data to confirm diagnosis of IBD and CRC.[25, 26] The strength of our large cohort is the long follow-up time of 15.5 years and the inclusion of 78 different general hospitals all over the country. Moreover, all of our data were confirmed by clinical chart review, including endoscopy- and pathology reports.

The population of IBD-related CRCs in the Dutch academic centers have been previously described by Lutgens et al. in 2009.[27] They found 149 IBD patients who developed CRC during an average follow-up of 15.5 years similar to our study. The authors of this paper did not assess the magnitude of the total baseline IBD population in the academic centers included. Therefore we cannot deduce the rate of IBD-related CRC in the academic centers from this original publication. However, as we have access to the same dataset, we were able to assess the magnitude of the IBD population in these seven academic hospitals. The total academic IBD population under study comprised 9950 IBD patients. This yields a rate of CRC in academic IBD patients of 149 cases in 9950 patients during 15.5 years of follow-up, which equals an annual incidence rate of 0.97 per 1000. Although this is slightly higher than the risk in non-academic centers, this risk is still very low compared to previous published studies.

Merging the data from the academic hospitals with our data from the general hospitals, we are able to provide a nationwide population rate for IBD-related CRC in The Netherlands. In total, 312 cases (149 in seven academic hospitals + 163 in 58 general hospitals) with IBD-related CRC were identified in 36,805 IBD patients during 15.5 years of follow-up. This equals a nationwide population rate of 0.05% per year. These data show that after combining patient populations from general hospitals and academic hospitals, the incidence of IBD-related CRC remains very low.

In general, an aggressive surveillance approach and high colectomy-rates could explain low CRC-rates. However, surveillance colonoscopies are not yet common practice in general hospitals in The Netherlands and most gastroenterologists in The Netherlands do not adhere to surveillance guidelines.[28] In our cohort, only 12% of our patients who developed CRC in IBD was included in a surveillance program. Given the low rate of surveillance we believe that an aggressive approach with surveillance and colectomies has not been a confounder in our study. Therefore we believe that our study indeed reflects a true nationwide incidence

of IBD-related CRC, and we demonstrate that the actual IBD-related CRC risk is limited for all IBD patients.

In our patient population from general hospitals we could confirm some of the previously established risk factors for developing CRC, including longer duration of IBD and the presence of concomitant pseudopolyps. Earlier, it has been demonstrated that PSC patients are at a vastly increased risk.[1] Because of our time-dependent analysis we could demonstrate that not only the presence of PSC is a risk factor, but that this risk increases over time with a RR of 1.05 per year duration.

We found a similar risk for developing CRC in patients with left-sided colitis and patients suffering from pan-colitis. This is in contrast with previous published studies originating from tertiary cohorts.[1, 29] Although this could be a true characteristic in the general, secondary cohort, caution should be used while interpreting these results due to the retrospective analyses of chart review. It could be hypothesized that patients with left-sided colitis progress to a more extensive colitis which was not correctly diagnosed during follow-up. It has been previously demonstrated that colonoscopy frequently underestimates the extent of colitis activity, as shown by histological evidence of colitis in macroscopically normal areas of the mucosa.[30-33] However, since we have taken into account both histological and endoscopic data we assume that this effect is limited in our cohort.

Our study identifies the use of immunosuppressives and also the use of anti-TNF as protective factors. We were not able to demonstrate a chemopreventive effect for 5-ASA. Multiple cohort and case-control studies have been conducted to assess the chemopreventive role of 5-ASA and have demonstrated conflicting results.[5, 34-38] These conflicting results may be explained by the retrospective nature of these studies and the lack of consistency between the studies. A meta-analysis of nine studies (3 cohort and 6 case-control studies), involving 1932 UC patients, demonstrated a protective association between 5-ASA usage and CRC (OR 0.51; 95% CI: 0.37-0.69) or a combined endpoint of CRC/dysplasia (OR 0.51; 95% CI: 0.38-0.69). However, 5-ASA usage was not associated with a lower risk of dysplasia (OR 1.18; 95% CI: 0.41-3.43). The minimal dosage and the needed duration of exposure to achieve this possible chemopreventive effect also remains unclear, although it has been suggested that a minimum of at least 1.2 - 2.4 grams is needed for the chemopreventive abilities of 5-ASA.[34, 39] It could be hypothesized that in our cohort either the dosage or the duration of 5-ASA usage or both were insufficient to be chemopreventive. We realize that medication use could have been prone to information bias due to the retrospective study design and caution is therefore needed when interpreting our results with regard to the chemopreventive effects of medication.This could also explain why more controls than cases used any kind of medication to treat their IBD. However, due to the retrospective design of this study it is

difficult to speculate about the reasons for prescribing medications and also the differences in medication prescribed amongst the two groups. Furthermore, no data are available on actual therapy adherence in our cohort. However, we have earlier demonstrated in 1100 IBD patients from the Netherlands, that therapy adherence is very high amongst Dutch IBD patients (at least 87%). [40] We are therefore convinced that non-adherence is probably not a significant confounder in our cohort.

Nonetheless, our results support a recently published theory that the signaling pathway via TNF-α/NF-κB in intestinal epithelial cells may be directly involved in colitis-associated carcinogenesis.[35] The authors suggested that maintenance therapy with anti-TNF may prevent the development of CRC in patients with longstanding IBD, which is in line with our results. The protective effect of thiopurines has not been previously reported. Earlier studies investigated the prophylactic effects of thiopurines but could not find a protective effect of these drugs.[5,36] It can be speculated that patients using thiopurines have a better control of inflammation and earlier reports demonstrated that the severity of inflammation is associated with a higher CRC risk.[5] However, we could not confirm such a correlation. In our analyses, neither severity of inflammation at onset of IBD nor maximum severity during follow up, predicted the development of CRC.

Older age was associated with an increased risk for developing CRC in our cohort. Older age is also known to be the most significant risk factor for diagnosis of sporadic CRC.[37, 38] Because the effect of age was modeled by a restricted cubic spline, no effect-size could be given. However, the increase of risk with age was small up to 55 years, but accelerated thereafter. This is comparable to sporadic CRC in which a vast majority is being diagnosed > 65 years old.[37, 38] Our study is limited by the exclusion of patients over 65 years of age with the suspicion of IBD-related CRC. Since we could not rule out the increased likelihood of interference of sporadic CRC in our cohort we decided to exclude these patients from further analysis. In our initial PALGA search we identified at most 59 patients with a suggestive IBD-related CRC in this age category, therefore the influence of excluding this patient group in our final analysis is limited.

This study was designed to establish risk factors for IBD patients in general hospitals. It has not been well established whether previously demonstrated risk factors solely apply to patients in tertiary referral centers and data on CRC characteristics and incidences of IBD patients from general hospitals are very limited. We therefore primarily focused on these patients and on purpose included all IBD patients, regardless of their extent of disease. Although it can be argued that this leads to inclusion of patients with limited or no risk of CRC, we believe that the exact extent of disease is not always well established. It has been demonstrated that colonoscopy frequently underestimates the extent of colitis activity, as shown by histological evidence of colitis in macroscopically normal areas of the mucosa.[30-33]

Therefore we decided to include all IBD patients in our cohort. Moreover, our cases with an IBD-related CRC comprised also patients with only ileal Crohn's disease (approximately 9%), and patients with only proctitis (4.5%).

The vast majority of our patients remained under treatment at the same general hospital after cancer diagnosis. Only two percent of cases was lost to follow-up directly at cancer diagnosis and another four percent was lost to follow-up within a half year after cancer diagnosis. This also included patients who thereafter were treated at another general hospital, i.e. because they moved to another part of the country. In total, 94% of our cases remained at the same general hospital for their cancer-treatment. Therefore we believe that our sample from the general, community practice is largely unbiased.



The total IBD population could not be determined in all 78 centers, since some centers merged over time, a process which was not uncommon in our country over the past 15 years. These mergers invariably obstructed reliable determination of IBD populations as they were always associated with gradual merging of databases, but the timing and impact of these exact merges were difficult to retrieve. Thus the numbers of IBD patients throughout the period under study could only be assessed with enough certainty in 58 hospitals.

Colonoscopy with multiple biopsies is currently recommended for early detection of dysplasia or asymptomatic early CRC in IBD patients, and newer techniques are developed to increase the probability of finding abnormalities during endoscopy.[39] Guidelines are based on the available literature with respect to the IBD-related CRC risk. In our nationwide cohort, 12% of cases were included in a dysplasia surveillance program compared with only 7% of the controls. Since the incidence rate was very low despite the fact that only 12% underwent surveillance, it is uncertain from our results whether surveillance colonoscopy is necessary for all IBD patients. Parameters which influence time to CRC in both referral and non-referral centers are needed to identify patients in need of earlier start of surveillance. Consequently, a risk-prediction tool should be developed for individually tailored CRC surveillance in IBD to avoid unnecessary burden and costs.

In conclusion, we have demonstrated that the risk of developing CRC in IBD patients is very low in The Netherlands. We identified several strong risk factors for developing IBD-related CRC in general, secondary hospitals, which may form a first step towards the development of a risk-prediction model that can be applied in daily clinical practice for an individualized approach to CRC surveillance in IBD patients.

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### Participating centers

MGVM Russel, Medisch Spectrum Twente, Enschede; TG Tan, Streekziekenhuis Midden-Twente, Hengelo; R van Roermund, Twenteborg hospital, Almelo; I Ahmad, Koningin Beatrix hospital, Winterswijk; PJ Wahab, Hospital Rijnstate, Arnhem; PC van de Meeberg, Slingeland hospital, Doetinchem; J van Bergeijk, hospital Gelderse Vallei, Ede; GW Erkelens, Reinier de Graaf Gasthuis, Delft; AJP van Tilburg, St. Franciscus Gasthuis, Rotterdam; H Geldhof and FC Beckering, IJsselland hospital, Capelle a/d IJssel; RNM Zeijen, Vlietland hospital, Schiedam; R Timmer, Sint Antonius hospital, Nieuwegein; HJA Jebbink, Medisch Centrum Leeuwarden, Leeuwarden; JH Voskuil, Hospital De Tjongerschans, Heerenveen; H Wolters, Hospital Nij Smellinghe, Drachten; JJ Nicolaï, Leyenburg Hospital, Den Haag; SDJ v.d. Werf, Westeinde hospital, Den Haag; A Stronkhorst, Catharina hospital, Eindhoven; P Boekema, Maxima Medisch Centrum, Eindhoven; L Oostenbrug, Atrium Medisch Centrum Heerlen/Brunssum, Heerlen and Brunssum; W Moolenaar, Medisch Centrum Alkmaar, Alkmaar; JR Vermeijden, Meander Medical Center, Amersfoort; H Doornewaard, Gelre hospitals, Apeldoorn; ML van Ierland-van Leeuwen, Onze lieve vrouwe gasthuis, Amsterdam; A Tan, Canisius Wilhelmina hospital, Nijmegen; M van Haastert, Martini hospital, Groningen; FJGM Kubben, Maasstad hospital, Rotterdam; M Schrijver, Bronovo hospital, Den Haag; WNHM Stuifbergen, St Elisabeth hospital, Tilburg; FHJ Wolfhagen, Tweesteden hospital, Tilburg and Waalwijk; M Ledeboer, Deventer hospital, Deventer; P Houben, Hospital Zeeuws Vlaanderen, Terneuzen; R ten Hove, Groene Hart hospital, Gouda; MCM Rijk, Amphia hospital, Breda; JPH Kuyvenhoven, Kennemer Gasthuis, Haarlem; R Breumelhof, Diakonessenhuis Utrecht, Utrecht; AC Poen, Isala hospital, Zwolle; HPM Festen, Jeroen Bosch hospital, Den Bosch; DL Schipper, Jeroen Bosch hospital, location Carolus, Den Bosch; WA de Boer, Hospital Bernhoven, Oss; MHMG Houben, Rode Kruis hospital, Den Haag; A Cats, N.K.I. Antonie van Leeuwenhoek hospital, Amsterdam; P Scholten, St Lucas Andreas hospital, Amsterdam; R Adang, VieCuri Medical Center, Venlo; S Schlotzhauer, Rijnland hospital, Leiderdorp; JC Thijs, Hospital Bethesda, Hoogeveen; SC Riemens, Diaconessenhuis, Meppel; EA Runhaar, Röpcke-Zweers-hospital, Hardenberg; S Klop, St Lucas Hospital, Winschoten; ACTM Depla, Slotervaart hospital, Amsterdam; LGJB Engels, Orbis Medical Center, Sittard; M Klemt, Westfries Gasthuis, Hoorn; RJLF Loffeld, De Heel Medical Center, Zaandam; AMC Witte, Diaconessenhuis, Leiden; PJ Bus, Laurentiushospital, Roermond; RPM Dahlmans, St. Jans Gasthuis, Weert; JJTh Smalbraak, Lievensberg hospital, Bergen op Zoom; HPC van Roermund, Franciscus hospital, Roosendaal; DJ Bac and RJTh Ou-

wendijk, Ikazia hospital, Rotterdam; H Vermeulen, Walcheren hospital, Vlissingen; F Waltman, Oosterschelde hospital, Goes; J Groen, St. Jansdal, Harderwijk; LA Noach, Hospital Amstelland, Amstelveen; PWE Haeck, Refaja Hospital, Stadskanaal; O van Baalen, Beatrix hospital, Gorinchem; HIF Royen, Talma Sionsberg, Dokkum; RCh Mallant, Flevohospital, Almere.

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# Chapter VII

# Age at diagnosis of inflammatory bowel disease influences early occurrence of colorectal cancer in inflammatory bowel disease patients; a nationwide long-term survey

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## ABSTRACT

**Background and aims:** Data on the clinical characteristics of patients with inflammatory bowel disease (IBD) related colorectal cancer (CRC) are scarce and mainly originate from tertiary referral centres. We studied patient-, and disease characteristics of IBD-related CRC in a nationwide cohort of IBD patients from general hospitals. Main outcome parameters were time to develop CRC, and factors associated with early development of CRC.

**Methods:** All IBD patients diagnosed with CRC between January 1990 and July 2006 were identified using a nationwide automated pathology-database (PALGA). Patient charts were assessed to confirm the diagnosis of IBD-related CRC and collect clinical data. We excluded patients > 65 years old to minimize interference with sporadic CRC. Early CRC was defined as CRC diagnosed < 8 years after IBD diagnosis. Statistical analysis was performed using descriptive statistics, independent *t*-tests, binary logistic regression and Cox-regression analysis.

**Results:** In 197 patients diagnosis of IBD-related CRC was confirmed (125 ulcerative colitis, 69 Crohn's disease, 3 unclassified colitis), 126 males (64%). Median time from IBD diagnosis to CRC diagnosis was 14.3 years (IQR 5-23); 62 patients (32%) developed early CRC. Type of IBD, gender, concomitant PSC, pseudopolyps, severity and extension of inflammation, and medication use were not related to early CRC development ($p>0.05$). IBD diagnosis at older age (HR 10 yrs older age 2.29; 95% CI 1.92-2.74, $p<0.001$) and continuous ongoing active inflammation during follow-up ($p=0.05$) were related to early CRC. Twenty-three patients (12%) had been included in a surveillance program prior to CRC diagnosis. Patients in the surveillance group had a significantly better tumor stage ($p=0.004$).

**Conclusions**: Our results emphasize the problem of a high proportion of IBD-associated CRC's developing before the recommended start of surveillance. Based on our results, we suggest that older age at onset of IBD could be an additional factor to start surveillance in IBD patients.

## INTRODUCTION

Patients with chronic colitis due to ulcerative colitis (UC) or Crohn's disease (CD) carry an increased risk of colorectal carcinoma (CRC).[1-3] Previous studies have mainly focused on the risk of acquiring inflammatory bowel disease (IBD)-related CRC.[4-9] However, data on clinical characteristics of IBD-related CRC cohorts, including factors that lead to earlier development of CRC, are scarce. Available studies have particularly focused on the relationship between age at onset of IBD and the interval to CRC development.[10-12] However, the results of these studies were inconsistent. Moreover, most studies focussing on the interval between IBD and CRC are based on specific tertiary cohorts including patients with a more severe and complicated disease.[10, 13, 14] Data on both patient-, and disease characteristics of patients with IBD-related CRC from non-referral, community care centres are lacking. It is therefore unknown whether the clinical characteristics of these high-risk tertiary referrals differ from the average IBD population in general hospitals.

Recently, the characteristics of patients with IBD-related CRC from academic medical centres in The Netherlands have been published.[14] Approximately 20% of all IBD-related CRCs in this cohort occurred in the first decade after onset of IBD. The cohort of 149 patients with IBD-related CRC mainly consisted of male UC patients with extensive disease. This was a selected population with results which may not reflect the total IBD population. Furthermore, the study did not report any risk factors that influence the interval between IBD and CRC in this academic population, and thus did not allow identification of any subgroup of IBD patients which would require earlier start of CRC surveillance.

Surveillance colonoscopies are an important strategy to detect CRC at an early stage and thereby decrease CRC-related morbidity and mortality.[15, 16] Currently, CRC surveillance is recommended to start 8-10 years after the onset of IBD in patients with extensive colitis and 15-20 years in those with left-sided colitis.[17, 18] More recent guidelines recommend a first screening colonoscopy 8-10 years after disease onset in all IBD patients irrespective of disease extent.[19, 20]

To implement evidence based surveillance strategies in the total IBD population, characteristics of patients with IBD-related CRC in general hospitals are needed. Moreover, parameters which lead to early development of CRC in general hospitals need to be determined to identify patients in need of earlier start of surveillance. For that reason, our aim was to assess patient characteristics and distinctive disease characteristics of IBD-related CRC in patients from general hospitals in The Netherlands.

## MATERIALS & METHODS

### Study population

IBD-related CRC patients in all 93 general hospitals in The Netherlands were identified using the nationwide network and registry of histo- and cytopathology (PALGA).[21] The PALGA database contains all pathology reports generated in the Netherlands from 1990 until present. These reports are all concluded with diagnostic terms in line with SNOMED® terminology. Each subject in the database has a unique identifier which allows tracking of individual patients over time and throughout the country. The following search criteria were used: (colon AND/OR all primary carcinoma, colon AND/OR all carcinoma in situ, colon AND/OR all micro invasive tumors, rectum AND/OR all primary carcinoma, rectum AND/OR all carcinoma in situ, rectum AND/OR all micro invasive tumors) AND (colitis AND/OR ulcerative colitis AND/OR indeterminate colitis AND/OR idiopathic colitis AND/ OR Crohn's disease).

Patients with histologically confirmed IBD and a synchronous or metachronous CRC diagnosed between January 1st, 1990 and July 1st, 2006 were included. Clinical data were needed to confirm the diagnosis of IBD-related CRC.

The study was approved by the Institutional Review Board of the Erasmus MC Rotterdam, The Netherlands.

### Data extraction

Further clinical data could be collected from 78 hospitals in The Netherlands. The results from the search were verified by the treating physicians in each hospital as well as by an external expert. Clinical data were collected from the patient charts, endoscopy reports and pathology reports. The following data were collected: type of IBD, age, gender, date of diagnosis of IBD and CRC, date of onset symptoms attributable to IBD, duration of disease, disease characteristics of IBD and CRC, history of colonic surgery, presence of concomitant PSC, use of medication, and surveillance details. Colonoscopies in the setting of dysplasia screening with multiple biopsies according to the surveillance guidelines were counted as surveillance colonoscopy.[17, 18] The complete medical history was assessed, including prior colonoscopies and pathology reports. Extent of disease was subdivided in five categories based on type and extent of inflammation: left-sided UC, extensive UC, limited CD, extensive CD or unclassified colitis. Limited CD was defined as <50% segmental CD including those with terminal ileitis or ileocoecal inflammation. Extensive CD was defined as >50% segmental CD. Severity of disease was graded as mild, moderate or severe colitis based on both histological and endoscopic features. Duration of medication-use during follow-up was divided into four categories (0-25%, 25-50%, 50-75%, >75% of duration of follow-up). Patients, who appeared to have chronic inflammation due to any other cause but IBD as well as those in whom a diagnosis of

CRC had not been confirmed histologically, were excluded for further analysis. "Early CRC" was defined as CRC diagnosed within 8 years after IBD diagnosis, irrespectively of disease extent.

### Statistical analysis

Statistical analysis was performed using descriptive statistics, independent samples *t*-tests, logistic regression, and Cox-regression analysis. Follow-up time was defined as time in years from start of diagnosis of IBD to diagnosis of CRC. Patients who were simultaneously diagnosed with IBD and CRC were excluded for all risk factor analyses with regard to the interval between IBD and CRC, since no comments can be made on the interval between IBD and CRC in these patients. Cox's proportional hazards regression was used to estimate univariable and multivariable hazard ratios to analyse the effect of several risk factors for early development of IBD-related CRC. Multivariate Cox regression was performed stepwise-backward in which all variables with a p-value below 0.10 were included, provided they had a plausible sign.[22] Univariate and multivariate logistic regression was used to identify clinical characteristics related to early CRC (<8 years after IBD diagnosis). Groups were compared based on type of IBD, gender, presence of concomitant PSC, pseudopolyps, rectal sparing, severity and extent of inflammation, medication use (ever used and duration of use), family history of CRC, and histological signs of dysplasia prior to diagnosis of CRC. Multivariate logistic regression was performed stepwise-backward in which all variables with a p-value below 0.10 were included. Statistical analysis was performed with SPSS for Windows software (version 15.0).



## RESULTS

### PALGA Search

Figure 1 represents a flow chart of the study population. The initial search in the PALGA system revealed 3738 patients with a diagnosis compatible with IBD-associated CRC (1941 males, 1797 females). After further analysis of the pathology excerpts within the PALGA search, 3211 (86%) patients were excluded for reasons of lack of histological confirmation of IBD or CRC, colonic inflammation diagnosed years after the diagnosis of CRC, or colitis due to other causes than IBD (e.g. diverticulitis).

Of the remaining 527 patients with a possible diagnosis of IBD-related CRC, 59 patients (11%) were > 65 years old. This group consisted of 37 males and 22 females, of whom 51 patients had UC and 8 patients had CD. It was decided to exclude these patients for further analysis for reasons of likelihood of sporadic, non-IBD related colorectal cancer.

In total, 468 patients were therefore eligible for detailed chart review to confirm the diagnosis of IBD-related CRC. Fifteen hospitals with a total of 38 (8%) patients were not willing to

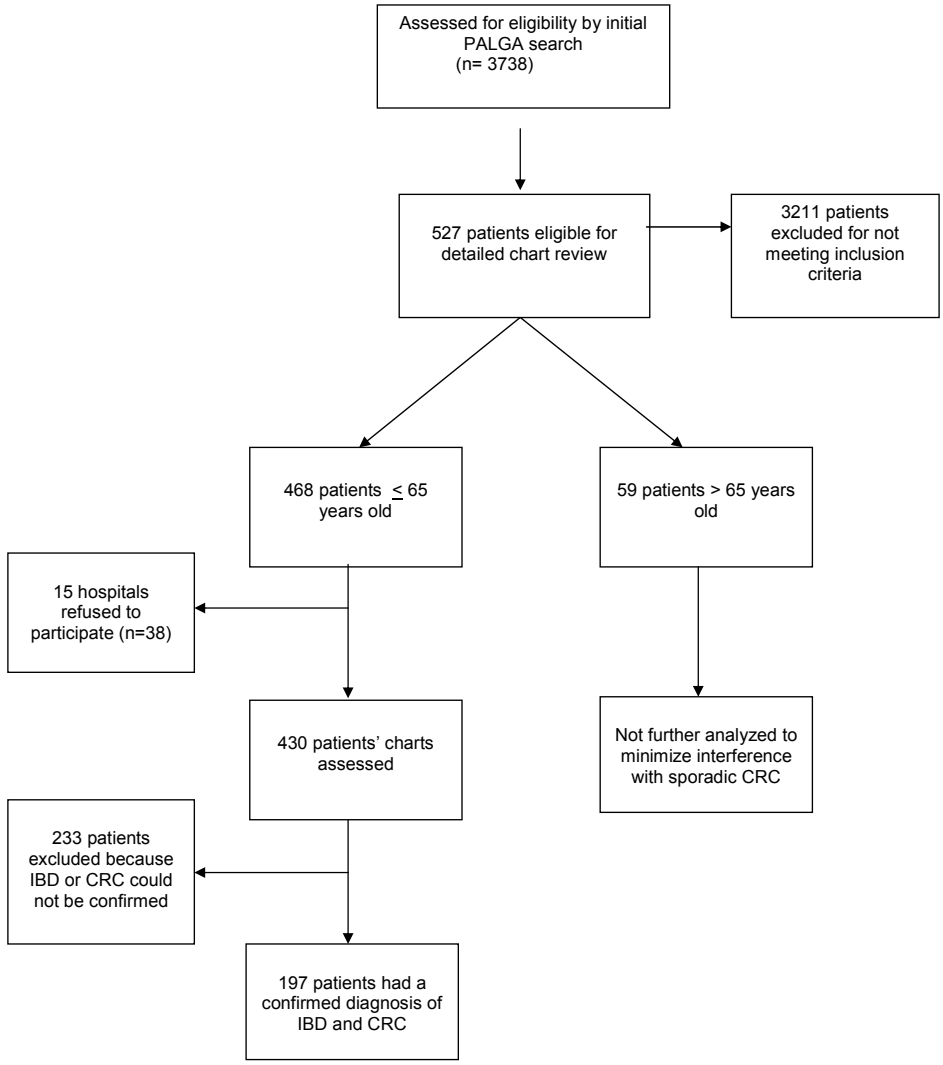


**Figure 1.** Flow chart study population

participate in the detailed chart review. In total, 430 patient charts, endoscopy- and pathology reports were assessed to confirm the diagnosis of IBD-related CRC and collect clinical data. In 197 (46%) out of these 430 patients, the histological suspicion of IBD-related CRC was confirmed based on additional clinical data, including endoscopy-, and full histology reports.

### Patient characteristics

Overall, in 197 patients ≤ 65 years old the diagnosis of IBD-related CRC was confirmed. Of these patients, 126 were male (64%), 125 had UC (64%), 69 had CD (35%) and 3 patients had unclassified colitis (2%). Median age (interquartile range (IQR)) at diagnosis of IBD was 32.8

years (IQR 22-48). Median age at CRC diagnosis was 50.6 years (IQR 42-59). Figure 2 shows the age at CRC diagnosis plotted against the age at IBD diagnosis. Additional case characteristics are listed in Table 1. In 113 (57%) out of 197 cases start of IBD complaints was not retrievable from the charts. Twenty-three patients (12%) had been included in a dysplasia surveillance program prior to CRC diagnosis (data on surveillance were missing in 9 patients (5%)). On average, patients were included in a dysplasia surveillance program after 10 years of disease (IQR 7.5-24) with an interval between each surveillance colonoscopy of 1 year (IQR 1-2.3).

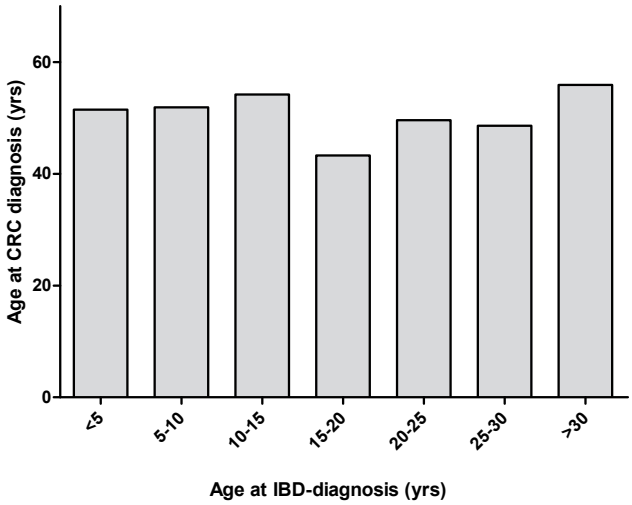


**Figure 2.** Age at IBD diagnosis vs age at CRC diagnosis
The age at IBD diagnosis is plotted against the age at which patients are diagnosed with CRC. This figure demonstrates that age at onset of IBD is not related to the age at which patients develop CRC.

### Tumor characteristics

Forty-seven percent of tumors were located in rectum (n=54) or sigmoid (n=40). In 73% of the cases (n=143) the tumor occurred in the colon segment affected by colitis. The location of chronic inflammation did not influence the location of the tumor, p=0.17. For UC patients, those with leftsided UC had a RR of 1.5 (95% CI 0.51-4.3, p=0.5) to develop a tumor in the right part of the colon compared with patients with pancolitis. Moreover, 8 (35%) out of 23 patients with a known left-sided UC developed a tumor in the right part of the colon.

Eighty-four patients (43%) had T3 tumors and 31 (16%) metastases at time of CRC-diagnosis. Additional tumor characteristics are listed in Table 2. The distribution in tumor sites differed between UC and CD patients. For 5 (3%) patients (4 UC and 1 CD), the exact tumor location could not be retrieved. In the remainder, seventy-eight out of 121 UC patients (64%) developed a tumor in the left colon, compared with 33 out of 68 CD patients (49%), p=0.022. Patients who were included in a surveillance program had a significantly better AJCC tumor stage (p=0.004).

**Table 1.** Patient characteristics

| | N - all cases (%) | N- simultaneously diagnosed IBD+CRC excluded (%) |
|---|---|---|
| **Nr of patients** | 197 | 176 |
| **Disease** | | |
| Ulcerative colitis | 125 (64) | 115 (65) |
| Crohn's disease | 69 (35) | 59 (34) |
| Unclassified colitis | 3 (2) | 2 (1) |
| **Gender** | | |
| Male | 126 (64) | 111 (63) |
| Female | 71 (36) | 65 (37) |
| **Median interval between IBD and CRC (IQR)** | 14.4 years (IQR 5-23) | 16.1 years (IQR 8-24) |
| **Median age at diagnosis IBD (IQR)** | 32.8 years (IQR 22-48) | 29.4 (IQR 22-45) |
| **Median age at diagnosis CRC (IQR)** | 50.6 years (IQR 42-59) | 50.2 (IQR 42-59) |
| **Disease extent** | | |
| Left-sided (UC) | 23 (12) | 20 (11) |
| Pancolitis (UC) | 57 (29) | 54 (31) |
| < 50% segmental colitis (limited CD) | 23 (12) | 16 (9) |
| > 50% segmental colitis (extensive CD) | 36 (18) | 34 (19) |
| Extensive unclassified colitis | 2 (1) | 1 (1) |
| *Unknown* | 56 (28) | 51 (29) |
| **Severity of disease** | | |
| Mild | 21 (11) | 17 (10) |
| Moderate | 62 (31) | 56 (32) |
| Severe | 73 (37) | 68 (39) |
| *Unknown* | 41 (21) | 35 (20) |
| **Pseudopolyps** | 72 (41) | 70 (40) |
| Unknown | 44 (22) | 35 (20) |
| **Concomitant PSC** | 19 (10) | 18 (10) |
| *Unknown* | 16 (8) | 11 (6) |
| **Positive family history CRC** | | |
| Negative | 82 (42) | 72 (41) |
| Positive 1st degree | 9 (5) | 7 (4) |
| 2nd degree | 4 (2) | 4 (2) |
| *Unknown* | 102 (52) | 93 (53) |
| **Ongoing active inflammation** | 38 (19) | 31 (18) |
| *Unknown* | 34 (17) | 27 (15) |
| **Colon surgery prior to onset IBD** | 7 (4) | 7 (4) |
| *Unknown* | 25 (13) | 19 (11) |
| **Rectal sparing (UC)** | 3 (2) | 3 (2) |
| *Unknown* | 49 (39) | 46 (40) |
| **Dysplasia found prior to CRC diagnosis** | 63 (32) | 61 (35) |
| *Unknown* | 3 (2) | 2 (1) |

Twelve (52%) out of 23 patients (AJCC tumor stage unknown in 1 patient) in the surveillance group had a stage I tumor compared with 31 (19%) out of 165 (AJCC tumor stage unknown

**Table 2.** Tumor characteristics

| | N (%) | N (%) (excluding simultaneously diagnosed IBD+CRC) |
|---|---|---|
| **Nr of patients** | 197 | 176 |
| **CRC location** | | |
| Rectum | 54 (27) | 48 (27) |
| Sigmoid | 40 (20) | 37 (21) |
| Descending colon | 9 (5) | 9 (5) |
| Splenic flexure | 10 (5) | 8 (5) |
| Transverse Colon | 17 (9) | 16 (9) |
| Hepatic flexure | 6 (3) | 6 (3) |
| Ascending Colon | 17 (9) | 14 (8) |
| Caecum | 27 (14) | 22 (13) |
| Double tumors | 12 (6) | 12 (7) |
| *Unknown* | 5 (3) | 4 (2) |
| **T stage** | | |
| Tis | 10 (5) | 9 (5) |
| T1 | 25 (13) | 22 (13) |
| T2 | 36 (18) | 33 (19) |
| T3 | 84 (43) | 74 (42) |
| T4 | 32 (16) | 29 (17) |
| Tx | 10 (5) | 9 (5) |
| **N stage** | | |
| N0 | 102 (52) | 88 (50) |
| N1 | 62 (32) | 59 (34) |
| N2 | 20 (10) | 18 (10) |
| Nx | 11 (6) | 11 (6) |
| **M stage** | | |
| M0 | 155 (79) | 134 (76) |
| M1 | 32 (16) | 32 (18) |
| Mx | 10 (5) | 10 (6) |
| **AJCC stage (6th edition)** | | |
| 0 | 10 (5) | 9 (5) |
| I | 45 (23) | 39 (23) |
| IIa | 32 (16) | 27 (16) |
| IIb | 6 (3) | 4 (2) |
| IIIa | 13 (7) | 13 (8) |
| IIIb | 35 (18) | 32 (19) |
| IIIc | 10 (5) | 7 (4) |
| IV | 34 (17) | 33 (19) |
| *Unknown* | 12 (6) | 9 (5) |
| **Metastases spread during follow-up** | 59 (30) | 54 (31) |
| **CRC in previous inflamed areas** | 143 (73) | 135 (77) |

in 8 patients) patients in the non-surveillance group. In addition, surveillance was associated with a better T-stage (p=0.002). Only 5 patients in the surveillance group (22%) had a T3 tumor at time of diagnosis compared with 67 patients (41%) in the non-surveillance group. Surveillance did not influence the metastases at time of diagnosis or during follow-up (p=0.9).

### CRC development within 8 years after IBD diagnosis

In three (1.5%) patients the exact date at which they had been diagnosed with IBD was unknown. These patients were therefore excluded for the following analyses with regard to the interval between onset of IBD and CRC diagnosis. Median interval between IBD and CRC with entry point confirmed diagnosis of IBD was 14.3 years (IQR 5-23). Overall, sixty-three patients (33%) developed CRC within eight years after IBD diagnosis, and 75 patients (38%) experienced CRC within the first decade after IBD diagnosis. In the group that developed CRC within 8 years after diagnosis of IBD, the median age at IBD diagnosis was 50.7 years (IQR 43-58), compared with a median age of 25.5 years (IQR 20-36) in those who developed CRC > 8 years of IBD, p<0.001. The median age at CRC diagnosis was 53.6 years (IQR 43-61), compared with a median age of 49.9 years (IQR 42-59) in those who developed CRC > 8 years of disease (p=0.27). Figure 3 shows that the median age at CRC diagnosis is independent of the duration of IBD. Table 3 presents the clinical characteristics of those who developed CRC within 8 years.

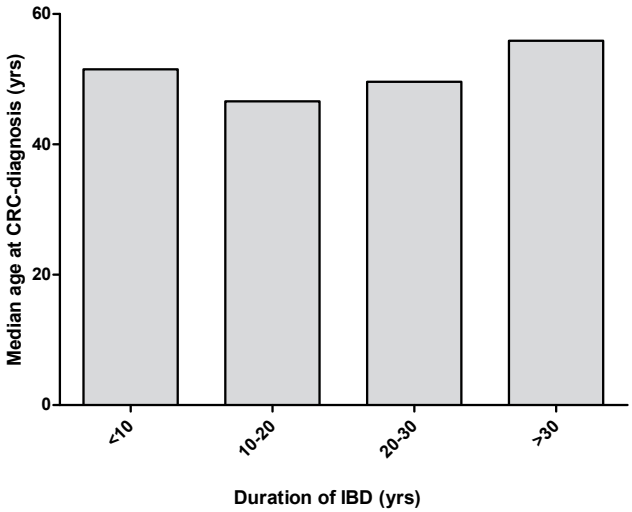


**Figure 3.** Age at CRC diagnosis is independent of duration of IBD
The duration of IBD is plotted against the median age at which patients developed CRC. This figure demonstrates that age at CRC diagnosis is independent of duration of IBD.

### Simultaneous diagnosis of IBD and CRC

Twenty-one patients were diagnosed with IBD and CRC simultaneously (10 had UC, 10 had CD, and 1 patient had unclassified colitis). Patient characteristics of this group are listed in Table 1 and tumor characteristics in Table 2. All these patients were > 37 years old at time of IBD diagnosis. One patient reported having had IBD-related complaints for 23 years from the

**Table 3.** One third of patients developed CRC within 8 years after IBD diagnosis: clinical characteristics of early CRC

| | Early CRC <8 years | p-value (univariate logistic regression) | RR (95% CI) (multivariate logistic regression) | p-value (multivariate logistic regression) |
|---|---|---|---|---|
| **Nr of patients (%)** | 62 (32) | | | |
| **Type of IBD (%)** | | p=0.49 | | - |
| Ulcerative colitis | 39 (32) | | | |
| Crohn's disease | 21 (31) | | | |
| Unclassified colitis | 2 (67) | | | |
| **Gender (%)** | | p=0.14 | | - |
| Male | 44 (36) | | | |
| Female | 18 (25) | | | |
| **Age at diagnosis IBD (%)** | | **p<0.001*** | **HR 10 years older age: 4.5 (2.7-7.2)** | **p<0.001*** |
| <20 | 1 (3) | | | |
| 20-30 | 4 (8) | | | |
| 30-40 | 8 (26) | | | |
| 40-50 | 17 (46) | | | |
| 50-60 | 20 (74) | | | |
| 60-65 | 12 (100) | | | |
| **Disease extent (%)** | | **p=0.005*** | | p=0.07 |
| Left-sided colitis (UC) | 11 (48) | | | |
| Pancolitis (UC) | 11 (20) | | | |
| < 50% segmental colitis (limited CD) | 12 (52) | | | |
| > 50% segmental colitis (extensive CD) | 5 (14) | | | |
| Extensive unclassified colitis | 2 (100) | | | |
| **Severity of disease (%)** | | **p=0.01*** | | p=0.25 |
| Mild | 13 (62) | | | |
| Moderate | 17 (27) | | | |
| Severe | 18 (25) | | | |
| **Pseudopolyps (%)** | | p=0.06 | | - |
| No | 30 (38) | | | |
| Yes | 17 (24) | | | |
| **Concomitant PSC (%)** | | p=0.7 | | -. |
| No | 49 (31) | | | |
| Yes | 5 (26) | | | |
| **Positive family history CRC (%)** | | p=0.98 | | - |
| Negative | 30(37) | | | |
| Positive 1st degree | 3 (33) | | | |
| 2nd degree | - | | | |
| **Ongoing active inflammation (%)** | | **p=0.01*** | **5.2 (1.6-16.3)** | **p=0.018*** |
| No | 30 (24) | | | |
| Yes | 18 (47) | | | |

**Table 3.** Continued

| | Early CRC <8 years | p-value (univariate logistic regression) | RR (95% CI) (multivariate logistic regression) | p-value (multivariate logistic regression) |
|---|---|---|---|---|
| **Colon surgery prior to onset IBD (%)** | | p=0.11 | | - |
| No | 45 (28) | | | |
| Yes | 4 (57) | | | |
| **Rectal sparing (UC) (%)** | | p=0.25 | | -. |
| Negative | 23 (32) | | | |
| Positive | 2 (67) | | | |

age of 19 onwards (data on start of symptoms missing in 6 patients). Of the 10 CD patients with a simultaneous diagnosis of IBD and CRC, 7 had limited CD (78%) against 2 patients with extensive CD (22%) (p=0.022). In 1 patient data on the extent of CD was missing. Of the 10 UC patient diagnosed simultaneously with IBD and CRC, in 6 patients the extent of IBD was known: 3 had left-sided colitis and 3 had pancolitis (p=0.35).

### Factors influencing the time interval between onset of IBD and CRC

As stated in the methods section, patients with simultaneous diagnosis of IBD and CRC were excluded for the following risk factor analysis with regard to the time interval between IBD and CRC.

Univariable Cox regression analysis showed that type of IBD, gender, presence of concomitant PSC, pseudopolyps, rectal sparing (UC patients), severity and extension of inflammation, a positive family history of CRC, presence of dysplasia prior to CRC diagnosis, or ongoing active inflammation of IBD without any remission during follow-up, were not significantly associated with early development of CRC (all p>0.05, Table 3). Diagnosis of IBD at older age was associated with early development of CRC (HR for 10 years older age 2.25; 95% CI 1.92-2.63).

The extent of inflammation did not correspond with the time to development of CRC (p=0.53). However, patients with pancolitis had more often been treated with 5-ASA (49/50=98%) compared to patients with left-sided colitis (15/20=75%), p=0.06. In addition, UC patients with left-sided colitis were more often diagnosed with IBD at an older age (median age 43.4 years; IQR 27-55) compared with UC patients suffering from pancolitis (median age 27.9 years; IQR 21-44), p=0.02.

For all medications (5-ASA, corticosteroids, azathioprine, methotrexate, anti-TNF, ursodeoxycholic acid, folic acid and ferrofumerate) no significant correlations with the time to develop CRC were found (Table 4). Duration of medication use did not significantly influence the time

to CRC diagnosis for any type of drug. Starting 5-ASA directly at the time of IBD diagnosis did not influence the interval between IBD and CRC (p=0.24).

**Table 4.** Parameters influencing a short interval between IBD and CRC development (univariate Cox regression)

| | Median time to CRC-diagnosis in years (IQR) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|
| **Nr of patients** | 173 (%)† | | |
| **Type of IBD** | | | p=0.53 |
| Ulcerative colitis | 15.7 (7.6-23.7) | 1.0 | |
| Crohn's disease | 17.3 (9.9-26.9) | 0.93 (0.67-1.28) | |
| Unclassified colitis | 10.6 (4.3-16.9) | 2.2 (0.55-9.09) | |
| **Gender** | | | p=0.53 |
| Male | 16.1 (9.8-23.1) | 1.0 | |
| Female | 16.2 (7.4-24.7) | 1.1 (0.81-1.51) | |
| **Age at diagnosis IBD** | | | **p<0.001*** |
| <20 | 24.5 (18.8-34.9) | 1.0 | |
| 20-30 | 19.8 (15.4-30.7) | 1.7 (1.1-2.7) | |
| 30-40 | 16 (8.3-21.6) | 3.9 (2.3-6.7) | |
| 40-50 | 12.1 (4.5-14.9) | 7.0 (4.0-12.2) | |
| 50-60 | 7.2 (4.2-8.4) | 21.0 (10.3-42.7) | |
| 60-65 | 3.5 (0.9-4.8) | 59.8 (22.1-161.7) | |
| **Disease extent** | | | p=0.3 |
| Left-sided colitis (UC) | 11.5 (2.5-22.8) | 1.0 | |
| Pancolitis (UC) | 17.7 (10.9-24.2) | 0.66 (0.39-1.12) | |
| < 50% segmental colitis (limited CD) | 12.7 (4.5-29.7) | 0.73 (0.38-1.41) | |
| > 50% segmental colitis (extensive CD) | 18.0 (13.4-25.8) | 0.65 (0.37-1.13) | |
| Extensive unclassified colitis | 4.3 (4.3-4.3) | 5.41 (0.69-42.5) | |
| **Severity of disease** | | | p=0.26 |
| Mild | 9.0 (2.8-22.7) | 1.0 | |
| Moderate | 18.9 (9.5-24.9) | 0.62 (0.36-1.01) | |
| Severe | 16.3 (8.5-22.2) | 0.72 (0.42-1.24) | |
| **Pseudopolyps** | | | p=0.7 |
| No | 17.7 (6.1-26) | 1.0 | |
| Yes | 16.0 (8-23.2) | 1.07 (0.76-1.5) | |
| **Concomitant PSC** | | | p=0.5 |
| No | 16.6 (8.1-25.1) | 1.0 | |
| Yes | 18.3 (8.2-23.9) | 1.19 (0.72-1.95) | |
| **Positive family history CRC** | | | p=0.19 |
| Negative | 16.1 (7.5-23.2) | 1.0 | |
| Positive 1st degree | 15.0 (10-20.3) | 1.23 (0.56-2.7) | |
| 2nd degree | 32.5 (20.2-37.3) | 0.43 (0.16-1.2) | |
| **Ongoing active inflammation** | | | p=0.11 |
| No | 17.4 (9.3-24.7) | 1.0 | |
| Yes | 14.5 (3.8-23.2) | 1.39 (0.93-2.07) | |
| **Colon surgery prior to onset IBD** | | | p=0.08 |
| No | 17.5 (9.7-24.7) | 1.0 | |
| Yes | 7.3 (2.1-23.2) | 1.97 (0.92-4.23) | |

**Table 4.** Continued

| | Median time to CRC-diagnosis in years (IQR) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|
| **Rectal sparing (UC)** | | | p=0.08 |
| Negative | 13.7 (7.5-20.8) | 1.0 | |
| Positive | 7.7 (4.8-12.4) | 2.91 (0.88-9.65) | |
| **Dysplasia found prior to CRC diagnosis** | | | p=0.23 |
| No | 15.4 (8.4-24.1) | 1.0 | |
| Yes | 17.6 (5.4-24.6) | 0.83 (0.61-1.13) | |

† 21 patients with simultaneous IBD and CRC were excluded for this risk factor analysis

### Multivariate analysis of factors related to the interval between IBD and CRC

Age at onset IBD, rectal sparing (UC patients), colorectal surgery prior to onset IBD, and ongoing active inflammation during follow-up were assessed in a multivariate Cox-regression analysis. After correcting for possible confounders, age at onset of IBD (HR 10 yrs older age 2.29; 95% CI 1.92-2.74, p <0.001) and ongoing active inflammation during follow-up (HR 1.5; 95% CI 1.0-2.29. p=0.04) were significantly correlated with a shorter interval between IBD and CRC. Figure 4 demonstrates the relationship between age at IBD diagnosis and time to develop CRC.

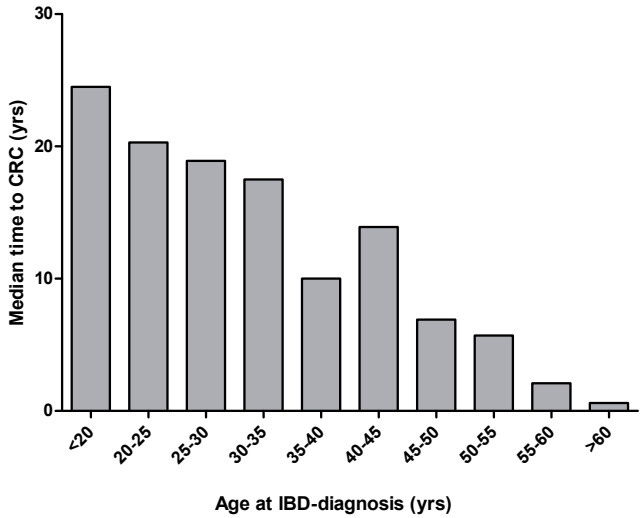


**Figure 4.** Age at IBD diagnosis is related to the time to develop CRC
This figure shows the time to develop CRC against the age at which patients were diagnosed with IBD. This shows that age at IBD diagnosis is related to the time to develop CRC.

**Table 5.** Medication use does not protect against early CRC

| | Cases | Median time to diagnosis CRC in years (IQR) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Nr of patients** | 159 (%)† | | - | |
| **5-ASA** | | | | p=0.69 |
| Yes | 137 (86) | 17.3 (9.8-24.2) | 0.91 (0.58-1.44) | |
| No | 22 (14) | 16.4 (3.3-28.1) | 1.0 | |
| **Thiopurines** | | | | p=0.97 |
| Yes | 36 (23) | 17.4 (13.1-24.6) | 1.01 (0.69-1.45) | |
| No | 123 (77) | 16.9 (8-24.5) | 1.0 | |
| **Corticosteroids** | | | | p=0.24 |
| Yes | 102 (64) | 17.6 (10.9-24.5) | 0.82 (0.59-1.14) | |
| No | 57 (36) | 15.9 (5-24.6) | 1.0 | |
| **MTX** | | | | p=0.47 |
| Yes | 2 (1) | 14.7 (11.6-17.8) | 1.68 (0.41-6.83) | |
| No | 157 (99) | 17.3 (8.8-24.5) | 1.0 | |
| **Anti-TNF** | | | | p=0.34 |
| Yes | 4 (3) | 17.2 (8.4-17.8) | 1.63 (0.6-4.46) | |
| No | 155 (97) | 17.2 (9-24.5) | 1.0 | |
| **Ascal** | | | | p=0.34 |
| Yes | 5 (3 ) | 17.2 (5.3-34.5) | 0.65 (0.26-1.6) | |
| No | 154 (97) | 15.4 (8.9-24.5) | 1.0 | |
| **NSAIDS** | | | | p=0.11 |
| Yes | 7 (4) | 14.7 (0.9-20.6) | 1.85 (0.86-3.98) | |
| No | 152 (96) | 15.7 (9.1-24.6) | 1.0 | |
| **Folic acid** | | | | p=0.71 |
| Yes | 16 (10) | 14.6 (10.6-27.4) | 1.11 (0.66-1.86) | |
| No | 143 (90) | 17.4 (8-24.5) | 1.0 | |
| **Calcium** | | | | p=0.36 |
| Yes | 10 (6) | 16.5 (11.2.21.4) | 1.34 (0.7-2.56) | |
| No | 149 (94) | 17.3 (8.8-24.5) | 1.0 | |
| **Ursodeoxy acid** | | | | p=0.57 |
| Yes | 13 (8) | 23 (17.6-24.1) | 0.85 (0.48-1.5) | |
| No | 146 (92) | 16.3 (8.5-24.5) | 1.0 | |
| **Ferrofumerate** | | | | p=0.25 |
| Yes | 47 (30) | 17.8 (11.8-26.2) | 0.82 (0.58-1.16) | |
| No | 112 (70) | 16.5 (8-24.4) | 1.0 | |

† In 14 cases data on medication use was not retrievable.

## DISCUSSION

We present a large nationwide general hospital study on the characteristics of IBD-related CRC. In this cohort we demonstrate early occurrence of IBD-related CRC and we show that a high proportion of IBD-associated CRC's develops before the recommended start of surveillance. Moreover, the patients who were included in a surveillance program had significantly

better tumor characteristics. We identified a subgroup of patients in need of earlier start of surveillance.

A large number of patients (32%) developed CRC within 8 years after diagnosis of IBD, which is before the recommended start of surveillance. Our results underline the results of two recently published academic cohorts, in which approximately 20% of IBD-related tumors occurred within 10 years after IBD diagnosis.[13, 14] Probably, start of IBD-related symptoms instead of interval since diagnosis better estimates the years at risk for developing CRC; however, the actual date of onset of symptoms that were in fact related to IBD are difficult to retrieve and may lead to recall bias. In our cohort, in 113 out of 197 cases (57%) data were lacking concerning the actual onset of IBD-related symptoms prior to the baseline diagnosis.

The guidelines for surveillance are currently being altered. The classic guidelines recommended to start bi-annual colonoscopy surveillance after 8-10 years for extensive colitis and 15-20 years for left-sided disease (from onset of symptoms).[17, 18] However, more recent guidelines suggest to perform a screening colonoscopy after 8-10 years of disease in all IBD patients, to assess the true microscopic extent of inflammation.[19, 20] Our data are in line with these adjustments, as location of IBD did not influence the time to develop CRC in our cohort.

However, one third of all cases occur before this newly recommended screening schedule. Diagnosis of IBD at older age is significantly related to early development of IBD-related CRC in our cohort. This has also been demonstrated in previous studies.[11, 13] In large contrast to the older age at which patients with early CRC were diagnosed with IBD, the median age at time of CRC diagnosis was equal compared with those who developed CRC > 8 years after IBD diagnosis. This suggests that age at onset of IBD, and not duration of disease is a leading factor for early development of CRC in IBD patients. This could among others be explained by the fact that in UC patients colonocyte telomeres shorten with age almost twice as rapidly as in normal controls.[23] Telemore-shortening is associated with the development of cancer and colonocytes of UC patients show premature shortening of telomeres, which might in part explain the increased and earlier risk of cancer in this disease. Future research is needed to support this hypothesis.

Strikingly, in 21 out of 197 patients (10.7%), IBD and CRC were diagnosed simultaneously. All these patients were > 37 years old at time of IBD diagnosis, which supports our notion that age at onset of IBD is probably a leading factor for early CRC. Most patients (15/21 patients) already had symptoms attributable to IBD before diagnosis.

Even though almost half of the patients with CRC had extensive colitis, the majority of IBD-related tumors were located in the left colon and already advanced tumor stages were

found at time of diagnosis. More advanced tumors (AJCC stage III tumor) were found in our non-academic cohort (30%) compared with the Dutch academic cohort (20%).[14] This might be explained by the fact that only 12% of our patients were included in a dysplasia surveillance program before development of CRC, against a slightly higher percentage (15%) in the academic cohort. This low adherence to colonoscopy surveillance in IBD patients reflects clinical practice in general hospitals with a presumed perception of low CRC risks in these populations. This perception has to change, as our findings support the inclusion of patients in surveillance strategies and show that surveillance was associated with earlier detection and thus improved tumor stage. Our findings are supported by previous studies, which also demonstrated that surveillance colonoscopies may detect CRC at an earlier stage and improve prognosis.[15, 16]

IBD patients with concomitant PSC and a positive family history of CRC are at increased risk of developing CRC.[4, 7, 24-26] However, we could not confirm that these factors also lead to earlier development of CRC, which is also endorsed by results from previous studies.[13, 27, 28] These results suggest that, although PSC and a familial predisposal of CRC are risk factors for acquiring CRC, they are not a driving force for earlier development of IBD-related CRC. It therefore remains a discussion whether we should perform surveillance colonoscopies more frequently in these patients. However, our results could be biased due to the relatively small number of patients with PSC in our non-academic cohort. Moreover, the number of patients with a positive family history of CRC might be under-recorded in a retrospective study. Therefore caution is needed in interpreting these results.

Use of medication and duration of medication use did not influence the interval between IBD and CRC in our cohort. Previous studies have demonstrated 5-ASA use to be protective for acquiring CRC.[5, 29-31] However, we could not confirm this in our cohort. This could be influenced by the retrospective data collection, in which duration of medication use was subdivided in four different periods and therefore not assessed as a continuous factor. Furthermore, medication use could have been prone to information bias due to the retrospective study design.

A recently publish study from Sweden demonstrated that male patients have an overall 60% higher rate of CRC than female patients.[32] However, there was no effect of sex on the RR within 10 years after IBD-diagnosis. Although we did not focus on gender differences, we can conclude that in our cohort also more male patients developed IBD-related CRC during our study-period of 15 years. However, we did not correct this for possible confounders as age and type of IBD. Although male patients were in the majority in our cohort, gender did not influence early development of CRC in our cohort. Although the Swedish study did not assess the time interval between IBD onset and CRC development, they could not identify a RR difference within 10 years of IBD, which supports our results.

Limitations of this study include the exclusion of patients over 65 years of age with the suspicion of IBD-related CRC. Advanced age is the most significant risk factor for diagnosis of sporadic CRC, with a vast majority being diagnosed when > 65 years old.[33, 34] Since we could not rule out the increased likelihood of interference of sporadic CRC in our cohort we decided to exclude these patients from further analysis. In our initial PALGA search we identified at most 59 patients with a suggestive IBD-related CRC in this age category, therefore the influence of excluding this patient group in our final analysis is limited.

Although we are aware of the limitations of a retrospective study design, this design was carefully chosen to fit our main aim to study the overall epidemiology of IBD-related CRC. Because of the considerable time-interval to development of CRC in IBD and the low frequency of IBD-related CRC in general hospitals, conducting a prospective study would not be feasible. Using a retrospective analysis, we were able to perform a large nationwide survey with a follow-up time of 15 years.

In conclusion, our results emphasize the problem of a high proportion of IBD-associated CRCs developing before the recommended start of surveillance. Secondly, we demonstrate that surveillance is associated with a better tumor stage. This underlines the need to identify a subgroup of patients that require earlier start of surveillance. Based on our results, we suggest that older age at onset of IBD could be an additional factor to start surveillance in IBD patients. Accordingly, we would recommend earlier start of surveillance and an immediate start at time of IBD diagnosis for patients diagnosed with IBD above the age of 45 years. Moreover, better registration of start of symptoms is needed. Adapting the surveillance guidelines and identifying patients in need of earlier start of surveillance will detect CRC at an earlier stage and may therewith improve prognosis.

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# Chapter VIII

# A colorectal cancer risk prediction model for inflammatory bowel disease patients in general hospitals: a first step towards individualized surveillance strategies

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## ABSTRACT

**Background and aims:** The incidence of colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients is increased. Endoscopic surveillance starting 8-10 years after IBD onset is therefore advised, but invasive and troublesome for patients. This necessitates methods for individually tailored CRC surveillance in IBD patients. A nationwide nested case-control study from The Netherlands demonstrated a low population rate for IBD-related CRC and identified several strong prognostic factors. Based on these data we aimed to develop a risk prediction model for IBD-related CRC that can be applied in daily clinical practice in general hospitals.
**Methods:** In 78 Dutch general hospitals**,** 173 cases with IBD-related CRC between January 1990 - July 2006 were compared with 393 IBD patients without CRC. In 58 randomly selected hospitals the total IBD population comprised 26,855 patients of whom 163 developed CRC during 15.5 years follow-up, which equals a population rate of 0.04%. Statistical analysis was performed using Poisson regression of time to CRC with time-dependent covariates.
**Results:** Based on previously established risk factors in the Dutch general hospitals, a prediction model was developed. The final prediction model, in which the maximum annual CRC risk did not exceed 0.7%, included age, gender, duration of primary sclerosing cholangitis, duration of IBD, extent of disease, and concomitant pseudopolyps.
**Conclusions**: In conclusion, this model is a first step towards individualized surveillance for IBD patients in general hospitals. According to our results we propose to start surveillance every 3 years in IBD patients with a predicted risk of 0.2% or higher. After further validation, the individualized risk estimates may well be useful for counseling IBD patients.

## INTRODUCTION

Due to the increased risk of colorectal carcinoma (CRC) in patients with inflammatory bowel disease (IBD), colonoscopy with multiple biopsies is currently recommended for early detection of dysplasia or asymptomatic early CRC in IBD patients.[1] Surveillance colonoscopies are an important strategy to detect CRC at an early stage and thereby decrease CRC-related morbidity and mortality.[2,3] Recent guidelines recommend to start surveillance after 8-10 years of disease in all IBD patients.[4, 5]

Recent studies indicated that the risk of IBD-related CRC is much lower than was previously reported.[6] We have earlier demonstrated by a nationwide nested case-control study that the risk for IBD-related CRC in The Netherlands is limited (chapter VI). This raises the question whether we need to perform surveillance in all IBD patients since CRC surveillance for all IBD patients is associated with unnecessary burden and costs. This necessitates methods for individually tailored CRC surveillance in IBD patients.

Several risk and protective factors for IBD-related CRC have been identified in epidemiologic studies. The established risk factors for IBD patients in tertiary centers included long disease duration, extent of disease to the hepatic flexure, co-presence of primary sclerosing cholangitis (PSC), the presence of pseudopolyps and a family history of sporadic CRC.[7-12] However, the available data mainly originate from tertiary referral centers. Earlier we demonstrated several strong prognostic factors for the general IBD population which differed from those previously established in tertiary cohorts. Age, duration of PSC and IBD, concomitant pseudopolyps and use of 5-ASA or immunosuppressives were strong prognostic factors in general hospitals.

Although numerous studies have identified relative risks for developing IBD-related CRC, no quantitative risk model is currently available to estimate the absolute risk or probability of developing IBD-related CRC. Previous studies have already demonstrated the performances of a prediction model in the setting of other cancers, e.g. Lynch syndrome, breast cancer and colorectal cancer.[13-15] An important role of prediction models is to inform patients about their prognosis, for example, after a cancer diagnosis has been made.[16] Another important area is decision support, including decisions on the need for further diagnostic testing (tests may be burdensome or costly to a patient), or therapy (e.g., surgery with risks of morbidity and mortality). Given the burden and costs to society associated with surveillance colonoscopy, a model that estimates an individual's probability of developing IBD-related CRC using risk factor information that can be obtained easily in a clinical setting may aid physicians and their patients in deciding on screening regimens.

We therefore elucidated further on the data from the Dutch nationwide nested case-control study, in which we identified several strong prognostic factors for the general IBD population in general hospitals (chapter VI). Based on the established risk factors for developing IBD-related CRC in this population, we developed a risk prediction model that can be applied in daily clinical practice for an individualized approach to CRC surveillance in IBD patients in general hospitals.

## MATERIALS & METHODS

### Study population used to estimate relative risk

We used data from a Dutch nationwide nested-case control study for the risk of IBD-related CRC in general hospitals (chapter VI). In short, the cohort consisted of 197 cases who were compared with 392 control patients (Table 1). The cases included all IBD patients diagnosed with CRC in 78 non-academic medical centers in The Netherlands in the period from January 1st, 1990 until July 1st, 2006. Control patients were defined as histological confirmed IBD patients who had not developed CRC in the same time-period. Controls were randomly selected and solely matched with cases for the time-period for being at risk of CRC.

**Table 1.** Patient characteristics

| | At start† | End of virtual follow-up | |
|---|---|---|---|
| | | Cases | Controls |
| **Nr of patients** | | 173 | 392 |
| **Disease** | | | |
| Ulcerative colitis | | 113 | 175 |
| Crohn's disease | | 58 | 207 |
| Unclassified colitis | | 2 | 10 |
| **Sex** | | | |
| Female | | 65 | 234 |
| Male | | 108 | 158 |
| **Age** | | | |
| <20 | 50 | 0 | 18 |
| 20-30 | 172 | 7 | 65 |
| 30-40 | 149 | 32 | 123 |
| 40-50 | 120 | 48 | 92 |
| 50-60 | 61 | 50 | 70 |
| 60-65 | 13 | 36 | 24 |
| **Duration of IBD** | | | |
| <10 | 474 | 52 | 259 |
| 10-20 | 60 | 56 | 87 |
| >20 | 31 | 65 | 46 |

**Table 1.** Continued

| | At start† | End of virtual follow-up | |
|---|---|---|---|
| | | Cases | Controls |
| **Extent IBD at onset IBD††** | | | |
| Left-sided UC | | 36 | 109 |
| Extensive UC | | 24 | 51 |
| Unknown UC | | 53 | 15 |
| < 50% segmental CD | | 16 | 120 |
| > 50% segmental CD | | 16 | 63 |
| Unknown CD | | 26 | 24 |
| Left-sided CU | | 0 | 7 |
| Extensive CU | | 0 | 2 |
| Unknown CU | | 2 | 1 |
| **Degree of inflammation at onset** | | | |
| Mild | | 23 | 108 |
| Moderate | | 30 | 131 |
| Severe | | 26 | 105 |
| Unknown | | 94 | 48 |
| **Concomitant pseudopolyps** | | | |
| No | | 68 | 298 |
| Yes | | 71 | 76 |
| Unknown | | 34 | 18 |
| **Duration of PSC** | | | |
| 0 | 555 | 156 | 387 |
| 0-5 | 3 | 5 | 1 |
| 5-10 | 3 | 7 | 1 |
| >10 | 4 | 5 | 3 |
| **Rectal sparing at onset IBD** | | | |
| Negative | | 122 | 360 |
| Positive | | 3 | 17 |
| Unknown | | 48 | 15 |
| **Positive family history CRC** | | | |
| Negative | | 72 | 260 |
| Positive 1st degree | | 7 | 12 |
| 2nd degree | | 4 | 11 |
| Unknown | | 90 | 109 |
| **Colon surgery prior to onset IBD** | | | |
| No | | 148 | 384 |
| Yes | | 7 | 5 |
| Unknown | | 18 | 3 |

† only shown for time dependent predictors

†† Onset IBD defined as date of diagnosis of IBD

UC: ulcerative colitis, CD: Crohn's disease, CU: unclassified colitis, IBD: inflammatory bowel disease, PSC: primary sclerosing cholangitis, CRC: colorectal carcinoma

### Relative risk factors for IBD-related CRC

The nested case-control study identified several strong prognostic factors for IBD-related CRC in general hospitals: age, duration of PSC and IBD, and concomitant pseudopolyps (Table 2). We included these previously established risk factors in our risk prediction analyses.

**Table 2.** Prognostic factors for the development of CRC

| Variable category | Rate ratio (95% CI) | p-value |
|---|---|---|
| **Age** | NA† | **p<0.001*** |
| **Sex** | | **p=0.17** |
| Female | 1.0 | |
| Male | 1.25 (0.91-1.73) | |
| **Duration of PSC (per year)** | 1.05 (1.01-1.10) | **p=0.02*** |
| **Duration of IBD (per year)** | 1.04 (1.02-1.05) | **p<0.001** |
| **Extent of IBD at onset** | | **p=0.07** |
| Left-sided UC | 1.00 | |
| Extensive UC | 1.18 (0.71-1.97) | |
| <50% segmental CD | 0.64 (0.41-1.00) | |
| >50% segmental CD | 0.84 (0.49-1.44) | |
| Unclassified colitis | 1.02 (0.28-3.74) | |
| **Concomitant pseudopolyps** | 1.92 (1.28-2.88) | **p=0.002*** |

† NA: not applicable, PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease.

†† The effect of age was modeled by a restricted cubic spline, therefore no effect-size can be given.

### Statistical analysis risk prediction model

Statistical analysis was performed using Poisson regression of time to CRC with time-dependent covariates. The total follow-up of all patients was split up in years from start of follow-up (1-1-1990) or diagnosis of IBD until end of follow-up (01-07-2006) or incidence of CRC. For every year, baseline predictors were noted (such as gender and characteristics of the disease at onset) and time-dependent predictors were calculated (such as age, duration of disease, duration of primary sclerosing cholangitis). For the analyses of the prognostic factors, cases with a synchronous diagnosis of IBD and CRC were excluded, as well as patients with an unknown date of diagnosis of IBD. The prognostic factors from the multivariable analyses were used to develop the prediction model. Variables with <5% positive or negative values were excluded (i.e. prior colonic surgery and family history of sporadic CRC). Predictors with a p-value below 0.10 were included, provided they had a plausible sign.[17] Age and sex were retained in the model irrespective of statistical significance. Continuous predictors (age and duration of IBD and PSC) were tested for non-linearity; if a predictor had a significantly non-linear effect we used a restricted cubic spline function for a flexible fit to the data.[18] Missing values for extent of IBD and pseudopolyps were multiply imputed using the nearest neighbour method.[19]

For practical application, we conveniently scaled the regression coefficients to simple integer values that can be added and subtracted. The sum mimics the linear predictor of the Poisson model and relates to an individual's estimated incidence rate of CRC per year. We used the sampling fraction of controls to the total cancer-free IBD population in the participating hospitals to adjust rates from the case-control design to the population level. Specifically, the model intercept from the case-control study was reduced by the logarithm of the ratio

of the population rate and the case-control rate. In total, 1.39% of all possible controls were included in the database, so we corrected the hazards for incidence accordingly and transformed them to probabilities per year.

All analysis were performed using R software (version 2.7.1, R Foundation for Statistical Computing, Vienna, Austria). This study has been approved by the Institutional review board of the Erasmus Medical Center, Rotterdam, The Netherlands.

## RESULTS

### Prediction model for developing IBD-related CRC

We simplified the earlier identified regression model to a prediction score and verified that almost no information was lost by calculating the correlation between prediction score and linear predictor, which turned out to be 0.997. Adjusting for the population rate, the maximum annual risk for developing CRC did not exceed 0.7% (Figure 1).

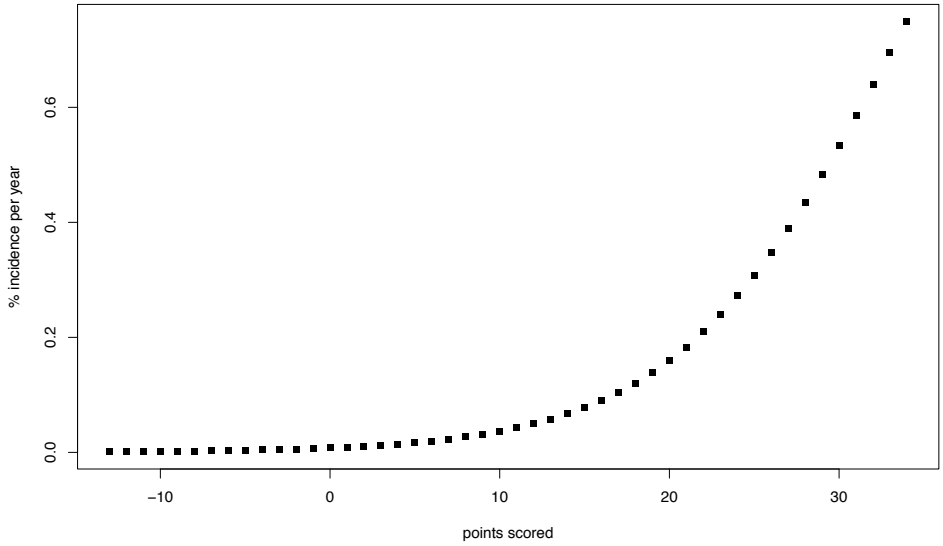


**Figure 1.** Individualized risk of developing IBD-related CRC

Three years of PSC had approximately the same effect as four years of IBD on the development of CRC and were assigned one point in the prediction rule. Male gender was assigned with 2 points and concomitant pseudopolyps were assigned with 4 points. In the prediction rule, add one point for extensive UC, subtract 3 points for limited CD or one point in case of extensive CD. (Table 3). Practical use of the model is illustrated with a hypothetical male patient, aged 50 years, diagnosed with IBD at age 22, extensive colitis with pseudopolyps,

concomitant PSC for 10 years. According to Table 4, his age score is 5 points, and total sum is 22 points. His probability for the development of CRC in the next year is 0.2% (Figure 1).

**Table 3.** Prediction model flowchart

| **Step 1: Choose the number of points for each patient characteristic mentioned below:** | |
|---|---|
| **Patient's characteristic** | **# of points** |
| **Duration of IBD** | 1 point for every 4 years of IBD |
| **Duration of PSC** | 1 point for every 3 years of PSC |
| **Gender** | |
| Male | 2 points |
| female | 0 points |
| **Location of IBD** | |
| Leftsided colitis (UC) | 0 points |
| Extensive colitis (UC) | 1 point |
| Limited CD | - 3 points |
| Extensive CD | - 1 point |
| Unclassified colitis | 0 points |
| **Concomitant pseudopolyps** | 4 points |
| **Step 2: Choose the # points that matches with your patients' age from Table 5** | |
| **Step 3: Read in Figure 1 patient's individual risk of developing IBD-related CRC within the next year** | |

**Table 4.** Points for age in the CRC prediction model

| Age | Points |
|---|---|
| **0-1** | -12 |
| **2-4** | -11 |
| **5-6** | -10 |
| **7-9** | -9 |
| **10-12** | -8 |
| **13-14** | -7 |
| **15-17** | -6 |
| **18-20** | -5 |
| **21-23** | -4 |
| **24-25** | -3 |
| **26-27** | -2 |
| **28-29** | -1 |
| **30** | 0 |
| **31** | 1 |
| **32-33** | 2 |
| **34** | 3 |
| **35** | 4 |
| **36** | 5 |

**Table 4.** Continued

| Age | Points |
|---|---|
| **37** | 6 |
| **38-42** | 7 |
| **43-44** | 6 |
| **45-50** | 5 |
| **51-52** | 7 |
| **53** | 7 |
| **54** | 8 |
| **55** | 9 |
| **56** | 10 |
| **57** | 11 |
| **58** | 13 |
| **59** | 14 |
| **60** | 15 |
| **61** | 16 |
| **62** | 18 |
| **63** | 19 |
| **64** | 20 |
| **65** | 22 |



## DISCUSSION

With this study we are the first to present a model that predicts the risk of developing IBD-related CRC in individual patients from general hospitals. It is a first step towards individualized surveillance for IBD patients and is expected to be easy to apply in a clinical setting.

Our model's estimates of the individual cancer risk did not exceed 0.7% per year, which is limited and in contrast with previous studies.[7, 8, 20, 21] However these studies were mainly referral-center-based. The CRC risk we found in IBD patients is similar to the risk of developing esophageal cancer in Barrett's esophagus, which is estimated around 0.5% per year.[22-27] In patients with Barrett's esophagus surveillance may reduce the incidence of invasive cancer and may be cost-effective.[28-30] Surveillance strategies enabled early detection of CRC in IBD patients and thus reduced the mortality from CRC in ulcerative colitis.[2, 31] Therefore, patients at risk of developing CRC should undergo surveillance colonoscopies. The question remains at what CRC risk surveillance should start in IBD patients to be cost-effective. Considering earlier publications dealing with surveillance strategies in Barrett's esophagus [29, 30] and gastric cancer [32] we propose to start surveillance when the individual risk for an IBD patient exceeds 0.2%, but this threshold requires further study. In clinical practice this will lead to a decrease

in the number of surveillance colonoscopies. This implies also reduced medical costs but most importantly for IBD patients, less invasive investigations.

Our risk prediction model is based on data from a nationwide non-academic cohort. The strength of this large cohort is the long follow-up time of 15.5 years and the inclusion of 78 different non-academic hospitals all over The Netherlands. Moreover, all data were confirmed by clinical chart review, including endoscopy- and pathology reports, minimizing the bias of misclassification. All CRC cases were included, irrespective of the development of CRC proximal to the greatest extent of disease or outside previous areas of chronic inflammation.

The Dutch nested case-control study confirmed some of the risk factors that were previously established in other cohorts, however not all known risk factors could be confirmed in this cohort of general hospitals. Previous reports originate mainly from specific tertiary cohorts, mostly including patients with a more extensive and severe disease. Our data demonstrated that risk factors for patients in general hospitals are different from those in specific tertiary cohorts. It was therefore decided to solely include in this prediction model the significant prognostic factors for patients in general hospitals, since we aimed to develop a prediction tool for the general IBD population.

Chemoprevention is currently being investigated as a promising option for reducing the risk of developing IBD-related CRC. However, medication use could not be included in our prediction-model. This is due to the retrospective analysis of the patients' charts, as a result of which the duration of use could not be assessed using time-dependent analysis. Experimental and clinical research suggest that regular intake of 5-aminosalicylate (5-ASA) drugs may reduce the occurrence of CRC in IBD patients.[10, 33, 34] However, data are still conflicting and more research should be performed to determine the exact optimal dosage and duration of 5-ASA therapy for primary prevention of dysplasia. Future research is needed before medication use can be implemented in a risk prediction model.

Although the model was based on cases and controls aged 65 and younger, one could project risk for older individuals. However, such assumption needs to be checked in independent data because risk factors and biologic mechanisms may differ among those developing IBD-related CRC at older age. For instance, there can be an interference with the development of sporadic CRC. Advanced age is the most significant risk factor for diagnosis of sporadic CRC, with a vast majority being diagnosed when > 65 years old.[35, 36]

Another limitation of our model is that we estimated our prognostic factors from a nested case-control study rather than from a cohort study. Although case-control studies have been used earlier in the development of risk prediction models [37, 38], our model estimates could be

subject to various sorts of bias, including recall bias. However most of our risk factors were consistent with earlier studies.[10-12] Moreover, prospective validation of the model needs to be performed to further validate the results.

In conclusion, this model is a first step towards individualized surveillance for IBD patients in general hospitals. According to our results we propose to start surveillance every 3 years in IBD patients with a predicted risk of 0.2% or higher. After further validation, this model may support physicians in deciding on starting surveillance.

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# Chapter IX

## Two third of patients with inflammatory bowel disease in clinical remission has mucosal inflammation

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## ABSTRACT

**Background and aims:** Routine endoscopic examination of inflammatory bowel disease (IBD) patients in clinical remission often reveals mucosal inflammation. We assessed the prevalence and severity of mucosal inflammation in IBD patients while clinically in remission, the clinical consequences, and the impact on the disease course.

**Methods:** All IBD patients from two Dutch referral centers who were in clinical remission and underwent a surveillance colonoscopy from 01/2001 to 12/2003 were included. Follow-up ended May 1st, 2009. Clinical data were collected from patient charts. Endoscopies and histology were reviewed. Statistical analysis was performed using independent *t*-tests, and non-parametric tests.

**Results:** We indentified 152 IBD patients (98 ulcerative colitis (65%), 46 Crohn's disease (30%), 8 unclassified colitis (5%); 85 (56%) males). Median follow-up was 6.8 years (IQR 6-8). In 105 patients mucosal inflammation was diagnosed: 51 (49%) had both endoscopic and histological inflammation (group A), 51 (49%) had histological inflammation only (group B), 2 (2%) patients had endoscopic lesions only. In 88% (n=92) treatment was not changed. Treatment was more frequently altered in group A than in group B (p=0.004). On follow up endoscopy, two years after the index procedure, patients in group A+B had more severe inflammation, both endoscopic and histological (p=0.04/p=0.001). In 39% (n=36) the inflammation resolved spontaneously. However, inflammation was not associated with more clinical relapses, surgeries or strictures.

**Conclusions:** A large proportion of IBD patients has mucosal inflammation without clinical symptoms. Although one third recovered without a change of therapy, inflammation, either endoscopic or histological, in patients who are clinically in remission is associated with more severe mucosal disease activity at two years follow-up. However, this did not translate in more complications or symptomatic flares during a 7 years follow-up.

## INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are two major types of inflammatory bowel diseases (IBD), and are characterized by their relapsing course of disease. Previously it has been demonstrated that the cumulative probability of a clinically relapsing course of disease for UC patients was 90% after 25 years of follow-up, with a 10-year colectomy rate of 24%.[1] In CD, patients present most frequently with an inflammatory type of disease (Montreal type B1), while 60% of the patients develop a stricturing or penetrating complication later on in their disease course.[2] In a 35-year follow-up of 507 CD patients, a 5-year cumulative relapse rate after diagnosis of 67% was demonstrated in patients who were in clinical remission.[3]

However, clinical symptoms are not an accurate measurement for disease activity.[4, 5] Recently, it was demonstrated that the clinical Crohn's disease activity index (CDAI) correlates poorly (40%) with the findings of disease activity during endoscopy.[4] Moreover, a prospective cohort of eighty-nine postoperative patients revealed that a large group of patients had recurrent lesions during endoscopy within one to three years after surgery, while only approximately one third of them also had symptomatic recurrence.[6]

Endoscopic mucosal healing (MH) seems to be a promising predictor for the course of disease and has been observed after treatment with traditional immunosuppressive agents and with anti-tumor necrosis factor (anti-TNF) agents.[7, 8] MH has been proposed as an important parameter in the individual follow-up of patients and may predict a decreased occurrence of long-term complications.[8] Although the endoscopic sub-study of ACCENT I showed no strong relationship between clinical remission and complete MH, there was a numerical trend for patients in which MH predicted a lower rate of CD-related hospitalizations.[9] A recent study demonstrated that complete MH in patients with early stage CD is associated with significantly higher steroid-free remission rates four years after start of therapy with less development of fistulas.[10] MH in UC after one year of treatment has been found to be a strong predictor for less surgery, and fewer subsequent complications.[1]

However, data are lacking on the prevalence of mucosal inflammation in patients in clinical remission and its consequences for clinical practice and the associated disease course. In the present study, we aimed to assess the prevalence and severity of endoscopic and histological inflammation in IBD patients in clinical remission encountered during surveillance colonoscopy, the therapeutic decisions following this finding, and the consequences of these decisions on the course of the disease.

## MATERIALS & METHODS

### Study population

All IBD patients who underwent a surveillance colonoscopy in the Erasmus Medical Center, Rotterdam and University Medical Center Utrecht, The Netherlands between January 2001 and December 2003, were identified. Patients were followed until May 1st, 2009. Inclusion criteria were: a diagnosis of IBD, as verified by endoscopy, histology or radiology.[12, 13] Patients had to be in clinical remission for at least a month before endoscopy. Clinical activity was defined as having one of the following symptoms: abdominal pain, diarrhoea, blood loss, fever, weight loss and/or a physician global assessment of clinical disease activity.

### Outcome parameters

Our primary outcome parameter was the prevalence and severity of active inflammation in IBD patients in clinical remission. Secondary outcome parameters were the impact of endoscopic disease activity on the course of disease during follow-up and the effect of adjustment of the therapeutic regimen in the long run. We distinguished between endoscopic and histological inflammation, to assess any disparities with regard to treatment strategy and course of disease.

### Data extraction

Detailed clinical data were collected from patient charts, endoscopy reports and pathology reports. The clinical data included: type of IBD, age, gender, date of IBD diagnosis, date of onset symptoms attributable to IBD, extent and severity of disease, history of colonic surgery, presence of concomitant PSC, time of diagnosis of PSC, use of medication and surveillance details. Colonoscopies in the setting of dysplasia surveillance in which two to four random biopsy specimens every 10 cm from the entire colon with additional samples of suspicious areas were taken, were counted as surveillance colonoscopy.[14, 15] The complete medical history was assessed, including prior colonoscopies and pathology reports. Symptoms and relapses at one month and one year prior to surveillance colonoscopy were noted as well as any change in treatment policy after surveillance colonoscopy. In addition, clinical details during follow-up including co-morbidity and concomitant dysplasia or colorectal carcinoma (CRC) were recorded. Extent of disease was subdivided in 6 categories based on type and extent of inflammation: left-sided UC, extensive UC, limited CD, extensive CD, limited unclassified colitis or extensive unclassified colitis. Extensive UC was defined as colitis beyond the splenic flexure. Limited CD was defined as <50% segmental colonic disease activity including those with ileitis terminalis or ileocecal inflammation. Extensive CD was defined as >50% segmental colonic CD activity. Severity of disease was graded as mild, moderate or severe colitis or ileitis based on both histological and endoscopic features. Endoscopic severity of disease was scored according to the four-point Mayo score as suggested by the most recent guideline for surveillance colonoscopies [16]: 0, normal; 1, mild disease (erythema, decreased

vascular pattern, mild friability, no contact bleeding); 2, moderate disease (marked erythema, absent vascular pattern, friability, erosions, contact bleeding); 3, severe disease (spontaneous bleeding, ulceration). Histological severity of disease was scored accordingly on a four-point scale: 0, no active histological disease activity; 1, mild active inflammation (cryptitis, but no crypt abscesses); 2, moderate active inflammation (few crypt abscesses); 3, severe active inflammation (numerous crypt abscesses).

Duration of medication use during follow-up was divided into four categories (0-25%, 25-50%, 50-75%, >75% of duration of follow-up). A relapse was defined as: recurrence of inflammation confirmed by endoscopy or by any other imaging tool, or an increase of complaints that required hospitalization, surgery or adjustment of medication. The latter is defined as increasing or initiating steroids (including budesonide, systemic or topical), mesalazine (systemic or topical), methotrexate (MTX), or anti-tumor necrosis agents (anti-TNF). The increase of purine antagonist dosage in case of a registered increase of discomfort was also scored as a relapse. MH was defined as the absence of mucosal ulcerations on endoscopy.[8]

### Statistical analysis

Statistical analyses were performed using descriptive statistics, independent *t*-tests, and non-parametric tests. Non-parametric tests ($\chi^2$) were used to assess correlations between mucosal inflammation and clinical characteristics. Two-sided p-values <0.05 were considered significant. Mann-Whitney U tests were used to compare two independent samples, and Kruskall-Wallis tests were used to compare more than two groups. Independent samples *t*-tests were used to compare the average time intervals for those with inflammation compared with those without inflammation, including duration of disease, age at onset IBD and time between colonoscopies. To compare characteristics of inflammation between UC and CD patients, the group unclassified colitis was combined with UC for statistical purposes. Statistical analyses were performed with SPSS for Windows software (version 15.0).

## RESULTS

### Patient characteristics

In total, 159 patients underwent a surveillance colonoscopy between January 2001 and December 2003. Seven patients were not in clinical remission and were therefore excluded. In total 152 patients were included (Table 1); 102 patients had UC (64%), 48 had CD (30%), and 9 patients were diagnosed with unclassified colitis (6%). Their median age at diagnosis of IBD was 26 years (IQR 20-34), and 85 patients (56%) were male. Median duration of disease at time of the index surveillance colonoscopy was 17.3 years (IQR 12-23). All CD patients had documented disease activity in the colon.

**Table 1.** Patient characteristics at baseline (prior to surveillance colonoscopy)

| | N (%) | UC (%) | CD (%) |
|---|---|---|---|
| **Nr of patients** | 152 | 106 | 46 |
| **Disease** | | | |
| Ulcerative colitis | 98 (65) | 98 (93) | - |
| Crohn's disease | 46 (30) | - | 46 (100) |
| Unclassified colitis | 9 (6) | 8 (8) | - |
| **Gender** | | | |
| Male | 85 (56) | 62 (59) | 23 (50) |
| Female | 67 (44) | 44 (42) | 23 (50) |
| **Median age at diagnosis IBD (IQR)** | 25.8 (20-34) | 25.9 (20-38) | 25.2 (21-32) |
| **Maximum disease extent** | | | |
| Proctitis (UC/CD) | 4 (3) | 3 (3) | 1 (2) |
| Left-sided colitis (UC) | 21 (14) | 21 (20) | - |
| Pancolitis (UC) | 65 (43) | 65 (61) | - |
| < 50% segmental colitis (limited CD) | 6 (4) | - | 6 (13) |
| > 50% segmental colitis (extensive CD) | 30 (19) | - | 30 (65) |
| Limited unclassified colitis | 1 (1) | 1 (1) | - |
| Extensive unclassified colitis | 7 (5) | 7 (7) | - |
| *Unknown* | 18 (12) | 9 (9) | 9 (20) |
| **Ileitis terminalis?** | | | |
| Yes | | | |
| *- backwash ileitis (UC)* | 10 (7) | 10 (9) | - |
| *- Crohn's lesions* | 16 (11) | - | 17 (35) |
| No | 56 (37) | 40 (38) | 16 (35) |
| Unknown / terminal ileum not seen | 70 (46) | 56 (52) | 14 (32) |
| **Severity of disease** | | | |
| Mild | 16 (11) | 15 (14) | 1 (2) |
| Moderate | 33 (22) | 26 (25) | 7 (15) |
| Severe | 62 (41) | 40 (38) | 23 (48) |
| *Unknown* | 41 (27) | 25 (24) | 16 (35) |
| **Pseudopolyps** | 44 (29) | 32 (30) | 12 (26) |
| *Unknown* | 28 (18) | 18 (17) | 10 (22) |
| **Continuous active inflammation** | 2 (1) | 2 (2) | - |
| *Unknown* | 6 (4) | 3 (3) | 3 (7) |
| **Concomitant PSC** | 28 (18) | 22 (21) | 6 (13) |
| **Colon surgery in history** | 15 (10) | 5 (5) | 10 (22) |
| **Disease characteristics CD†** | | | |
| Stricture | | | 8 (19) |
| Fistulas | | | 8 (19) |
| Inflammatory | | | 40 (100) |
| Peri-anal | | | 10 (23) |
| Extra-intestinal | | | 1 (2) |
| **Relapse during the last year** | 20 (13) | 14 (13) | 6 (13) |
| *Unknown* | 5 (3) | 3 (3) | 2 (4) |
| **Relapse during last month** | - | - | - |

† missing data in 3 patients

### Details surveillance program

For 90 patients (59%), the index colonoscopy was their first surveillance colonoscopy. The other patients had on average one surveillance colonoscopy prior to this index endoscopy (IQR 1-2). Patients were included in a surveillance program after a median of 16 years of disease (IQR 10-22), with a median time interval of two years between each surveillance colonoscopy (IQR 2-3).

### Primary outcome parameter

*Mucosal inflammation while in clinical remission*

Table 2 depicts the disease characteristics found during index surveillance colonoscopy. In total, 105 patients (69%) had active mucosal inflammation. Twenty patients (13%) relapsed in the 12 months prior to the surveillance colonoscopy. Eighteen of these patients (90%) did have active mucosal inflammation during colonoscopy. The percentage of UC patients and CD patients with active disease, subdivided into histological and endoscopic inflammation is shown in Table 3. There was no significant difference in the frequency of inflammation among CD patients compared with UC patients (p=0.5).

**Table 2.** Disease characteristics during index surveillance colonoscopy

| | N-<br>No Inflammation (%) | N-<br>Asymptomatic inflammation (%) |
|---|---|---|
| **Nr of patients** | 47 | 105 |
| **Disease** | | |
| Ulcerative colitis | 32 (68) | 66 (63) |
| Crohn's disease | 14 (30) | 32 (31) |
| Unclassified colitis | 1 (2) | 7 (7) |
| **Gender** | | |
| Male | 24 (51) | 61 (58) |
| Female | 23 (49) | 44 (42) |
| **Median age at diagnosis IBD (IQR)** | 24.9 (20-31) | 26.6 (21-36) |
| **Median duration of IBD (IQR)** | 20.3 (14-28) | 16.4 (12-22) |
| **Concomitant PSC** | 6 (13) | 22 (21) |
| **Maximum disease extent** | | |
| Left-sided colitis (UC) | 8 (20) | 17 (18) |
| Pancolitis (UC) | 22 (55) | 46 (49) |
| < 50% segmental colitis (limited CD) | 2 (5) | 4 (4) |
| > 50% segmental colitis (extensive CD) | 7 (18) | 20 (21) |
| Limited unclassified colitis | 1 (3) | - |
| Extensive unclassified colitis | - | 7 (7) |
| *Unknown* | *7* | *11* |
| **Ileitis terminalis?** | | |
| Yes: - *backwash ileitis (UC)* | - | 4 (4) |
| - *Crohn's lesions* | - | 5 (5) |
| No | 29 (62) | 55 (52) |
| Terminal ileum not seen | 18 (38) | 41 (39) |

**Table 2.** Continued

| | N- No Inflammation (%) | N- Asymptomatic inflammation (%) |
|---|---|---|
| **Pseudopolyps in history** | 12 (34) | 32 (36) |
| *Unknown* | 12 | 16 |
| **Relapse during the last year** | 2 (4) | 18 (18) |
| **Relapse during last month** | - | - |
| **Abnormalities during surveillance** | | |
| Inflammation | 0 | 105 (100) |
| Dysplasia | 7 (15) | 7 (7) |
| Colorectal cancer | 1 (2) | - |
| Pseudopolyps | 8 (17) | 22 (21) |
| **Treatment schedule** | | |
| None/expectative | 47 (100) | 92 (88) |
| Increasing dose | - | 2(2) |
| Changed to another drug | - | 6 (6) |
| Endoscopy schedule altered | - | 1 (1) |
| Another drug added to current regimen | - | 4 (4) |
| **Median time to next colonoscopy (IQR)** | 2.2 (1.8-3.2) | 2.0 (1.2-2.8) |
| **Effect treatment (next colonoscopy)** | | |
| None | 5 (12) | 20 (20) |
| Less inflammation | 1 (2) | 30 (30) |
| Mucosal healing | 19 (46) | 23 (23) |
| More inflammation | 16 (39) | 23 (23) |
| Dysplasia | - | 3 (3) |
| *Unknown* | 6 | 6 |

**Table 3.** Frequency of endoscopic and histological inflammation without clinical symptoms

| | Total (%)† | UC-patients (%) | CD-patients (%)† |
|---|---|---|---|
| **Nr of patients** | 152 | 106 | 46 |
| **No inflammation** | 47 (31) | 33 (31) | 14 (31) |
| **Endoscopic + histological activity (group A)** | 51 (34) | 39 (37) | 12 (27) |
| **Only histological activity (group B)** | 51 (34) | 33 (31) | 18 (40) |
| **Only endoscopic activity** | 2 (1) | 1 (1) | 1 (2) |

† Accurate data on endoscopic inflammation was missing in 1 patient

### *Severity of disease*

Table 4 shows the histological scoring of disease activity by endoscopy and histology. In 97 out of 152 patients (64%), no visible inflammation was seen during surveillance colonoscopy. However, histological examination revealed that only 42 patients (28%) had no mucosal ac-

tivity. In 51 patients (34%), both endoscopic and histological inflammation was found (group A), and in 51 patients (34%) only histological inflammation could be demonstrated (group B).

**Table 4.** Endoscopic and histological disease activity during surveillance colonoscopy

| | | Histological severity of disease | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | No activity | Mild | Moderate | Severe | Dysplasia | Cancer | Total |
| Endoscopic severity of disease | No activity | 40 (26%) | 39 (26%) | 10 (7%) | - | 7 (5%) | 1 (1%) | 97 (64%) |
| | Mild | 2 (1%) | 26 (17%) | 11 (7%) | 3 (2%) | 4 (3%) | | 46 (30%) |
| | Moderate | - | 1 (1%) | 2 (1%) | 2 (1%) | - | | 5 (3%) |
| | Severe | - | - | - | 1 (1%) | 1 (1%) | - | 2 (1%) |
| | missing | - | 2 (1%) | - | - | - | - | 2 (1%) |
| **Total** | | 42 (28%) | 68 (45%) | 23 (15%) | 6 (4%) | 12 (8%) | 1 (1%) | 152 |

Use of medication in the year prior to surveillance or in the month prior to surveillance was not associated with inflammation in group A and B (all p>0.05) (Table 5). In addition, duration of usage of 5-ASA, immunosuppressives, corticosteroids, MTX, ursodeoxycholic acid in the year prior to surveillance, was not related to overall inflammation (group A and B combined), nor to group A or group B separately (all p>0.05).

**Table 5.** Medication use in year prior to surveillance colonoscopy

| | Inflammation Yes | Inflammation No | p-value |
|---|---|---|---|
| **Nr of patients** | 105 | 47 | |
| **5-ASA** | 87 (83) | 42 (89) | n.s. |
| **Thiopurines** | 28 (27) | 11 (23) | n.s. |
| **Corticosteroids** | 27 (26) | 11 (23) | n.s. |
| **MTX** | 2 (2) | - | n.s. |
| **Anti-TNF** | - | 1 (2) | n.s. |
| **NSAIDS** | - | - | n.s. |
| **Folic acid** | 13 (12) | 10 (21) | n.s. |
| **Ursodeoxycholic acid** | 12 (11) | 7 (15) | n.s. |

## Secondary outcome parameter

*Therapeutic strategies after surveillance colonoscopy*

In 13 patients with endoscopic and/or histological inflammation the therapeutic strategy was adjusted after endoscopy. Thus, in 92 of the 105 (88%) cases with endoscopic or histological inflammatory activity, treatment was not changed (Table 2). The decision to change treatment strategy was significantly associated with the endoscopic (p<0.001) and histological (p=0.001) severity of disease. In 2/95 (2%) patients without disease activity the strategy

was altered, against 7/39 (15%) patients with mild endoscopic inflammation, 2/3 (40%) with moderate, and 2/2 (100%) of patients with severe endoscopic inflammation.

*Follow-up*

In total, from 119 patients (78%) data were available until the end of the study-period. Six patients (4%) died of causes unrelated to IBD and 27 patients (18%) were lost to follow-up. Overall time of follow-up was 6.8 years (IQR 6-8). Of the 33 patients that died or were lost to follow-up, median time of follow-up was 3 years (IQR 1.7-4.9). Median time-interval between the index surveillance colonoscopy and the next colonoscopy was 2.1 years (IQR 1.5-2.9). Patients with inflammation had the next colonoscopy on average 2 years later (IQR 1.2-2.8), and those without inflammation 2.2 years later (IQR 1.8-3.2), p=0.44. Of the 40 patients without inflammation during the first surveillance colonoscopy, 15 patients (38%) were found to have mucosal inflammation at the subsequent colonoscopy (data missing in 7 patients).

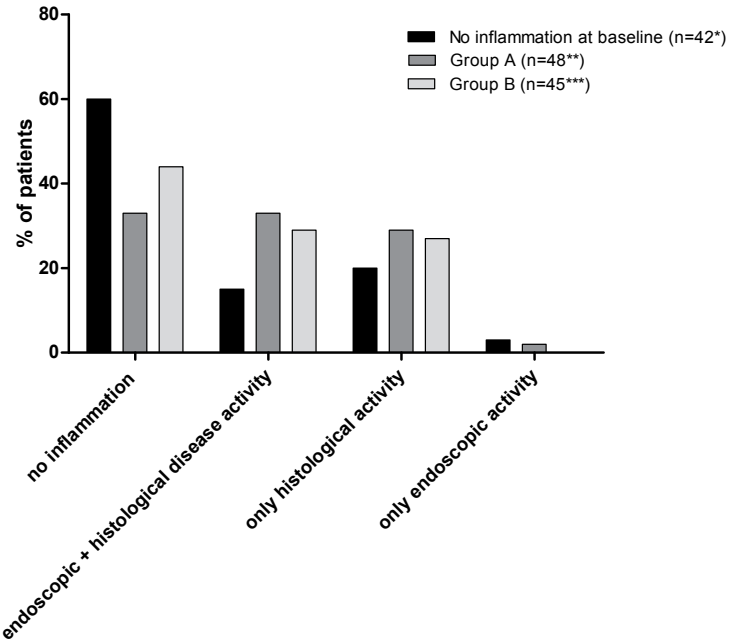


**Figure 1.** The frequency of mucosal inflammation during the follow-up colonoscopy (2 years later)
Group A includes patients with both endoscopic and histological inflammation.
Group B includes patients with histological inflammation only.

*Data on the next colonoscopy missing in 7 patients
** Data on the next colonoscopy missing in 4 patients
*** Data on the next colonoscopy missing in 6 patients

*Two-years prognosis of mucosal inflammation at index endoscopy*

Two years after the index surveillance colonoscopy, 26% of all patients had endoscopic inflammation (35/135, data on the follow-up colonoscopy was missing in 17 patients), while another 26% (n=35/135) had histological disease activity only (Figure 1).

In 39% of the 93 patients (n=36) in both group A and B no inflammation was found at the 2 years follow-up endoscopy. Of the patients without inflammation at baseline, 36% (15/93) had inflammation at the second endoscopy while mucosal inflammation was found in 61% (57/93) of patients with inflammation at index colonoscopy (group A+B). Of the patients with both endoscopic and histological inflammation at first endoscopy, 29% (n=15) were found to have histological inflammation only, but in 33% (n=16) both endoscopic and histological inflammation was observed. Of the patients in group B, 27% (n=12) had only histological inflammation during the second colonoscopy but 29% (n=13) developed both endoscopic and histological inflammation. The proportion of patients with mucosal inflammation during the next colonoscopy was not significantly different between group A and B, p=0.14. Patients with inflammation (group A+B) did not have more pseudopolyps during the next colonoscopy than patients without inflammation (p=0.34).

In patients with inflammation (group A+B) the inflammation worsened, both endoscopic as histological (p=0.04 and p=0.001) with a more extended inflammation (endoscopic p=0.09, histological p=0.007). In total 29/93 patients with inflammation had both endoscopic and histological inflammation compared with 6/42 (15%) of the patients without inflammation at baseline. Moreover, in group A+B, 36/93 (39%) had no histological disease activity during the next colonoscopy, compared with 25/40 (60%) in the group without inflammation at baseline.

*The effect of changing treatment strategy (2 years later)*

Interfering with the treatment strategy did not influence the disease activity at the next colonoscopy: 56/88 patients (64%) with a wait and see policy had inflammation, either endoscopic or histological (data missing in 4 patients), compared with 8/12 patients (67%) in whom treatment was changed (data missing in 1 patient), p=0.38.

In 16 of the 83 (19%) patients with a wait and see policy, the mucosal inflammation did not worsen or improve at two years, in 26 patients (30%) the inflammation improved, and in 20 patients (23%) the inflammation worsened. In 21 patients no residual inflammatory activity could be found (24%). Data missing for 9 patients. In 25% of patients in whom the treatment strategy was altered no effect was seen on the severity of inflammation (4/12), in 5 (42%) patients the inflammation improved, in 3 patients (25%) the inflammation worsened and in 1 patient (8%) no inflammation was seen. Data missing for 1 patient.

Altering the treatment strategy did not result in an improved situation two years later: 20/86 (28%) in the wait and see-group the inflammation worsened compared with 3/12 (23%) in whom the treatment was adjusted, p=0.27. The choice of treatment strategy did not influence the maximum severity of inflammation or the maximum extent of disease, both endoscopic and histological, or the presence of pseudopolyps (all p>0.05).

*Long-term influence of mucosal inflammation at first endoscopy (total follow-up period)*

Inflammation at baseline was not associated with the progression of inflammation during the entire follow-up period (endoscopic p=0.173, histological p=0.25), nor with an ongoing active inflammatory disease (p=0.65) or more relapses during follow-up (p=0.18): 21/105 patients (21%, data missing in 4 cases) with inflammation had a relapse during follow-up compared with 5/47 patients (12%, data missing in 4 cases) without inflammation. Inflammation did not lead to a higher mortality rate (p=0.35). In 15 patients the maximum extent of disease during follow-up was unknown. None of the remaining 144 patients developed a new stricture or fistulizing disease during follow-up. There was no significant difference in the number of surgeries performed between the groups with and without inflammation (p=0.09). Of the 105 patients with inflammation, 17 developed dysplasia which was found during surveillance colonoscopy (16%), compared with 6 out of 48 patients without any inflammation (13%), p=0.6.

*Influence of microscopic mucosal inflammation only (group B) on long-term prognosis*

Patients in group B did not have a different course of disease than those in group A. All the outcome measurements for course of disease during follow-up as discussed above were not significant (p > 0.05).

## DISCUSSION

We demonstrate a high prevalence of endoscopic or histological disease activity in IBD patients who are in clinical remission. Additionally, we show that in a large proportion of patients histological inflammation is diagnosed without any signs of active disease during endoscopy. The incentive to treat patients in clinical remission but with inflammation found during endoscopy appears to be low in clinical practice. Although 39% of the patients with inflammation spontaneously recovered, endoscopic and/or histological inflammation without any symptoms is associated with more severe mucosal inflammation at two years follow-up. However, we could not demonstrate a worse clinical course during long-term follow-up in this patient group.

Our results are in contrast with a previously published study, which reported that endoscopy had little additional value compared to non-invasive disease indices as patient-reported stool frequency or bloody stools.[17] The authors concluded that clinical symptoms in UC are predictive for mucosal inflammation and can be used as surrogate makers. In the present study, we demonstrate that two third of IBD patients in clinical remission has mucosal inflammation. This underscores the limited reliability of clinical symptoms in UC patients as surrogate markers for mucosal inflammation.

We confirm that inflammatory activity can be present in endoscopic normal mucosa.[18, 19] Earlier studies already demonstrated that endoscopic appearance alone tends to underestimate the extent of disease relative to histological evaluation.[20-23] This could be important information for clinical practice, as it has been demonstrated that in patients with quiescent UC, histological evidence of an acute inflammatory cell infiltrate, crypt abscesses, or mucin depletion is correlated with a two- to three-fold increase in the relapse rate.[22] However, in our study-population we could not confirm the latter.

In our cohort mucosal inflammation did not result in a worse outcome with respect to course of disease during 7 years of follow-up. This could be explained by the fact that a large group of patients with inflammation at baseline (38%) did not reach MH during follow-up. MH has been linked with a lower risk of relapse, a reduced risk of colorectal cancer, a decreased need for surgery, and improved QoL.[24] This would underline the need to abolish disease activity and aim for MH in clinical practice. However, in contrast to well-cited randomized controlled trials that stress the importance of MH [9-11], we could not confirm that mucosal inflammation leads to a worse course of disease in patients without clinical symptoms.

These conflicting data could be explained by a difference in study population. In contrast to previous studies which included IBD patients with a CDAI score of 220 to 400, the present study only included patients who were in clinical remission.[8, 9] It could be hypothesized that inflammation without clinical activity represents a different disease entity with other consequences for follow-up than symptomatic mucosal inflammation. Moreover, in our study a large proportion of patients with PSC (18%) were included, while in literature the prevalence of PSC is only 5% of IBD patients.[25] Disease activity of IBD in PSC patients is often mild and occasionally completely asymptomatic and associated with a low colectomy rate.[26] In our cohort only 20% of CD patients had a structuring and/or fistulizing disease, while it had been previously demonstrated that 60% of CD patients develops a stricturing or penetrating disease. This low rate of strictures and fistulas could be explained by the relatively small number of patients with terminal ileitis in our cohort. Moreover, all the patients in our cohort, both UC and CD patients, had a colitis. This was also the sole indication for their colonoscopy as we only included patients who received a surveillance colonoscopy. All in all, our cohort could

therefore consist of a subset of IBD patients with an uncomplicated disease, who all seemed to have responded well to treatment. Caution is therefore needed in extrapolating our results to patients who are not treated well or to those with a complicated course of disease. Future research is needed to identify a possible subgroup of patient who might never develop a complicated course of disease.

Patients with histological inflammation, but endoscopic free of inflammation, had a similar prognosis as those who also had endoscopic signs of inflammation. Therefore, biopsies may represent a better indicator for the severity and extent of disease.

It seems that physicians do not consistently treat mucosal inflammation when patients are in clinical remission. The decision to interfere appears to be mostly guided on endoscopic findings, as treatment was more often changed when endoscopic inflammation was found than when only histological inflammation was found. Nonetheless, changing therapy seemed not more successful than the wait and see policy, since in both groups 60-70% of patients still had inflammation two years later. However, only in a small number of patients therapy was changed, more often so in patients with a more severe disease activity. Caution is therefore needed in interpreting the results. Nonetheless, 39% had a spontaneous recovery. This suggests that if we aim to assess MH, a substantial proportion of patients could be unnecessary exposed to drugs.

In conclusion, we report a high prevalence of endoscopic and/or mucosal disease activity in a cohort of IBD patients in clinical remission. Furthermore, we could not confirm that mucosal healing results in a more favorable course of disease during 7 years of follow-up. We could not show a beneficial effect of active treatment and moreover found spontaneous recovery of inflammation in one third of the patients. We therefore conclude that the clinical benefit of unconditionally treating all patients with mucosal inflammation in order to improve long term prognosis needs to be further investigated.

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# Chapter X

# A short course of corticosteroids prior to surveillance colonoscopy to decrease mucosal inflammation in inflammatory bowel disease patients: results from a randomized controlled trial

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## ABSTRACT

**Background and aims:** Inflammation is a known pitfall of surveillance colonoscopy for inflammatory bowel disease (IBD) as it is difficult to differentiate between inflammation and true dysplasia**.** This randomized controlled trial assessed the effectiveness of a low dose of corticosteroids prior to surveillance colonoscopy to decrease mucosal inflammation.

**Methods:** IBD patients scheduled for surveillance colonoscopy between July 2008 – January 2010 were eligible to participate. Patients were randomized to either two weeks daily 20 mg prednisone and calcium plus vitamin D prior to surveillance colonoscopy or no treatment. All biopsies were reviewed by an expert gastrointestinal pathologist who was blinded for medication-use. Statistics were performed using chi-square tests, non-parametric tests and binary logistic regression.

**Results:** Sixty patients (M/F 30/30, UC/CD 31/29) participated: 31 (52%) in the treatment arm and 29 (48%) in the control group. In the treatment arm, 247 biopsies were scored against 262 in the control group. In the treatment arm 27 out of 247 biopsies (10.9%) had a score > 1 on the Geboes scale, against 50 out of 262 biopsies (19.1%) in the control group, p=0.013. In total, 58% of the treatment arm against 66% of the control group had endoscopic or histological mucosal inflammation (p=0.6). There was a trend for patients in the treatment arm to have less severe inflammation compared with the control group, however this was not significant (p=0.12).

**Conclusions:** In our cohort, a short course of corticosteroids decreases the overall histological disease activity in individual biopsies without major side-effects. Moreover, there is a trend for corticosteroids to decrease the maximum severity of both endoscopic and histological disease activity per patient.

*Clinical trial registration number EudraCT:2008-001427-61*

## INTRODUCTION

Patients with inflammatory bowel disease (IBD) are recommended to undergo surveillance colonoscopies for their increased risk of colorectal cancer (CRC). Recent guidelines suggest to perform a screening colonoscopy after 10 years of disease in all IBD patients, to assess the true microscopic extent of inflammation.[1-3] Thereafter surveillance colonoscopies should be conducted yearly, 3-yearly or 5-yearly according to duration and extent of disease and additional risk factors such as primary sclerosing cholangitis and a family history of CRC.[3] There is evidence that cancer and dysplasia tends to be detected at an earlier stage in patients who are undergoing surveillance and these patients have a correspondingly better prognosis. There is indirect evidence that it is effective at reducing the risk of death from IBD-associated CRC and that it is acceptably cost-effective.[4]

However, there are some limitations to colonoscopic surveillance. One of the pitfalls is active inflammation during surveillance. This firstly may impair endoscopic evaluation and detection of preneoplastic lesions. Secondly, determination of the presence of dysplasia in a diffuse background of regenerating epithelium or active inflammation can be challenging.[5] By histology, low-grade dysplasia is difficult to distinguish from regenerative changes as a result of inflammation.[6] Moreover, there is a large degree of interobserver disagreement among pathologists for the detection and grading of dysplasia in the presence of active inflammation.[7, 8] Thus, the level of agreement on the diagnosis of low-grade dysplasia may be as low as 43%, even among expert pathologists.[9] Therefore, surveillance biopsies cannot be accurately assessed when active mucosal inflammation is present. For these reasons, surveillance colonoscopies may need to be repeated or rescheduled in patients with active inflammation. This is a burden for both patients as well as the endoscopy unit.

The Swedish Gastroenterological Association recommends a course of oral corticosteroids 3-4 weeks prior to a surveillance colonoscopy in patients with mild-to-moderate chronic active UC.[10] However, to our knowledge, there are no studies available to support this recommendation. Furthermore, there is controversy on the capability of corticosteroids to induce mucosal healing. Corticosteroids have not been proven to induce short-term mucosal healing. In the GETAID study, patients with active colonic or ileocolonic CD received high doses of prednisolone (1mg/kg/day) until clinical remission (3-7 weeks).[11] Although 92% of patients achieved clinical remission, only 29% (38/131) also exhibited endoscopic remission. No data were available in this study on the histological remission. Nonetheless, this study showed that although steroids are very efficacious to induce rapid symptom control, this may not be accompanied by a similar restoration of mucosal integrity in the ileum and colon. Moreover, the use of corticosteroids is often associated with unwanted side-effects attributable to their absorption and pharmacological (systemic) action or to their suppression of endogenous adrenal function.[12]

We questioned whether prednisone is effective and safe to decrease mucosal inflammation to optimize surveillance colonoscopy. The aim of this randomized controlled study was to assess whether a low dose of two weeks daily 20 mg prednisone prior to surveillance colonoscopy is effective in decreasing mucosal inflammation.

## MATERIALS & METHODS

### Patient selection

IBD patients scheduled for a surveillance colonoscopy between July 1, 2008 and December 31, 2009 in the Erasmus Medical Center, Rotterdam or the Tweesteden Hospital, Tilburg, The Netherlands were eligible to participate in this randomized controlled trial (RCT). Exclusion criteria were diabetes, pregnancy, hypertension, and known adverse reactions to earlier use of prednisone. The study was approved by the Institutional review boards of both hospitals.

### Randomization

After obtaining informed consent, patients were randomized to two weeks daily 20 mg prednisone and calcium plus vitamin D prior to surveillance colonoscopy or no treatment. Numbered, opaque, sealed envelopes containing the treatment allocation were prepared before the trial. The randomization order was determined per center in blocks. Patients were randomized after they agreed to participate in the study. Patients in the treatment arm were asked to fill out a short questionnaire at the day of their colonoscopy in order to assess therapy adherence. No interim analyses were performed. The pathologist was blinded for the use of premedication prior to surveillance.

### Hypothesis and primary outcome

We hypothesized that short-term low dose corticosteroid treatment prior to surveillance decreases the active asymptomatic inflammation in patients undergoing surveillance colonoscopy. Our primary endpoint was therefore the presence of active inflammation in histopathology biopsies in asymptomatic patients. Secondary endpoints included safety of a short course of prednisone in this setting.

### Data extraction

Surveillance colonoscopies were performed according to the current clinical guidelines, and the protocol was consistent over the entire study period.[13, 14] No special techniques (e.g. narrow band imaging or chromo-endoscopy) were used.

Detailed clinical data from cases and controls were collected from the patient charts, endoscopy reports and pathology reports. The clinical data included: type of IBD, age, gender, time

of diagnosis of IBD, extent and severity of disease, history of colonic surgery, concomitant primary sclerosing cholangitis (PSC), time of diagnosis of PSC, use of medication and surveillance details. Furthermore, the presence of pathologic findings during endoscopy and/or in the pathology report, presence of active inflammation during surveillance colonoscopy, severity of inflammation, severity of inflammation mentioned in pathology report and the management of the pathological findings were included.

Extent of disease was subdivided in four categories based on type and extension of inflammation: left-sided ulcerative colitis (UC), extensive UC, limited Crohn's disease (CD), and extensive CD. Limited CD was defined as < 50% segmental CD including those with terminal ileitis or ileocecal inflammation. Extensive CD was defined as >50% segmental CD. Severity of disease was graded as mild, moderate or severe colitis based on both histological and endoscopic features. The final grade for total severity of disease combined the endoscopic and histological data and represented the maximum combined severity of disease. Endoscopic severity of disease was scored according to the four-point Mayo score as suggested by the most recent guidelines for surveillance colonoscopies [3]: 0, normal; 1, mild disease (erythema, decreased vascular pattern, mild friability, no contact bleeding); 2, moderate disease (marked erythema, absent vascular pattern, friability, erosions, contact bleeding); 3, severe disease (spontaneous bleeding, ulceration). MH was defined as the complete absence of endoscopic mucosal ulcerations that were observed at baseline.[15]

Symptoms and relapses at one month and one year prior to surveillance colonoscopy were noted as well as any change in treatment policy after surveillance colonoscopy. Patients' symptoms attributable to IBD were measured including bloody stool, diarrhea, abdominal pain, weight loss, and fever. Clinical remission was defined as the absence of these symptoms in the month prior to colonoscopy. A relapse was defined as: recurrence of inflammation confirmed by endoscopy or by any other imaging tool, or an increase of complaints that required hospitalization, surgery or adjustment of medication. The latter is defined as increasing or initiating steroids (including budesonide, also topical), mesalazine (also topical), methotrexate (MTX), or anti-tumor necrosis agents (anti-TNF). The enhancement of purine antagonist dosage in case of a registered increase of discomfort was also scored as a relapse.

All surveillance colonoscopies were re-assessed by an expert gastroenterologist. All biopsies were re-assessed by a blinded expert gastrointestinal pathologist. For each biopsy the percentage of lamina propria eosinophils and neutrophils as well as intraepithelial lymphocytes was assessed and scored according to the Geboes grading scale for histological assessment of biopsies (range 0 - 5.4).[16] High points correspond with high inflammatory activity.

### Sample size:

Calculations of sample size were based on the ability to detect a clinically important difference in mucosal inflammation of 25% between the two groups. Based on clinical practice, we assumed that one out of four IBD patients who undergo surveillance colonoscopy has mucosal inflammation. We thus estimated a target sample size of 28 patients in each group (two tailed, $\alpha$=0.05, $\beta$=0.20).

### Statistical analysis

Statistical analyses were performed using descriptive statistics, chi-square tests, non-parametric tests and univariate binary logistic regression. Independent *t*-tests were used to compare mean age at onset IBD, mean duration of disease and mean age at entering the study. The two treatment groups were compared using chi-square tests and Mann-Witney U-tests. First, all histopathological biopsies from all patients were assessed separately in one batch, independent of patient characteristics. The scores of all individual biopsies from the treatment arm were compared with the scores of the biopsies from the control group. Secondly, the maximum severity of histological inflammation was assessed per patient. These scores were thereafter used to describe the maximum histological severity of disease per patient. Thirdly, using univariate and multivariate binary logistic regression the influence of other patient characteristics on mucosal inflammation was assessed, to identify possible confounders. P-values $< 0.05$ were considered significant. Parameters with a p-value $< 0.1$ were included in a multivariate logistic regression model, using the stepwise forward method. In this binary logistic model, overall inflammation, endoscopic inflammation, and histological inflammation based on the original pathology report as well as on the Geboes criteria were assessed as separate outcome measures. A score of $\leq 1$ on the Geboes scale was compared with a score of $> 1$. Statistical analyses were performed with SPSS for Windows software (version 15.0).

## RESULTS

### Patient characteristics

Overall, 136 patients were assessed for eligibility (Figure 1). In total 76 patients were excluded for not meeting the inclusion criteria. The remaining 60 patients gave informed consent and were randomized for the study: 31 (52%) in the treatment arm and 29 (48%) in the control group. In total, 31 patients (52%) had UC, and 29 (48%) had CD. Fifty percent of the patients was female (n=30). Median age at onset IBD was 25 years (IQR 19.2-37), median age at surveillance was 46.4 years (IQR 36-56). Median duration of IBD at inclusion of the study was 13.4 years (IQR 10-19). Additional patient characteristics are listed in Table 1.

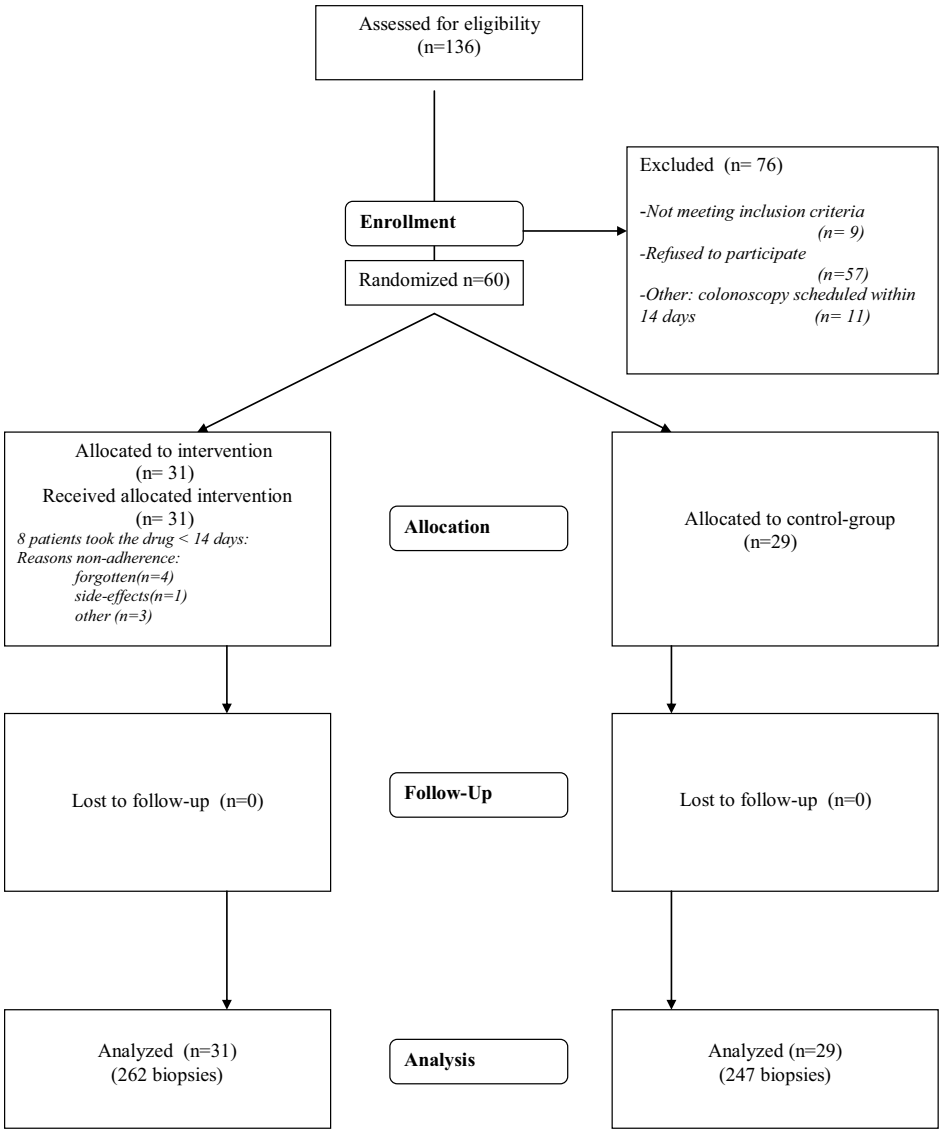


**Figure 1.** Flow chart of the study population

### Characteristics surveillance program and findings prior to surveillance colonoscopy

The patients had entered a surveillance program after a median of 13 years of disease (IQR 9-19), with a time-interval of 2 years (IQR 1.5-2) between each surveillance colonoscopy. On average, patients had had one surveillance colonoscopy in the past. Twenty-seven participants underwent their first surveillance colonoscopy. For the other 33 patients, the last surveillance colonoscopy was on average 1.9 years ago (IQR 1.4-2.0). During their last surveillance colonoscopy, inflammation was found in 21 cases (63%), of whom 13 were now

**Table 1.** Patient characteristics and clinical characteristics prior to surveillance colonoscopy

| | N-total | Treatment arm | Control group | p-value |
|---|---|---|---|---|
| **Nr of patients** | 60 | 31 (52) | 29 (48) | |
| **Gender** | | | | p=0.61 |
| Male | 31 (52) | 12 (39) | 19 (66) | |
| Female | 29 (48) | 19 (61) | 10 (35) | |
| **Type of IBD** | | | | **p=0.044*** |
| Ulcerative colitis | 30 (50) | 17 (55) | 13 (45) | |
| Crohn's disease | 30 (50) | 14 (45) | 16 (55) | |
| **Median age at diagnosis IBD (IQR)** | 25 (19.2-37) | 23.2 (18.8-31.2) | 31.5 (19.6-43.8) | **p=0.03*** |
| **Median age at entry study (IQR)** | 46.4 (36-56) | 43.5 (36.5-55) | 48.4 (34.5-57.3) | p=0.28 |
| **Median duration of disease (IQR)** | 13.4 (10-19) | 15.6 (10.4-24.7) | 12.3 (9.9-17.9) | p=0.24 |
| **Maximum disease extent in history** | | | | p=0.10 |
| Left-sided colitis (UC) | 15(25) | 6 (20) | 9 (31) | |
| Pancolitis (UC) | 16 (27) | 6 (20) | 10(35) | |
| < 50% segmental colitis (limited CD) | 11 (18) | 7 (23) | 4 (14) | |
| > 50% segmental colitis (extensive CD) | 17 (28) | 11 (37) | 6 (21) | |
| Unknown | 1 (2) | 1 (3) | - | |
| **Ileitis terminalis?** | | | | p=0.47 |
| Backwash ileitis (UC) | 2 (3) | 1 (3) | 1 (3) | |
| Crohn's lesions | 14 (23) | 9 (29) | 5 (17) | |
| No | 42 (70) | 19 (63) | 23 (79) | |
| Unknown / terminal ileum not seen | 2 (2)) | 2 (6) | - | |
| **Severity of disease** | | | | **p=0.05*** |
| Mild | 11 (19) | 7 (23) | 4 (14) | |
| Moderate | 24 (40) | 8 (26) | 16 (57) | |
| Severe | 23 (40) | 16 (52) | 8 (29) | |
| Unknown | 1 (2) | - | 1 (11) | |
| **Pseudopolyps** | 17 (28) | 10 (32) | 7 (24) | p=0.57 |
| **Ongoing continuous active inflammation** | - | - | - | - |
| **Concomitant PSC** | 8 (13) | 4 (13) | 4 (14) | p=1.0 |
| **Colon surgery in history** | 7 (12) | 4 (13 | 3 (10) | p=1.0 |
| **Rectal sparing (UC)** | - | - | - | - |
| **Relapse during the last year** | 7 (12) | 4 (13) | 3 (10) | p=1.0 |
| **Relapse during last month** | - | - | - | - |
| **IBD-related symptoms during last month** | 3 (5) | 1 (3) | 2 (7) | p=0.61 |
| *Bloody stool* | 1 (2) | - | 1 (3) | p=0.48 |
| *Diarrhea* | 3 (5) | 1 (3) | 2 (7) | p=0.61 |
| *Abdominal pain* | 1 (2) | - | 1 (3) | p=0.48 |
| *Fever* | - | - | - | - |
| *Weight loss* | - | - | - | - |
| **Dysplasia in history** | 2 (3) | 1 (3) | 1 (3) | p=1.0 |

randomized in the treatment arm and 9 in the control group. Pseudopolyps had been found in 5 patients (15%); 2 in the treatment arm, and 3 in the control group. Low-grade dysplasia had been found in 2 patients (1 in the treatment arm and 1 in the control group), and in none of the patients high-grade dysplasia or CRC had been found. In the patient in the treatment arm, a tubulovilleous adenoma with low-grade dysplasia was found during colonoscopy. In the patient in the control group the low-grade dysplasia was found in the presence of active mucosal inflammation.

### Therapy adherence

In the treatment arm, almost all patients completed their 14-day course of study-medication according to prescription (median 14 days, IQR 13-14). In total, 8 patients took their medication <14 days prior to surveillance colonoscopy, of whom 3 patients took their medication <80% of the total duration (<11 days). Two patients did not fill out the questionnaire on adherence. Reasons for non-adherence were: the patient forgot to take the drug (n=4), because of side-effects (n=1), because of practical issues e.g. the colonoscopy was re-scheduled (n=2) or the pharmacist delivered the drug too late (n=1). Excluding these patients did not influence the results of all analyses below (all p>0.05). These patients were therefore not excluded for further analyses.

### Results primary outcome

Table 2 describes the findings during surveillance colonoscopy.

**Table 2.** Clinical characteristics during surveillance colonoscopy

| | Treatment arm | Control group | p-value |
|---|---|---|---|
| **Nr of patients** | 31 (52) | 29 (48) | - |
| **Inflammation –Total†** | 18 (58) | 19 (66) | p=0.57 |
| **Endoscopic inflammation** | 10 (32) | 14 (48) | p=0.21 |
| **Histologic inflammation** | 16 (52) | 17 (59) | p=0.59 |
| **Histologic Geboes score** | | | p=0.12 |
| 0 | 1 (3) | - | |
| 1 | 19 (63) | 14 (48) | |
| 2 | 3 (10) | 4 (14) | |
| 3 | 4 (13) | 5 (17) | |
| 4 | 1 (3) | 3 (10) | |
| 5 | 2 (7) | 3 (10) | |
| Unknown | 1 (3) | - | |
| **Maximum disease extent (endoscopic)** | | | p=0.27 |
| No inflammation | 21 (68) | 14 (48) | |
| Leftsided colitis (UC) | 2 (7) | 7 (24) | |
| Pan-colitis (UC) | 3 (10) | 4 (14) | |
| < 50% segmental colitis (limited CD) | 4 (13) | 2 (7) | |
| > 50% segmental colitis (extensive CD) | 1 (3) | 2 (7) | |

**Table 2.** Continued

| | Treatment arm | Control group | p-value |
|---|---|---|---|
| **Maximum disease extent (histological)** | | | p=0.45 |
| No inflammation | 13 (42) | 12 (41) | |
| Left-sided colitis (UC) | 1 (3) | 4 (14) | |
| Pancolitis (UC) | 5 (16) | 8 (28) | |
| < 50% segmental colitis (limited CD) | 7 (23) | 1 (3) | |
| > 50% segmental colitis (extensive CD) | 5 (16) | 4 (14) | |
| **Ileitis terminalis?** | | | p=0.55 |
| Backwash ileitis (UC) | 1 (3) | - | |
| Crohn's lesions | 2 (7) | - | |
| No | 19 (61) | 19 (66) | |
| Terminal ileum not reached | 9 (29) | 10 (35) | |
| **Severity of disease (endoscopic)** | | | p=0.21 |
| No activity | 21 (68) | 15 (52) | |
| Mild | 9 (29) | 8 (28) | |
| Moderate | - | 5 (17) | |
| Severe | 1 (3) | 1 (3) | |
| **Pseudopolyps** | 5 (16) | 5 (17) | p=0.91 |
| **Dysplasia** | 1 (2) | - | p=0.33 |
| **Colorectal Carcinoma** | - | - | - |

† Endoscopic + histological data combined

### *Endoscopic findings*

In total, 10 (32%) patients of the treatment arm compared with 14 (48%) patients in the control group had endoscopic inflammation (p=0.21). There was also a trend for patients in the treatment arm to have less severe endoscopic inflammation and a minor extent of disease (endoscopically), however, this was not significant (all p>0.05). Both groups had a similar prevalence of pseudopolyps during surveillance colonoscopy (5 patients in both groups, 16-17%).

### *Mucosal inflammation*

Figure 2 demonstrates the number of patients with mucosal inflammation amongst the treatment group compared with the control group. In total, 58% of patients in the treatment arm compared with 66% of patients in the control group had active mucosal inflammation, either endoscopic or histological (p=0.6).

### *Overall histological severity of disease*

In total, 510 biopsies were analyzed according to the Geboes criteria (Table 3). In the treatment arm, 247 biopsies were scored against 262 in the control group. In the treatment arm 27 out of 247 biopsies (10.9%) had a score > 1 on the Geboes scale, against 50 out of 262 biopsies (19.1%) in the control group, p=0.013.

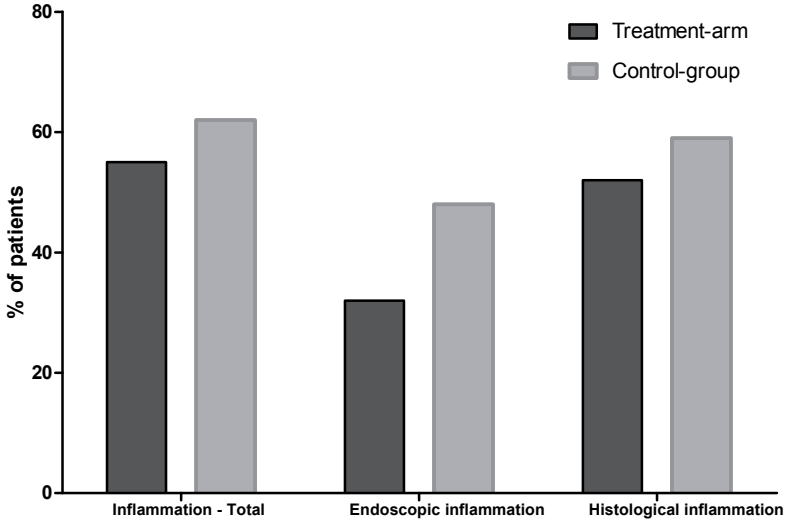


**Figure 2.** This figure presents the number of patients with inflammation in the treatment arm compared with the control group. The group "total inflammation" comprises patients with mucosal inflammation, either histological and/or endoscopic.

**Table 3.** Histological severity of disease in individual biopsy samples among the treatment arm and control group

| | Total | Treatment arm | Control group | p-value |
|---|---|---|---|---|
| **Histologic Geboes score** | | | | **p=0.04*** |
| 0 | 94 (15) | 45 (18) | 49 (19) | |
| 1 | 338 (66) | 175 (71) | 163 (62) | |
| 2 | 27 (5) | 11 (5) | 16 (6) | |
| 3 | 37 (7) | 12 (5) | 25 (10) | |
| 4 | 7 (1) | 2 (1) | 5 (2) | |
| 5 | 6 (1) | 2 (1) | 4 (2) | |

*linear association

*Maximum histological severity of disease*

Figure 3 shows the frequency distribution of the various grades of the Geboes score amongst the patients in the treatment arm compared with those in the control group. There was a trend for patients in the treatment arm to have less severe inflammation compared with patients in the control group, however this was not significant (p=0.12). Excluding the patients who did not take their medication according to prescription did not influence the results above (all p >0.05). Type of IBD, gender, time-interval since the prior surveillance colonoscopy, location of disease in medical history, age at onset IBD, and age at onset surveillance did not influence the presence of overall inflammation, nor the presence of endoscopic or histological inflammation (all p>0.05).

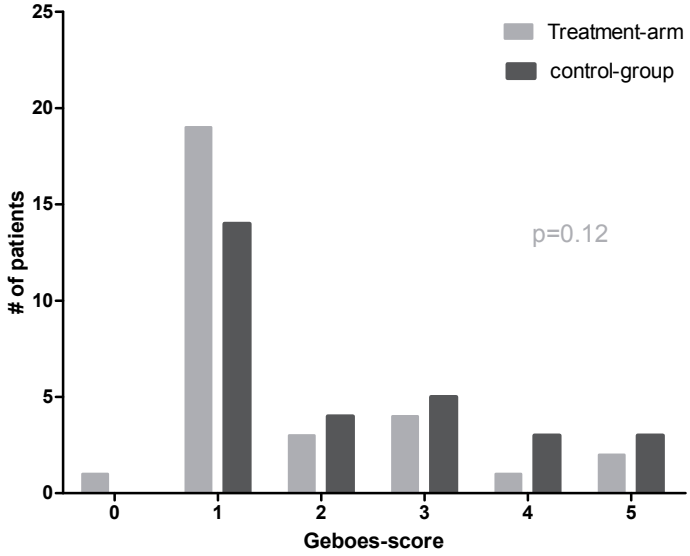


**Figure 3.** This figure represents the frequency distribution of the various grades of the Geboes score amongst patients in the treatment group compared with patients in the control group.

*Dysplasia and CRC*

Two patients, one in the treatment arm and one in the control group, had been diagnosed with dysplasia prior to the surveillance colonoscopy (patient 1, one year before surveillance colonoscopy; patient 2, 16 years before entering the study). However, no dysplasia was found during the surveillance colonoscopy in these patients. In one other patient (treatment arm) low-grade dysplasia was diagnosed during the surveillance colonoscopy. No CRC was diagnosed during the surveillance colonoscopies.

## Results secondary outcome

*Side-effects corticosteroids*

In total 12 out of 31 patients (39%) reported to have suffered from side-effects including mood swings (n=4), headache (n=1), a swollen face (n=3), increased appetite (n=2), fatigue (n=1), and edema (n=1). No major side-effects occurred. Eighteen out of 29 patients (62%) in the control group filled out a form on their feelings prior to surveillance colonoscopy: 3 patients had had a headache, 2 had sleepless nights and 1 patient had some vaguely complaints of not feeling well prior to colonoscopy.

## DISCUSSION

This randomized controlled trial is the first study to show that a short course of corticosteroids prior to surveillance colonoscopy is able to decrease colonic mucosal inflammation without major side-effects. By assessing the histology, we demonstrated that prednisone does indeed decrease the overall disease activity in individual biopsies. Moreover, there is a trend of diminished disease severity on endoscopy and histology per individual patient.

In our cohort, 62% of the cases appeared to have asymptomatic inflammation during surveillance colonoscopy. Previous publications demonstrated that during a period of active disease, it is almost impossible to differentiate between inflammation and true dysplasia.[6, 9] Our study underlines the importance of optimizing circumstances for surveillance colonoscopy as a large proportion of patients in clinical remission appears to have mucosal inflammation. Surveillance guidelines state that surveillance should be performed in patients with a quiescent disease. However, as symptoms are a poor predictor of disease activity, it is a priori unknown which patient has active mucosal inflammation. The high proportion of asymptomatic patients in our cohort underlines the need for pre-emptive treatment of inflammation in all patients undergoing surveillance colonoscopy. This is not only important for surveillance colonoscopy, but also for newer surveillance techniques like fluorescence endoscopy, in which inflammation does also seem to interfere with the finding of dysplasia.[17]

In contrast to the general disbelief in the capability of prednisone to decrease mucosal inflammation, we show that treatment with 20mg of prednisone for 14 days prior to surveillance colonoscopy significantly decreases the overall histological severity of inflammation in individual biopsies. Although a large proportion of patients remained to have mucosal inflammation, there was a trend for prednisone to decrease inflammation compared with those who were not treated. Moreover, there was a trend for prednisone the lead to lower maximum disease activity in individual IBD patients, both by endoscopy and histology, as well as a reduced maximum extent of disease activity. The efficacy of prednisone on diminishing mucosal inflammation indicates that corticosteroids may be able to achieve short-term mucosal healing. Overall, we support the notion to give patients a short course of oral corticosteroids prior to surveillance colonoscopy.[10] Our results demonstrate the efficacy and safety of this approach. Because of known side-effects of prednisone, we decided to use a treatment scheme of 20mg prednisone daily for a period of two weeks. Future extended prospective studies are needed to determine the optimal dose and duration of therapy to confirm the trend which was found in our study.

This study was not designed for the detection of dysplasia. As only one patient was diagnosed with dysplasia, we were unable to assess the effect of prednisone on the evaluation

of dysplasia in our cohort. By histology, low-grade dysplasia is difficult to distinguish from regenerative changes as a result of inflammation.[6] In those cases the term "indefinite for dysplasia" is often used in histology reports. As a short course of prednisone lowers the active inflammation, we believe it will therefore positively affect the evaluation of dysplasia and will lead to less diagnoses of "indefinite for dysplasia".

Most patients took their medication according to prescription. Only 3 patients responded to have a less than 80% adherence rate (<11 days). Since no data are available on the optimal duration of prednisone usage to diminish inflammation, we decided not to exclude these patients from our analysis. Excluding the patients who took their medication <14 days did not significantly influence our results (all $p>0.05$). This indicates that future studies are needed to elucidate the optimal dosage and duration of prednisone use prior to surveillance.

In conclusion, our study is the first to assess the use of a low dose of corticosteroids prior to surveillance colonoscopy to overcome mucosal inflammation, which could affect the histological assessment of dysplasia. We demonstrate that, in our cohort, a short course of corticosteroids decreases the disease activity in individual biopsies. Moreover, there is a trend for corticosteroids to lead to a less maximum severity of disease activity and also for a lesser extent of disease per patient. Contrary to previous studies, corticosteroids might be able to decrease mucosal inflammation and may even induce mucosal healing in IBD patients. Larger studies are needed to confirm our results.

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# Chapter XI

## Patients' preferences regarding shared decision-making in the treatment of inflammatory bowel disease: results from a patient empowerment study

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## ABSTRACT

**Background and aims:** Shared decision-making is gaining favor in clinical practice, although the extent to which patients want to be involved in choosing their treatment varies substantially. Because data are lacking on the preferences of patients with chronic diseases such as inflammatory bowel disease (IBD), we wanted to assess IBD patients' preferences about being involved in such decisions.

**Methods:** Adult IBD patients were asked to anonymously complete an online survey on their preferences. Non-parametric tests ($\chi^2$) were used to determine the relationship between responses and respondents.

**Results:** The questionnaire was completed by 1067 patients, 617 with Crohn's disease and 450 with ulcerative colitis. Patients' mean age was 43 years (SD 13.7); the majority were female (66%). In total, 866 patients (81%) reported it as "very important" to be actively involved in the decision-making process, and another 177 (17%) rated it as "quite important". When asked how their treatment could be improved, 537 patients (50%) wanted close, equitable collaboration with their physician. This preference was significantly associated with a disease duration of $\leq$ 8 years (p=0.03). Gender and type of IBD were not significantly associated with patients' preferences.

**Conclusions:** This study demonstrates IBD patients' desire to be actively involved in the decision-making process. Further research is needed on physicians' perspectives on shared decision-making, and on finding predictive factors for developing a model for shared decision-making in IBD.

## INTRODUCTION

Shared decision-making is increasingly advocated as an ideal model of treatment decision-making.[1-3] In this model the physician has the responsibility to inform the patients and to give them advice, whereas the actual decisions on how to act on this information are made in collaboration between the patient and physician.[4]

Patients and physicians vary substantially in the degree to which they are comfortable with patients' involvement in decision-making.[5, 6] The literature available on patients' preferences of shared decision-making has mainly focused on healthy persons or restricted populations, especially cancer patients.[7-11] Other studies are limited by small sample sizes or hypothetical scenarios.[12-14] Patients' information needs and decision-making can change during treatment, as demonstrated in breast cancer patients.[15] Healthy persons' preferences can therefore not be extrapolated to sick patients who need medicinal treatment.

Patients with chronic diseases may have different preferences regarding shared decision-making than healthy patients who are put in a hypothetical scenario. A systematic review of the effects of shared decision-making suggested that shared decision-making is especially suitable for long-term decisions and/or in case of a chronic disease.[16] However, further data on the preferences of patients with inflammatory bowel disease (IBD) are lacking.

IBD is the heading for two major chronic gastrointestinal diseases of unknown origin: ulcerative colitis (UC) and Crohn's disease (CD). In 2004, as many as 1.4 million persons in the United States and 2.2 million persons in Europe suffered from these diseases.[17] The incidence of IBD has been increasing over the years, which for UC varies greatly between 0.5 and 24.5/$10^5$ inhabitants, and for CD varies between 0.1 and 16/$10^5$ inhabitants worldwide.[18, 19] The prevalence rates of IBD reach up to 396/$10^5$ inhabitants [19]. Patients with IBD have a decreased quality of life, both influenced by symptoms and treatments.[20, 21] Several therapeutic strategies, including the wide use of immunosuppressants, have been advocated in the treatment of these chronic diseases, each with its own risks and benefits.[22]

Patient empowerment is becoming increasingly important in the management of chronic diseases.[23] This model posits that patients are responsible for their choices and also the consequences of their choices. As a result of empowerment, patients may develop a greater sense of self-efficacy regarding various disease and treatment-related behaviors, and may express changes in life priorities and values. Due to empowerment, patients are also expected to better self-manage not only their disease, but also their lives.[24] It has been suggested that patients show better adherence when they are actively involved in the decision-making process.[5,16] Non-adherence is an important reason for relapsing disease in IBD.[25] Shared

decision-making can therefore be used to educate patients about the utmost importance of adherence to medication and the necessity to commit and follow-through on their treatment.

It is unknown to what extent IBD patients actually want to be involved in the decision-making regarding the most appropriate therapeutic strategy for their disease. The purpose of this patient empowerment study was to assess IBD patients' preferences with regard to their involvement in the decision of treatment choices.

## METHODS

### Questionnaire

A patient empowerment study was performed in collaboration with the Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN). A questionnaire was developed by members of the CCUVN working in close collaboration with a panel of IBD patients not associated with the CCUVN. During several meetings, patients discussed the issues of shared decision-making and questioned to what extent they wanted to be involved in the decision-making about their treatment strategies. The questionnaire mirrors the outcome of these discussions. After the questionnaire had been framed, an independent physician advised the panel on the scientific and medical content of the questionnaire.

In close-ended questions, patients were asked how they assessed a possible active involvement in the decision-making of their own treatment. In open-ended questions patients were asked what they should know or receive from their treating-physicians in order to be better treated for their disease. After pilot testing on a panel of IBD patients, the questionnaire was further optimized. This panel consists of IBD patients whose opinions are regularly solicited for such purposes and therefore have an extensive expertise on evaluating questionnaires. The questionnaire is listed in Figure 1.

### CCUVN respondents

The definitive questionnaire was placed on the website of the CCUVN from December 2006 – January 2007. The CCUVN has approximately 10,250 members, of whom 9,509 have registered their gender and age. Of these 9,509 registered CCUVN members, 65% are female and 66% are $\leq$ 50 years old. Adult IBD patients were asked to fill out the questionnaire anonymously.

A randomly selected group of patients from our outpatient IBD clinic was used to confirm the representativeness of the internet population. Patients were asked to fill out the questionnaire before they visited their physician and were assured their answers would stay anonymous. Patients who already cooperated in the online questionnaire were excluded.

**Figure 1.** The questionnaire

| |
|---|
| What type of inflammatory bowel disease (IBD) do you have? |
| a) Crohn's disease |
| b) Ulcerative Colitis |
| c) Unclassified collitis |
| How long has it been since you were diagnosed with IBD? |
| a) 0-2 years |
| b) 3-8 years |
| c) 9-15 years |
| d) longer than 15 years |
| What is your gender? |
| a) Male |
| b) Female |
| How old are you? |
| … years old |
| Are you a member of the Dutch Crohn and Colitis organisation (CCUVN)? |
| a) Yes |
| b) No |
| If you think about the decisions your physician makes concerning your medical treatment, how satisfied are you with the extent to which your physician involves you in these decisions? |
| a) Very satisfied |
| b) Satisfied |
| c) Dissatisfied |
| d) Very dissatisfied |
| How important is it for you that your physician involves you in the decisions concerning your medical treatment? |
| a) Very important |
| b) Quite important |
| c) Quite unimportant |
| d) Totally unimportant |
| How satisfied are you with the time and attention that your physician spends on you during your visits to the outpatient clinic? |
| a) Very satisfied |
| b) Satisfied |
| c) Dissatisfied |
| d) Very dissatisfied |
| Do you think that your medical treatment prescribed by your physician could be improved? |
| a) Yes |
| b) No |
| How could the treatment prescribed by your physician could be improved? |

| What does a patient like you need to know / receive to be able to get better treatment for your disease (multiple answers may be given) | |
|---|---|
| a) | More knowledge of the cause of my disease |
| b) | More knowledge of my disease in general |
| c) | More knowledge of any new medications (and when they are in particular suitable) |
| d) | A checklist to fill out, so my doctor and I can improve my treatment in close consultation |
| e) | More knowledge of what my doctor needs to be able to improve my treatment |
| f) | A close collaboration with my doctor, based on equivalence |
| g) | Information on websites, flyers and current research |
| h) | To get in touch with fellow-sufferers or hands-on experts |
| i) | Nothing |
| Do you have any suggestions to improve the collaboration with your treating physician? | |

### Statistical analysis

Statistical analysis was performed using descriptive statistics and chi-square tests. Ordinal survey items were compared using non-parametric tests ($\chi^2$). Groups were compared based on age, gender and duration of disease, which was subdivided into $\leq$ 8 years of disease and >8 years of disease. The cut-off of 8 years concerning duration of disease was chosen by the panel of IBD patients. The patients decided to divide duration of disease in four categories (0-2 years, 3-8 years, 9-15 years, and >15 years). For statistical purposes this was combined in two groups, "short duration of disease" and "long duration of disease". Mann-Whitney U tests were used to assess differences in responses among the online group and the outpatient clinic group. The statistical software SPSS version 15.0 for windows was used for all statistical analyses.

## RESULTS

### *Study population*

In total, 1,093 patients filled out the questionnaire online. Twenty-six patients were excluded from analysis, due to lack of information on their type of IBD (n=24) or on their gender (n=2). Patient characteristics are shown in Table 1. Of the 1,067 patients included in the analysis, 617 had CD (58%) and 450 had UC (42%). The mean age of patients was 42.9 years old (SD 13.7), duration of disease was > 8 years in 575 patients (54%) and 703 patients (66%) were female.

**Table 1.** Patient characteristics

| | Online group (%) | Outpatient clinic group (%) |
|---|---|---|
| **Number** | 1,067 | 169 |
| **Disease** | | |
| Crohn's disease | 617 (58) | 125 (74) |
| Ulcerative colitis | 450 (42) | 41 (24) |
| Unclassified colitis | - | 3 (2) |
| **Female gender** | 703 (66) | 84 (50) |
| **Mean age (SD)** | 42.9 $\pm$ 13.7 | 38.7 $\pm$ 14.4 |
| **Duration of disease** | | |
| 0-2 years | 179 (17) | 22 (13) |
| 3-8 years | 313 (29) | 54 (32) |
| 9-15 years | 277 (26) | 43 (25) |
| >15 years | 298 (28) | 50 (30) |
| **Decreased quality of life** | 531 (50) | 100 (59) |
| **Member CCUVN** | 1,001 (94) | 61 (36) |

The CCUVN has approximately 10,250 members, of whom 9,509 have registered their gender and age. Of all members, 10% filled out our questionnaire, which, in addition, is fully representative of all CCUVN members with regard to age and gender. Of the 9,509 registered CCUVN members, 65% are female and 66% are $\leq$ 50 years old, which is comparable to the demographics in our group (66% female; mean age 43 years)

### Patients' satisfaction with current practise

In total, 980 patients (92%) were satisfied or very satisfied with the extent to which their physician currently involves them in the decision-making concerning their medical treatment (Table 2). With regard to the time and attention given by the physician during visits to the out-patient clinic, 949 patients (89%) were at least "satisfied". The current medical treatment as prescribed by the treating physician could be improved according to 216 patients (20%). Patients' suggestions to improve current treatment are listed in Table 3.

### Active involvement in decision-making very important for IBD patients

Patients' assessments of the involvement in the decision-making are shown in Figure 2. In total, 866 patients (81%) called it "very important" to be actively involved in the decision-making of their medical treatment options. Another 177 patients (17%) rated active involvement in this decision process as "quite important".

**Table 2.** Patients' satisfaction concerning current treatment in the online group compared with the outpatient clinic group

| | Online group | Outpatient clinic group | p-value |
|---|---|---|---|
| **Satisfaction with current involvement in treatment? (%)** | | | n.s. |
| Very Satisfied | 665 (62) | 110 (65) | |
| Satisfied | 315 (30) | 42 (25) | |
| Dissatisfied | 54 (5) | 8 (5) | |
| Very dissatisfied | 33 (3) | 2 (1) | |
| No answer given | - | 7 (4) | |
| **Satisfaction time and attention from physician during clinic visit? (%)** | | | **p=0.04*** |
| Very Satisfied | 674 (63) | 118 (70) | |
| Satisfied | 275 (26) | 38 (22.5) | |
| Dissatisfied | 90 (8) | 10 (5.9) | |
| Very dissatisfied | 28 (3) | 1 (1) | |
| No answer given | - | 2 (1) | |
| **Could the current medical treatment prescribed by physician be improved? (%)** | | | n.s. |
| Yes | 216 (20) | 33 (20) | |
| No | 851 (80) | 120 (71) | |
| No answer given | - | 16 (10) | |

**Table 3.** Patients' suggestions to improve current treatment in the online group

| | N (%) |
|---|---|
| **Number** | 1,067 |
| **Close collaboration with the physician, based on equivalence** | 537 (50) |
| **More knowledge of the cause of disease** | 496 (47) |
| **More knowledge of disease in general** | 427 (40) |
| **More knowledge of any new medications** | 579 (54) |
| **A checklist to fill out, improve treatment in close consultation with physician** | 289 (27) |
| **More knowledge of what the doctor needs to be able to improve treatment** | 232 (22) |
| **Information on websites, flyers and current research** | 384 (36) |
| **To get in touch with fellow-sufferers or hands-on experts** | 324 (30) |

### Patients require close collaboration with physicians to improve treatment regimen

When asked what is important for patients to be better treated for their disease, 537 patients (50%) requested a close, equitable collaboration with their physician (Table 3). Duration of disease was significantly associated with this response: 307 of 575 patients with $\leq$ 8 years of disease (53%) against 230 of 492 patients (47%) with > 8 years of disease (p=0.03) wanted good collaboration with the physician to be based on equivalence (Figure 3). In answer on this same question, 289 patients (27%) suggested a checklist to fill out in order to improve

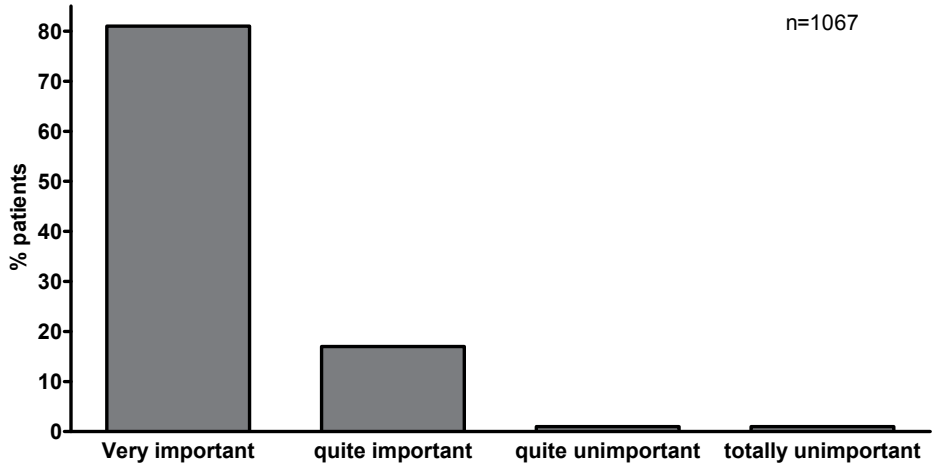


**Figure 2.** IBD patients' assessments of shared decision-making

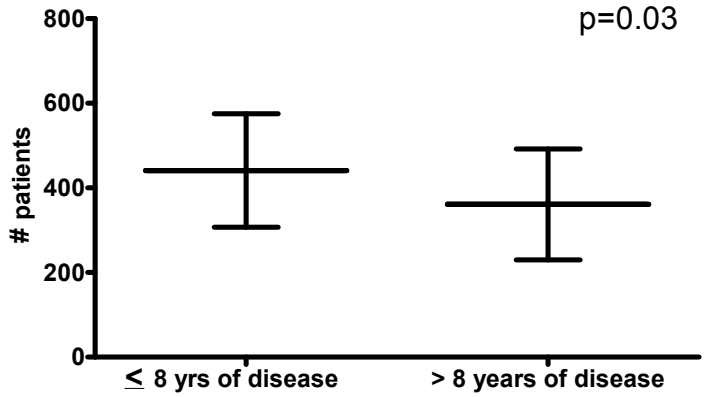


**Figure 3.** IBD patients' demands for improving treatment: a good collaboration with physician, based on equivalence

upon their current treatment regimen, again in close collaboration with their physician. This was also significantly associated with the duration of disease: 24% (140/ 575) of the patients with a short duration of disease (≤ 8 years) against 30% (149/492) of the patients with a long duration of disease (> 8 years) suggested this option of a checklist (p=0.03). In total, 579 patients (54%) wanted more information on new medication options in order to improve their treatment; 496 patients (47%) wanted more knowledge about the cause of their disease, and 579 patients (54%) wanted more general information on their disease.

In none of the questions were gender and type of IBD significantly associated with patients' assessments of shared decision-making.

### Shared decision-making among patients in the outpatient clinic group

In total, 169 patients from our outpatient IBD clinic completed the questionnaire: 125 had CD (74%), 41 had UC (24%) and 3 patients had unclassified colitis (2%). The mean age of patients was 38.7 years old (SD 14.4), duration of disease was > 8 years in 93 patients (55%) and 84 patients (50%) were female. Of the outpatient clinic group, 61 patients (36%) were member of the CCUVN. Patient characteristics are shown in Table 1. Patients' satisfaction concerning current treatment in the outpatient clinic group are listed in Table 2. Compared with patients in the online group, IBD patients in the outpatient clinic group were more satisfied with the time and attention that was given to them during their visit to the IBD clinic (p=0.04). Both groups were equally satisfied with their current treatment and their involvement in this treatment.

Patients' preferences regarding shared decision-making are demonstrated and compared with the preferences of those in the online group in Table 4. In total, 147 patients (87%) called it "very important" to be actively involved in the decision of their medical treatment options. Another 18 patients (11%) rated active involvement in this decision process as "quite important". This percentage was even higher compared with the online group (p=0.03). A close equitable collaboration with their physician was requested by 112 patients (67%). This percentage was significantly higher compared with the online group (p<0.001).

**Table 4.** Patients' preferences on shared decision-making in the online group and outpatient clinic group

| | Online group | Outpatient clinic group | p-value |
|---|---|---|---|
| **Overall assessment of shared decision-making (%)** | | | **p=0.003*** |
| Very important | 866 (81) | 147 (87) | |
| Quite important | 177 (17) | 18 (11) | |
| Quite unimportant | 13 (1) | 2 (1) | |
| Totally unimportant | 11 (1) | - | |
| No answer given | - | 2(1) | |
| **Requesting a close, equitable collaboration with their physician (%)** | 537 (50) | 112 (67) | **p<0.001*** |

## DISCUSSION

This large survey demonstrates that a significant proportion of patients with inflammatory bowel disease prefer active involvement in the decision-making process of the treatment of their disease. Half of these patients want an equitable relationship with their physician to improve their treatment regimen, and more than half of all patients want to be better informed about their disease and new medication options. Patients with shorter duration of disease report preferring more involvement in the decision-making process. This can be

explained by the fact that these patients are more often in the active phase of their disease and therefore need frequent adjustments in their treatment strategy.[26]

Patient participation in decision-making has been advocated for many reasons. Patients who are active participants in the process of their care, e.g. asking questions, expressing their opinions and stating preferences regarding treatment, have measurably better health outcomes than patients who do not participate in the decision-making.[2, 5, 13, 15, 27] Patients who feel that they have participated in decision-making are also more likely to follow through on those decisions than patients who do not participate in this process. This is very important in a chronic disease such as IBD, since non-adherence to therapy is one of the many possible reasons for relapsing disease.[25] Moreover, non-adherence is in general associated with higher healthcare costs and in case of 5-ASA medication, non-adherence may even be associated with a higher risk of colorectal cancer.[28] Improving adherence is therefore of great importance for improving health outcomes in IBD.

Since shared decision-making is based on collaboration between patients and doctors, not only patients' perspectives are of interest for shared decision-making, but doctors' perspectives and preferences should be included as well. However, there are relatively few studies on physicians' preferences for decision-making.[29-31] A cross-sectional survey of a nationally representative sample of US physicians demonstrated that 75% of the physicians (780/1,050) preferred to share the decision-making with their patients.[2, 30] Nonetheless, data on preferences of doctors treating especially chronically ill patients, such as IBD patients, are lacking.

Another factor that involves shared decision-making is the working knowledge base which is influenced by research evidence and evaluation and synthesizing of the evidence. In a chronic disease such as IBD, patients need to be treated with specific medication, which has to be taken consequently and most often has to be continued indefinitely. Each kind of treatment has its own possible benefits, risks and side-effects and there is a considerable variability in the progression of the disease in individual patients and patients' individual responses to medication. This complicates the implementation of shared decision-making in the treatment of IBD. Further research on predictive factors for individual response to therapies is necessary to develop a model for shared decision-making in IBD. Based on these predictive factors, not only physicians but also patients should be able to decide which side-effects and treatment-associated risks they are willing to accept for a possible treatment benefit.[32] In shared decision-making, information on treatment options is exchanged and patients are involved in the final decision.

Internet surveys are generally limited by their lack of information on response rates and generalizability. The CCUVN has approximately 10,250 members, of whom 9,509 have registered

their gender and age. Of all members, only 10% filled out our questionnaire, which was however fully representative for all CCUVN members with regard to age and gender. Additional patient characteristics of the total CCUVN population are unknown and representativeness of our respondents based on the type of IBD cannot be verified. However, the type of IBD was not significantly associated with patients' preferences of shared decision-making.

We recognize that our respondents are all CCUVN members and therefore are not representative of all Dutch IBD patients. Therefore a control group of IBD patients from an outpatient IBD practice was used. These patients showed even a higher preference rate for shared decision-making and therefore verified the preferences from the online population.

Another limitation of our study is that information is lacking on current clinical practice with regard to shared decision-making. Our aim was solely to assess patients' preferences on decision-making and the extent to which they wish to be involved in this process. Our study presents a new focus to improve standard care and to be able to develop a model to implement shared decision-making in clinical practice in the future.

This study is a patient empowerment study and uses a non-validated questionnaire which was developed by IBD patients to obtain pure information on patients' preferences. Using a patient-based questionnaire distributed through the internet, we were able to reach a large nationwide patient group while obtaining information anonymously without intentional or unintentional interference by healthcare providers. A group from our outpatient IBD clinic was used as control group to verify the results. This group confirmed the need for shared decision-making in IBD patients.

In conclusion, this patient empowerment study demonstrates that IBD patients prefer active involvement in the decision-making process concerning the treatment of their disease. This is of importance to respect patients as persons, but above all to improve health outcomes. Limited data are available on factors influencing shared decision-making in IBD. It is therefore a challenge to implement shared decision-making in the healthcare of IBD in the future. Further research is needed on physicians' perspectives on shared decision-making and on developing a model to implement shared decision-making in clinical practice using predictive factors. Nonetheless, our results demonstrate that most IBD patients are ready to implement shared decision-making to improve their treatment strategy.

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# Chapter XII

## Inflammatory bowel disease patients are insufficiently educated about the basic characteristics of their disease and the associated risk of colorectal cancer

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## ABSTRACT

**Background and aims:** Limited data are available about inflammatory bowel disease (IBD) patients' knowledge of disease and associated risks. We assessed patients' knowledge of disease and its associated risks/complications, and their perspectives on current recommendations for colectomy when low-grade dysplasia is found.

**Methods:** IBD patients at a regional patient information day were asked to anonymously complete a survey (group A). A 2nd group was recruited online through the Dutch IBD patients' association (group B).

**Results:** In group A, 109 IBD patients completed the survey (76% Crohn's disease, 24% ulcerative colitis, 78% female). Thirty-three patients (30%) were unaware of their disease localization; 30% thought IBD shortened their life-expectancy; 26% thought it was likely for a severe complication to occur during colonoscopy. Patients estimated their 10-year colorectal carcinoma (CRC) risk at 25%. Mean perceived CRC-associated mortality risk was 13% . Patients would agree to colectomy if their current CRC risk was at least 53% and 70% would refuse physicians' recommendation for colectomy if dysplasia were detected with a 20% risk of concomitant CRC. Group B (n=393 IBD patients) verified the results above. However, fewer patients (52%) would refuse physicians' recommendation for colectomy, p=0.01.

**Conclusions:** IBD patients are ill-informed about their disease and its associated risks. Improvement of patient education is necessary to appropriately involve patients in the decision-making process.

## INTRODUCTION

Patients' perceptions as a part of patient empowerment and shared decision-making are becoming increasingly important in therapeutic strategies of chronic diseases like inflammatory bowel disease (IBD).[1] Patient empowerment includes that patients are responsible for their choices and the associated consequences. As a result, patients are expected to better self-manage not only their disease, but also their lives.[2] Patient empowerment is also important for shared decision-making, in which the decisions regarding treatment strategies are made in collaboration between patient and physician.[3] A previous study has demonstrated that IBD patients want to be involved in the decision-making of their treatment strategy.[4] Patients' perceptions and their accurate knowledge of their disease and treatment options are therefore of utmost importance for follow-up on these guidelines in daily practice. Before shared decision-making can be implemented in clinical practice, we need to investigate the following four aspects.

Firstly, knowledge to which extent IBD patients are informed about the general characteristics of their disease is needed. Limited data are available on whether IBD patients are aware of the type of IBD they suffer from, where their disease is localized, and what kind of medication they are taking. However, this information is highly needed as it forms the basis for their decision-making.

Secondly, limited data are available about how IBD patients perceive complications associated with their disease. Although it has been earlier demonstrated that patients misperceive the risks and benefits of their therapeutic strategies[5], it is unknown how patients perceive their life-expectancy as a result of their chronic disease and no data are available on how patients understand the risks of colorectal cancer (CRC). Adequate knowledge about these complications is needed to be able to make a well-based shared decision on strategies to minimize these risks like colonoscopy and prophylactic colectomy.

Thirdly, because of the increased CRC risk, IBD patients are recommended to undergo surveillance colonoscopy after 8-10 years of disease.[6, 7] It is therefore important to know how patients perceive the risks and benefits of colonoscopy since these perceptions might influence patients' adherence to surveillance colonoscopy. For the general population it is known that fear and pain are an important barrier for compliance with screening sigmoidoscopy.[8] But whether these data translate to IBD patients is unknown.

Finally, limited data are available on patients' thresholds to undergo colectomy if dysplasia is detected during surveillance colonoscopy. Current recommendations for the management of dysplasia advise to discuss the option of colectomy once low-grade dysplasia is found be-

cause of the 20% risk of concomitant CRC.[9] However, the final decision rests with the patient. Without sufficient knowledge of the CRC risk, patients are unable to make an appropriate decision regarding the management of dysplasia.

For these reasons, the aim of our study was to assess patients' knowledge of their disease, their CRC risk and the benefits of colonoscopy. Additionally, we wanted to assess patients' threshold at which they would agree to undergo colectomy in the presence of dysplasia.

## MATERIALS & METHODS

### Questionnaire

IBD patients were asked to anonymously complete a self-administered survey regarding their knowledge of disease, disease associated risks and risks of colonoscopy. The questionnaire was originally developed in English and consisted of questions to assess patients' knowledge regarding their type of IBD, extent of disease, medication-use, the influence of IBD on their life-expectancy, need for future colectomy, perceived benefits of colonoscopy, perceived risks of CRC and perceived risk of dying from CRC.[10] Patients were also asked to mark on a magnifier scale their threshold to undergo colectomy if dysplasia were detected during surveillance colonoscopy (Figure 1). This survey was translated to Dutch and pilot-tested in a sample of patients from our outpatient IBD clinic and in a representative sample of patients from the Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN). Patients were thereafter interviewed to ensure full comprehension of the survey and the magnifier scale. Results and comments from the interviews were used to optimize the questionnaire. The questionnaire was distributed in a paper version ("group A") as well as an online version ("group B"). These two independent groups of patients were used to increase validity and generaliziblity. To verify the results of the magnifier scale, a visual analogue scale was used in the online survey to assess patients' thresholds to undergo colectomy if dysplasia were detected. The final questionnaire comprised of 42 questions.

### Hospital anxiety and depression scale + brief illness perception questionnaire

The standardized hospital anxiety and depression scale (HADS) was used to assess a probable psychiatric diagnosis for anxiety or depression. A score of $\geq$ 11 on the HADS scale was defined as a clinical score indicating probable presence of a psychiatric diagnosis. A score of 8-10 was defined as a subclinical score, being suggestive of a mood or anxiety disorder. Patients' illness perceptions were analyzed using the brief illness perception questionnaire (brief IPQ).[11] The brief IPQ is a standardized nine-item scale designed to rapidly assess the cognitive and emotional representations of illness. Five items assess cognitive illness representations, two items assess emotional representations and one item assesses illness comprehensibility.

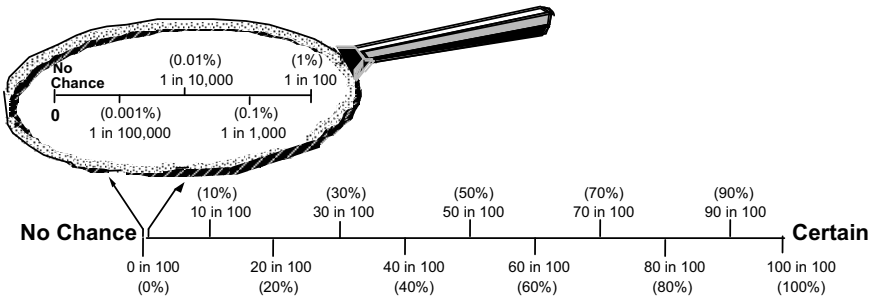
**Imagine the following scenario:**

After having colonoscopy, your doctor sees pre-cancerous changes but no colon cancer. Your doctor is concerned because patients with ulcerative colitis who have these kinds of pre-cancerous changes in their colon sometimes turn out to have colon cancer even though the colonoscopy didn't find it.

Because of this concern, your doctor recommends that you have your entire colon removed right now.

The surgery to remove the colon is called a J-pouch (which creates a pouch out of the intestine and connects it to the anus). You would **not** have an external bag and would have normal bowel movements through your anus (usually about 5-8 a day).

1. If this scenario happened to you: I would agree to have my entire colon removed with a J-pouch surgery if my doctor told me that **I had a pre-cancer and my chance of having colon cancer right now** was at least:




2. If my doctor told me that these pre-cancerous changes mean there is **at least a 20% chance that I have cancer somewhere in my colon right now** (but it cannot be seen by colonoscopy), and recommended a J-pouch surgery to remove my colon, would you have surgery?

   a. Yes, I would have surgery
   b. No, I would not have surgery

   **If No,** what would change your mind? (please circle yes or no for each)

   1. A higher chance of cancer yes no
   2. More symptoms of ulcerative colitis yes no
   3. A 2nd opinion from a different doctor yes no
   4. Other_____
   5. Nothing would change my min

3. Imagine one change to the scenario. You could not have a J-pouch surgery, but would need a permanent external bag (a bag on your abdomen to collect stool).

Would you have surgery? (circle one)

1. No
2. Yes - but the chance of having cancer right now would have to be higher than 20%
3. Yes - but the chance of having cancer right now would have to be lower than 20%

**Figure 1.** Sample questions from questionnaire to assess threshold for colectomy.

For statistical purposes each group was subdivided in two groups: those with a low brief IPQ-score (equal or lower than the median score) and those with a high score (higher than the median score).

## Study population

Patients were recruited at a regional IBD patient information day. In total, 300 IBD patients attended this meeting that was organized by 15 different hospitals from the south-west part

of The Netherlands. These patients were asked to anonymously complete a paper version of the survey ("group A") before the lectures of the information day had started. A second group of patients was nationwide recruited through the CCUVN from January 11th, 2008 until April 11th, 2008. These patients were asked to complete the survey online ("group B"). All patients received the same questionnaire, and no additional instructions were given to either group. This study has been approved by the Institutional Review Board of the Erasmus Medical Center, Rotterdam, The Netherlands.

### Statistical analysis

Statistical analyses were performed using descriptive statistics, independent *t*-tests, Kruskal-Wallis and binary univariate logistic regression. Ordinal survey items between more than two groups were compared using the Kruskal-Wallis test and between two groups using independent *t*-tests and univariate binary logistic regression analyses. Independent-samples *t*-tests were used to compare the average answers given on the magnifier scale. Mann-Whitney U-tests were used to assess differences in responses among group A and B. Two-sided p-values $< 0.05$ were considered significant. Parameters analyzed for possible associations with patients' perceptions needed to be significant in both study groups before they were accepted to influence patients' perceptions in the final results. Group A and group B were compared based on age, gender, disease duration, type of IBD, HADS- and brief IPQ-score. Disease duration was categorized in four categories (< 8, 8-10, 11-20, and >20 years). Patients were also asked for their disease activity with regard to bowel movements and abdominal pain during the two weeks prior to completing the survey. Statistical analyses were performed with SPSS for Windows software (version 15.0).

## RESULTS

### Patient characteristics

In group A, 118 patients completed the paper version of the survey, of which 9 patients were excluded because information regarding their gender or age was missing. Of the remaining 109 patients, 83 had Crohn's disease (CD) (76%) and 26 had ulcerative colitis (UC) (24%) (Table 1). Their median age was 38 years (IQR 30-52), and 85 patients (78%) were female. Of the 76 patients that could report the extent of their disease, 33 out of 56 CD patients (59%) and 16 out of 20 UC patients reported to have extensive colitis (80%, p=0.08).

In group B, 393 patients completed the survey online, of whom 207 had CD (53%), 178 had UC (45%) and 8 had unclassified colitis (2%). Their median age was 44 years old (IQR 34-53), and 274 patients (70%) were female. Of the 281 patients that knew the extent of their IBD, 86

**Table 1.** Patient characteristics

| | Paper group (%) | Online group (%) | p-value |
|---|---|---|---|
| **N** | 109 | 393 | - |
| **Disease** | | | |
| Crohn's disease | 83 (76) | 207 (53) | **p<0.001*** |
| Ulcerative colitis | 26 (24) | 178 (45) | |
| Unclassified colitis | - | 8 (2) | |
| **Female** | 85 (78) | 274 (70) | n.s. |
| **Median age (IQR)** | 38 (30-52) | 44.1 (34-53) | n.s. |
| **Duration of disease ≤ 10 yrs** | 65 (60) | 220 (56) | n.s. |
| **Concomitant PSC** | 5 (5) | 10 (3) | n.s. |
| **Positive family history CRC** | 7 (6) | 67 (17) | **p=0.005*** |
| **# reported exacerbations of IBD per year** | | | n.s. |
| 0 | 22 (20) | 8 (20) | |
| 1-2 | 46 (42) | 216 (55) | |
| 3-5 | 16 (15) | 55 (14) | |
| >5 | 19 (17) | 42 (11) | |
| *Unknown* | 6 (6) | - | |
| **Prior hospital admissions for IBD** | | | n.s. |
| 0 | 30 (27) | 139 (35) | |
| >1 | 79 (73) | 254 (65) | |
| Median # hospitalizations (IQR) | 2 (1-5) | 2 (1-4) | |
| **HADS score – depression** | | | |
| Clinical (≥ 11) | 8 (8) | 24 (6) | n.s. |
| Subclinical (8-10) | 7 (7) | 61 (16) | **p=0.016*** |
| **HADS score – anxiety** | | | |
| Clinical (≥ 11) | 15 (14) | 54 (14) | n.s. |
| Subclinical (8-10) | 19 (18) | 63 (16) | |
| **Median Scores Brief IPQ (IQR)** | | | |
| Cognitive | 35 (31-38) | 35 (31-38) | n.s. |
| Emotional | 11.5 (8-15) | 11 (7-14) | |
| Comprehensibility | 7 (5-8) | 7 (5-9) | |

out of 207 CD patients (42%) and 66 out of 178 UC patients (37%) reported to have extensive colitis (p=0.4).

Group A and group B were similar with regard to age, gender, and duration of disease. However, there were significantly more CD patients in group A (76%) than in group B (53%), p<0.001. More patients in group B reported to have a direct family member with previous CRC (17%) than in group A (6%), p=0.005.

Although group B was recruited online, it forms a representative sample of the total CCUVN population (n=10,250) of which approximately 65% are female and 66% are ≤ 50 years old.

### General knowledge of disease

General knowledge of disease was similar in both study groups (Table 2). Overall, patients were well aware of the medication they use: 83% of patients in group A (n=90) were able to answer which medication they used. Of both groups, approximately one-third of patients was unaware of the localization of their disease. A similar proportion believed that IBD shortens their life-expectancy. Type of IBD did not influence this perception (group A: p=0.86; group B: p=0.73). In group B, 41% of CD patients (85/207) and 35% of UC patients (63/178) thought IBD would shorten their life-expectancy (p=0.9). Approximately half of all patients (group A: 56%, n=61 / group B: 49%, n=188) thought it was unlikely for them to need a colectomy in the future. This was similar for UC patients and CD patients (p>0.05). Regarding the complications of colonoscopy, 26% of group A (n=28) thought it was likely for a severe complication (like a severe bleeding or perforation) to occur during colonoscopy. Having had more colonoscopies over their life did not influence this perception, nor did type of IBD, gender and duration of disease (all p>0.05). These results were similar for group B.

**Table 2.** Patients' general knowledge of their disease

| | Paper group (%) | Online group (%) | p-value |
|---|---|---|---|
| **How do you think IBD will affect how long you will live?** | | | n.s. |
| It will lengthen my life | 2 (2) | 1 (0) | |
| No affect | 74 (68) | 241 (61) | |
| It will shorten my life | 32 (30) | 151 (38) | |
| *No answer given* | 1 (1) | - | |
| **How likely is it that you will have to have your colon taken out because of ulcerative colitis over the next 10 years?** | | | n.s. |
| Certain | 6 (6) | 11 (3) | |
| Very likely | 4 (4) | 20 (5) | |
| Likely | 21 (19) | 107 (27 ) | |
| Unlikely | 39 (36) | 150 (38) | |
| Very unlikely | 19 (17) | 35 (9) | |
| No chance | 3 (3) | 3 (1) | |
| I have no idea | 17 (16) | 67 (17) | |
| **What are the chances of having a major complication (requiring surgery) during a colonoscopy?** | | | n.s. |
| Certain | | | |
| Very likely | 2 (2) | 1 (0) | |
| Likely | 4 (4) | 10 (3) | |
| Unlikely | 22 (20) | 93 (24) | |
| Very unlikely | 49 (45) | 207 (53) | |
| No chance | 30 (28) | 78 (20) | |
| *No answer given* | 2 (2) | 4 (1) | |

**Table 2.** Continued

| | Paper group (%) | Online group (%) | p-value |
|---|---|---|---|
| **How much of your colon is involved with ulcerative colitis?** | | | n.s. |
| Most or all of my colon is involved | 49 (45) | 155 (39) | |
| Only the left side of my colon is involved | 14 (13) | 75 (19) | |
| Just the rectum is involved (proctitis) | 13 (12) | 51 (13) | |
| Not sure | 33 (30) | 112 (29) | |
| | | | |
| **Which medication are you currently taking?†** | | | |
| -Oral 5ASAs | | | |
| *Yes* | 52 (48) | 209 (53) | |
| *No* | 46 (42) | 184 (47) | |
| | | | |
| -5ASA enemas | | | |
| *Yes* | 14 (13) | 35 (9) | |
| *No* | 84 (77) | 357 (91) | |
| | | | |
| -5ASA suppository | | | |
| *Yes* | 5 (5) | 27 (7) | |
| *No* | 92 (84) | 366 (93) | |
| | | | |
| -Steroid enema | | | |
| *Yes* | 8 (7) | 28 (7) | |
| *No* | 90 (83) | 365 (93) | |
| | | | |
| -Oral steroids | | | |
| *Yes* | 28 (26) | 83 (21) | |
| *No* | 70 (64) | 310 (79) | |
| | | | |
| -Immunomodulator | | | |
| *Yes* | 43 (39) | 151 (38) | |
| *No* | 55 (51) | 242 (62) | |
| | | | |
| -Anti-TNF | | | |
| *Yes* | 15 (14) | 40 (10) | |
| *No* | 82 (75) | 353 (90) | |
| | | | |
| -Cyclosporine | | | |
| *Yes* | 1 (1) | - | |
| *No* | 97 (89) | 393(100) | |

† 10% of the paper-group did not report their medication use

### Perceived CRC risk

Patients' estimated CRC risks and perceived benefits of colonoscopy are shown in Figure 2. CRC risks were perceived similar by CD patients and UC patients (p>0.05). In a four-scale multiple-choice question ranging from "certain" to "no chance", 19% of group A (n=21) estimated their chance of developing CRC in the next 10 years at least as "likely", compared with 29% of group B (n=118), p=0.01 (Table 3). However, when asked to quantify their CRC risk on a magnifier scale ranging from 0 to 100, both patient groups assessed this CRC risk at 25% (SD 29). Twenty-seven percent of group A (n=28) and 39% of group B (n=153) estimated their

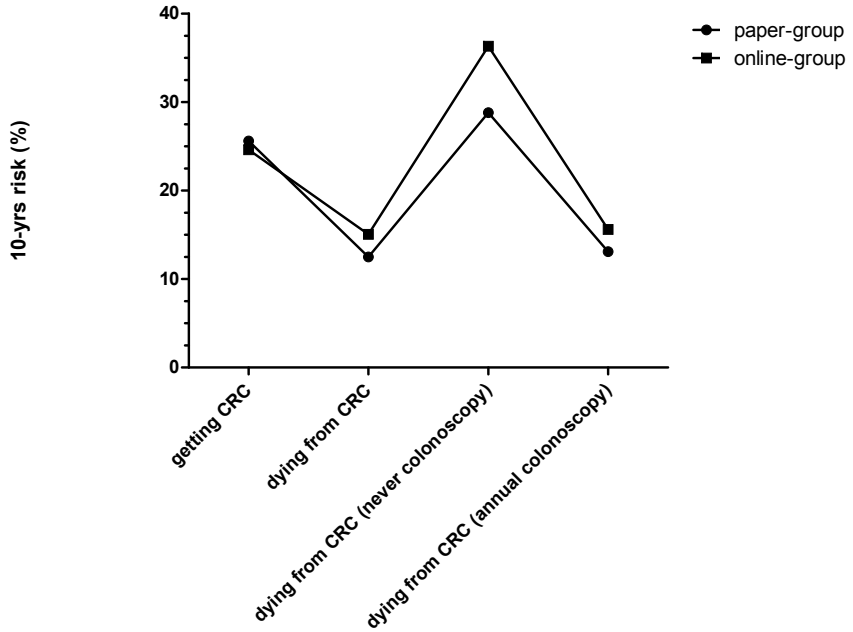



**Figure 2.** Perceived 10 years risks of CRC and benefits of colonoscopy.

**Table 3.** Patients' perspectives on their CRC-risk

| | Paper-group (%) | Online-group (%) | p-value |
|---|---|---|---|
| **Patients' mean perceived 10-years risk of (SD):** | | | |
| getting CRC | 25 (SD 29) | 24 (SD 19) | n.s. |
| dying from CRC | 13 (SD 19) | 15 (SD 17) | n.s. |
| dying from CRC (never colonoscopy) | 29 (SD 29) | 36 (SD 28) | **p=0.02*** |
| dyring from CRC (annual colonoscopy) | 13 (SD 17) | 15 (SD 16) | n.s. |
| | | | |
| **How likely do you think it is that you will get colon cancer in the next 10 years?** | | | **p=0.008*** |
| Certain | - | 1 (0) | |
| Very likely | 2 (2) | 13 (3) | |
| Likely | 19 (17) | 104 (27) | |
| Unlikely | 55 (51) | 214 (55) | |
| Very unlikely | 26 (24) | 52 (13) | |
| No chance | 1 (1) | 9 (2) | |
| *No answer given* | 6 (6) | - | |
| | | | |
| **Over the next 10 years, is your chance of Getting colon cancer higher, lower or the same as having a heart attack?** | | | n.s. |
| Higher | 28 (26) | 153 (39) | |
| Lower | 31 (28) | 83 (21) | |
| About the same | 46 (42) | 157 (40) | |
| *No answer given* | 4 (4) | - | |

**Table 3.** Continued

| | Paper-group (%) | Online-group (%) | p-value |
|---|---|---|---|
| **How does IBD affect your chance of getting colon cancer? It makes my chance:** | | | **p=0.001*** |
| Much higher | 15 (14) | 79 (20) | |
| A little higher | 64 (59) | 261 (66) | |
| No difference | 22 (20) | 41 (10) | |
| A little lower | 5 (5) | 9 (2) | |
| Much lower | 3 (3) | 3 (1) | |
| **I think that I worry about developing any type of cancer:** | | | n.s. |
| More than others my age | 34 (31) | 161 (41) | |
| About the same as others my age | 52 (48) | 161 (410 | |
| Less than others my age | 5 (5) | 12 (3) | |
| I don't worry about cancer | 18 (17) | 59 (15) | |
| **How much control do you feel you have over your colon cancer risk?** | | | n.s. |
| None at all | 23 (21) | 91 (23) | |
| Slight amount | 49 (45) | 173 (44) | |
| Moderate amount | 21 (19) | 71 (18) | |
| Large amount | 13 (12) | 56 (14) | |
| Total control | 3 (3) | 2 (1) | |
| **How would you say that yearly colonoscopy affects your chance of <u>DYING</u> from colon cancer?** | | | **p=0.016*** |
| Increases my chance | 6 (6) | 5 (1) | |
| Does not change my chance | 13 (12) | 46 (12) | |
| Decreases it a little | 47 (43) | 135 (34) | |
| Decreases it a lot | 37 (34) | 201 (51) | |
| Eliminates the chance | 4 (4) | 6 (2) | |
| *No answer given* | 2 (2) | - | |

CRC risk higher than the risk of a heart attack, p=0.1. The perceived influence of IBD on the CRC risk was different between the two groups: in group A, 73% (n=79) assessed the CRC risk to be increased by their disease versus 87% in group B (n=340), p=0.001. In group A, 22 patients (20%) thought IBD did not influence their CRC risk, and 8 patients (7%) even thought IBD decreased the CRC risk. The extent to which patients worry about getting cancer and to which they think they can self-manage their CRC risk were equal between both groups.

### Factors influencing patients' perceived CRC risk

The perceived likelihood of CRC in the multiple-choice question was positively related to having >5 flare-ups per year (group A: p=0.03, group B: p<0.001), having had cancer in the medical history (both groups p=0.02), and knowing individuals with previous CRC (group A: p=0.03, group B: p=0.049). Being in clinical remission at the time of answering the questionnaire, was related to a lower perceived 10-year CRC risk (group A: p=0.03, group B: p=0.02).

Females estimated the exact magnitude of the risk on average higher (group A 29%/ group B 27%) than males (group A 13%/ group B 20%), (group A: p=0.008, group B: p<0.001). Disease duration and type of IBD were not related to this perception (p>0.05).

### Perceived CRC-associated mortality rate

IBD patients' mean perceived risk of dying from CRC in the next 10 years was 13% (SD 19.1) in group A and 15% (SD 17.1) in group B (Table 3). This was not different among CD patients and UC patients (p>0.05). In group A, patients estimated the 10-year CRC-associated mortality rate if one never undergoes a colonoscopy, at 29% (SD 29.1). If one annually undergoes a colonoscopy, the mean perceived 10-year CRC-associated mortality rate was 13% (SD 17.3). The benefits of colonoscopy were perceived higher in group A than in group B (p=0.02): in group B, patients perceived the 10-year CRC-associated mortality rate if one never undergoes a colonoscopy higher (mean 36%) than those in group A (mean 29%), whereas the risk of dying if one annually undergoes colonoscopy were equal in both groups (p=0.16).

### Factors related to patients' perceived CRC-associated mortality rate

Older patients estimated the 10-year CRC-associated mortality rate higher than younger patients (p=0.002). In group A, the mean perceived risk among patients > 40 years old was 18% (SD 23), versus 7% (SD 13) among patients < 40 years old. Younger patients gave higher estimations of the benefits of colonoscopy than older patients (p=0.04). Patients > 40 years old perceived the 10-years CRC risk with annual colonoscopy to be 17% (SD 19), against 10% (SD 15) among those < 40 years old. These results were similar in group B.

### Patients' threshold for colectomy

Patients would agree to colectomy if their CRC risk *at that moment* was at least 53% (SD 31.3) for those in group A and 51% (SD 26) for those in group B (Table 4). This threshold was equal for CD patients and UC patients (p>0.05). Patients were asked what they would do if their physician recommended colectomy with a J-pouch because pre-cancer was found, which meant a 20% risk of having cancer. Thirty percent of group A (n=33) would agree with their physician against 48% of group B (n=189), p=0.006. Forty-six percent of group A (n=50) and 54% of group B (n=212) said this percentage would not change if they could not have restorative ileoanal J-pouch surgery and a permanent external bag (ileostomy) was the only surgical option (p=0.35). However, 37% of group A (n=40) and 45% of group B (n=175) demanded a higher chance of cancer before willing to agree to an external bag (p=0.49).

### Anxiety and depression-scores

In group A and group B, 14% of patients had a positive clinical score for anxiety on the HADS. Nineteen patients in group A (18%) and 63 patients in group B (16%) had a positive subclinical score for anxiety. Eight patients in group A (8%) and 24 patients in group B (6%) had a

clinical score for depression. In group B, 61 patients (16%) had a subclinical HADS depression-score, against seven patients (7%) in group A (p=0.016). The HADS-scores were inconsistently related to patients' perceptions in both groups.

**Table 4.** Patients' threshold for colectomy

| | Paper group (%) | Online group (%) | p-value |
|---|---|---|---|
| **Patients' mean threshold for colectomy (SD)** | 53 (SD 31) | 51 (SD 26) | n.s. |
| **Following recommendation for colectomy** | | | **p=0.006*** |
| Yes | 33 (30) | 189 (48) | |
| No | 68 (62) | 204 (52) | |
| **What would change patients mind for following recommendations after all?** | | | n.s. |
| A higher chance of cancer | 13 (12) | 53 (14) | |
| More symptoms of my colitis | 13 (12) | 55 (14) | |
| A 2nd opinion from a different doctor | 27 (25) | 69 (18) | |
| Nothing would change my mind | 2 (2) | 4 (1) | |
| *No answer given* | 8 (7) | - | |
| **Influence of external bag on patients' threshold** | | | n.s. |
| No | 50 (46) | 212 (54) | |
| Yes, higher CRC-risk is required | 40 (37) | 175 (45) | |
| Yes, lower CRC-risk is required | 6 (6) | 6 (2) | |
| *No answer given* | 13 (12) | - | |

### The influence of illness perception on patients' risk perceptions

Median score on the brief IPQ cognitive scale was 35 (IQR 31-38), on the emotional scale 11.5 (IQR 7-15) and for comprehensibility 7 (IQR 5-9). In both study groups, the emotional brief IPQ-score was related to the perceived CRC risk (both groups $p < 0.005$): those with a high emotional score perceived the CRC risk higher (group A: mean 36, SD 36) than those with a low emotional score (group A: mean 19, SD 22). Neither an association between the emotional score and other perceptions, nor the influence of the cognitive and comprehensibility score on patients' perceptions could be confirmed in both groups.

## DISCUSSION

This nationwide survey demonstrates that IBD patients are ill-informed about their disease. Although they know which medication they take and what kind of IBD they suffer from, many patients are unaware of the localization of their disease and misperceive their life-expectancy, CRC risk and the possible benefits of colonoscopy. In addition, our results show that most IBD patients are not prepared to follow recommendations for colectomy if dysplasia were detected and that they would tolerate a high risk of cancer before agreeing to colectomy.

In general, IBD patients were ill-informed about the characteristics and complications of their disease. One-third of patients was unaware of the localization of their disease, suggesting that patients are not well informed about the basic characteristics of their disease. Moreover, about one third of patients (approximately 40% of CD patients and 35% of UC patients) thought IBD would shorten their life-expectancy. Published data on mortality in IBD are controversial, which complicates a correct interpretation of patients' perceptions. A recent meta-analysis on the mortality risk in CD patients demonstrated that the mortality risk for CD patients is indeed increased compared with the general population.[12] However, a meta-analysis on the mortality risk among UC patients demonstrated no increased mortality risk compared with the background population, suggesting that UC patients are not well informed about their disease and not brought up-to-date on recent knowledge from literature.[13]

IBD patients estimated their 10-year CRC risk at 25%, independently of their disease duration. Although most patients consider this to be "unlikely", they truly overestimate their CRC risk when compared to the literature. Epidemiological studies have demonstrated a CRC risk of 1-2% after 10 years of IBD which further increases with a prolonged duration of IBD.[7, 14] Our results are combined for CD patients and UC patients, since both groups reported similar perceptions of their CRC risk. Females estimated the CRC risk higher than males, which is in concordance with results from a population-based sample from the UK.[15] Although in our cohort there was no gender-difference in the HADS and brief IPQ-scores, the difference in perceptions is possibly explained by other known psychosocial differences between men and women.[16] For example, females generally score higher than males on scales of anxiety, which might have been of influence of a higher risk perception.

Approximately 26% of patients thought that it was likely for a severe complication to occur during colonoscopy, while previous studies have demonstrated that this risk is very low (<1%).[17, 18] Most patients believed that annual colonoscopy substantially decreased their CRC-associated mortality risk over the next 10 years with an absolute risk reduction of 16-20%. This estimate is poorly substantiated in the literature. Although this literature suggests that surveillance colonoscopy reduces mortality, the evidence is indirect and limited.[19] Patients' overestimations of the benefits of colonoscopy might therefore reflect physicians' uncertainty based on the literature. Younger patients were more positive about the benefits of colonoscopy and their CRC-associated mortality risk. This was also seen in patients' perceived risks of cardiovascular diseases in both a population-based sample and among patients with diabetes or hypertension.[20, 21]

Patients demand at least a 53% chance of having concomitant cancer before agreeing to a colectomy. Current recommendations for the management of dysplasia advise to discuss the option of colectomy once low-grade dysplasia is found because of the 20% risk of concomi-

tant CRC.[9] In group A, only one-third of patients were willing to follow these recommendations and 38% of patients demanded a higher CRC risk before accepting a colectomy. This may reflect the belief that surveillance alone is sufficient to reduce their CRC risk or sincere disagreement about when it is worth undergoing colectomy. A second explanation might be that patients are poorly informed about the risks and complications that may occur when cancer is neglected.

Sufficient knowledge of their disease and its complications is of utmost importance for patients to make informed choices about the management of their disease. However, patients currently overestimate the risks of complications caused by their disease or during colonoscopies. Our findings are similar to studies in patients with functional bowel disorders, which demonstrated that these patients often misperceive their disease.[22-24] For example, one in seven patients with irritable bowel syndrome (IBS) thinks IBS predisposes to CRC.[22] For IBS patients, a structured educational program improved patients' knowledge of disease.[25] Our study demonstrates that such a program is strongly needed for IBD as well. Future research should first evaluate current educational efforts to develop a structural educational program for IBD.

To interpret the brief IPQ-scores in our cohort we compared the results to those of patients with other illnesses.[11] IBD patients were not more emotional or cognitive occupied with their disease than patients with type 2 diabetes. On the other hand, IBD patients had higher IPQ-scores than patients with asthma or minor illnesses (allergies, colds, headaches). Patients with a myocardial infarction had similar emotional scores (mean 10.4) as IBD patients (mean 11.5), but scored lower on the cognitive scale (mean 31 vs. 35).

A limitation of our study is the generalizability of the results. First, patients were put in a hypothetical scenario with regard to their threshold for colectomy. Although this is in fact an effective method for standardization, it is still possible that patients would answer differently when put in a real-life situation. Secondly, although the magnifier scale is a validated risk assessment tool, patients may not have understood the given scenarios. To verify the results of the magnifier scale, a visual analogue scale was used in the internet survey which verified the results of the magnifier scale. Additionally, patients responded consistently when the threshold questions were asked in different ways (i.e., colectomy for a 20% chance of CRC was too low for most patients no matter how it was asked). Therefore, we think that this limitation has not influenced our results significantly.

We recognize that our study could be prone to selection bias. Since patients filled out the questionnaire anonymously, the actual burden of disease could not be verified in both groups. Furthermore, we recognize that patients in group B are almost all member of the CCUVN and are therefore not representative of all Dutch IBD patients. However, one would

expect that patients who join a patients' association or visit an information day are more occupied with their disease and therefore better informed about their disease and the associated risks. This assumption would even strengthen our conclusion that IBD patients are ill-informed about their disease and therefore we believe that the influence of selection bias on our results is limited. The high rate of females that completed our survey can be explained by the fact that females are known to be more likely to participate in surveys than men.[26-28]

Group A and group B were similar with regard to age, gender, and duration of disease. However, the paper group comprised more CD patients (76%) than the online group (53%). This might be explained by the fact that group A consisted of patients who were currently treated in a hospital in the south-west part of The Netherlands. It has been demonstrated that CD patients have greater healthcare utilization than UC patients.[29] The online group consisted of more patients who had a family member with CRC (17%) than in the paper group (6%). However, multivariate analysis demonstrated that these two differences in the two patient groups did not influence the results.

Caution should be used when analyzing results generated by two different media. Therefore, both study groups were analyzed separately. In general, the results were similar. Although more patients in the online group thought they were "likely" to develop CRC due to their IBD, both groups quantified this risk equally. More patients in the online group than in the paper group would follow their physician's recommendations concerning colectomy with a J-pouch. It could be hypothesized that the online group represents patients that are better educated because they seek information online and at the CCUVN. A second hypothesis is that these patients have heard stories from fellow-sufferers about their experiences with colectomy. Therefore they could be less afraid of this surgical procedure and its impact on daily-life. Our results suggest that a patients' organization may be useful for educating patients and helping them in the process of shared decision-making. Previous published data suggested that an IBD patients' organization might lead to better therapy adherence.[30] The benefit of a patients' organization has also been demonstrated in glaucoma patients, in which members of the "glaucoma club" showed significantly better knowledge of disease and therapy adherence.[31]

In conclusion, IBD patients are ill-informed about their disease and misperceive the associated risks and complications. Only few seem prepared to follow current recommendations for colectomy if dysplasia were detected. Our findings imply that improvement of patient education is necessary in order to appropriately involve patients in the decision-making process. An IBD patients' organization can support patient education and may help patients in the process of shared decision-making. A model needs to be developed to implement shared decision-making in clinical practice using predictive factors and detailed guidelines for patient education.

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# Chapter XIII

## Patient's perspectives important for early anti-Tumor Necrosis Factor treatment in inflammatory bowel disease

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## ABSTRACT

**Background and aims:** We hypothesized that limited information is given to patients on the risks and benefits of individual therapy, and feedback is lacking to verify if patients correctly interpreted the given information. We assessed the perspectives of patients with inflammatory bowel disease (IBD) concerning the treatment-associated risks/benefits of infliximab.

**Methods:** Patients were asked to complete a survey regarding the benefits and risks of infliximab. Results are reported as descriptive statistics. Comparisons between groups were analyzed using independent *t*-tests and the Kruskal-Wallis test.

**Results:** In total, 152 IBD patients completed the questionnaire. Fifty-seven percent (78/138) estimated the 1-year remission rate from infliximab to be > 50%. Seventy-one percent (104/146) indicated they would not take a drug with risks reflecting those estimated for infliximab if the 1-year remission rate was < 75%. Crohn's disease patients and those recalling a discussion regarding the risks/benefits of infliximab treatment had higher estimates of the 1-year remission rate with infliximab than ulcerative colitis patients (p=0.03) and patients who did not recall previous information (p=0.03). Perceptions were independent of age and disease duration.

**Conclusions:** IBD patients misperceive the risks and benefits of infliximab. The majority of patients would not accept treatment-related risks if the 1-year remission rate was < 75%. Counseling on treatment-associated risks and benefits should be ameliorated.

## INTRODUCTION

Inflammatory Bowel Disease (IBD) is the heading for two major chronic gastrointestinal diseases of unknown origin: ulcerative colitis (UC) and Crohn's disease (CD). Several therapeutic strategies have been advocated in the treatment of IBD, each with its own risks and benefits. However, conventional treatments have not been able to change the natural course of disease.[1] Increasing use of immunosuppressants in CD did not significantly decrease the number of intestinal complications of CD or the need for surgery.[2] It is unknown whether earlier implementation of immunosuppressants in the disease course (referred to as early aggressive treatment) will prevent this disabling disease course.

Infliximab is a chimeric monoclonal IgG1 antibody directed against tumor necrosis factor alpha, which is conventionally (i.e. step-up therapy) reserved for patients who have failed both corticosteroids and immunomodulators. Large randomized trials have confirmed the efficacy of infliximab in the treatment of both CD and UC.[3-5] A recent open randomised trial investigated the benefit of early combined immunosuppression compared to conventional management in patients with newly diagnosed CD.[6] Combined immunosuppression consisted of infliximab and azathioprine and conventional treatment consisted of corticosteroids, followed, in sequence, by azathioprine and infliximab. In patients that were recently diagnosed with CD, combined immunosuppression early in the disease course was more effective than conventional therapy for the induction of remission and reduction of corticosteroid use.[6]

Serious side-effects of infliximab are rare, but can include serum sickness-like reaction, sepsis and opportunistic infection, and autoimmune disorders.[7] The risk of lymphoma in IBD patients while taking infliximab has been a controversial topic. A systematic analysis of the literature on the treatment-associated risks of infliximab calculated a 0.2% risk of lymphoma and a 0.4% risk of dying from sepsis.[8] Although the risk has not been clearly quantified, there appears to be a small, but real, increased risk of lymphoma in IBD patients who are treated with anti-TNF.[9, 10]

There are limited data about how patients feel about these risks and the possible benefits of early aggressive therapy and what risks they are willing to take for a potential benefit of remission. Shared decision-making is increasingly advocated as an ideal model of treatment decision-making.[11] In this model the physician has the responsibility of informing the patients and to give them advice, whereas the actual decisions on how to act on this information are made in collaboration between the patient and physician. A critical step in this decision making process is the communication towards the patients, especially concerning the possible risks and benefits of a given treatment and the availability of other treatment options. In order to be able to make a well-based decision, patients should be aware of the chance of

responding to the therapy and the risk of side-effects. We hypothesized that, although shared decision-making is gaining favor, limited information is given to the patients on risks and benefits of anti-TNF in clinical practice and that patients misinterpret the given information. Feedback is lacking to see if the patients have interpreted the information correctly. Our aim of this study was therefore to assess IBD patients' perspectives of the treatment-associated risks and benefits of infliximab.

## MATERIALS & METHODS

A questionnaire was developed based on an English questionnaire which was recently developed in the USA.[12] The questionnaire was translated to Dutch and pilot-tested in a sample of patients from our outpatient IBD clinic. Ten patients were interviewed to ensure full comprehension of the survey. Results and comments from the interviews were used to optimize the questionnaire. The final questionnaire consisted of fifteen closed-ended multiple-choice responses. Between September 1st and October 1st, 2006, all patients from the outpatient IBD clinic in our referral center were asked to anonymously complete the survey. The survey consisted of questions concerning respondent characteristics, current and past use of infliximab, estimations of the initial response rate to infliximab at 2 weeks and 1 year, and estimations of serious side-effects of infliximab. Finally, patients were given the description of a hypothetical new drug for the treatment of IBD, that unbeknownst to the patient, mirrored the estimated risks for infliximab. Patients were asked for the minimal demanded benefit in order to accept this high-risk medication. The results are reported as descriptive statistics. Ordinal survey items were compared between more than two groups using the Kruskal-Wallis test and between two groups using independent *t*-test. Groups were compared based on age, gender, duration of disease, type of IBD, minimal demanded benefit for a hypothetical new drug and current or past use of infliximab. Duration of disease was subdivided in five different groups (<1 year, 2-5 years, 6-10 years, 11-19 years and > 20 years of disease).

## RESULTS

### Patient characteristics

One hundred and sixty-five questionnaires were completed. Thirteen questionnaires were excluded since these patients had only answered the demographic questions of the survey and one patient claimed not to have IBD. Patient characteristics are shown in Table 1. Of the 152 patients, 118 had CD (78%), 22 had UC (15%), and 12 had indeterminate colitis (8%). The mean age of patients was 38.3 years (SD 13.5), and 61% was female.

**Table 1.** Patient characteristics

| | Crohn's disease | Ulcerative colitis | Indeterminate colitis | Total |
|---|---|---|---|---|
| **N** | 118 | 22 | 12 | 152 |
| **Female (%)** | 75 (64) | 11 (50) | 7 (58) | 93 (61) |
| **Mean Age, years (SD)** | 38.42 ±12.8 | 30.82 ±13.5 | 50.25 ±12.9 | 38.26 ±13.5 |
| **Duration of disease > 10 years, n (%)** | 70 (59) | 5 (23) | 6 (50) | 82 (54) |
| **Infliximab-users, n (%)** | 66 (56) | 8 (36) | 6 (50) | 80 (53) |

The questionnaire and number of respondents to the questions are listed in Table 2. Seventy-seven percent of the patients (117/152) had heard of infliximab prior to this survey and 53% (80/165) were currently receiving infliximab or had received infliximab in the past.

**Table 2.** Questionnaire with number of respondents

| | Yes | No | Not sure | Total |
|---|---|---|---|---|
| **Have you heard of infliximab?** | 117 (77%) | 28 (18%) | 7 (5%) | 152 |
| **Are you currently using infliximab?** | 42 (28%) | 106 (70%) | 4 (3%) | 152 |
| **Have u used infliximab in the past?** | 60 (40%) | 81 (53%) | 11 (7%) | 152 |
| **Have you ever had a discussion about the risks and benefits of infliximab with a health care provider?** | 76 (50%) | 59 (40%) | 17 (11%) | 152 |
| **Patients' estimates of the chance of remission from infliximab after 2 weeks** | | Figure 1 | | 137 |
| **Patients' estimates of the chance of remission from infliximab after 1 year** | | Figure 2 | | 138 |
| **Patients' estimates of the risk of lymphoma associated with infliximab compared to the general population** | | Figure 3 | | 135 |
| **Patients' estimates of the risk of dying from a serious side effect of infliximab as compared to the general population** | | Figure 4 | | 138 |
| **Patients' minimal demanded benefit of a drug with a death rate of 1/250** | | Figure 5 | | 146 |

### Limited information is shared on risks and benefits of infliximab

In total, 40% of patients recalled having spoken about the risks and benefits of infliximab with their treating physician or nurse practitioner. Fifty-three percent (81/152) could not remember such a conversation and 7% (11/152) were not sure if this discussion had ever taken place. Of the 80 past or current infliximab-users 61 patients (76%) could remember having spoken about the risks and benefits of infliximab, 8 patients (10%) were not sure and 11 patients (14%) did not recall such a conversation.

### High perceived remission rates of infliximab

Patients' estimates of clinical remission after 2 weeks and 1 year of treatment with infliximab are demonstrated in Figures 1 and 2. Fifty-four percent of patients (74/137) estimated the remission rate to be greater than 50% after two weeks of infliximab and 57% (78/138) estimated a remission rate greater than 50% after 1 year.

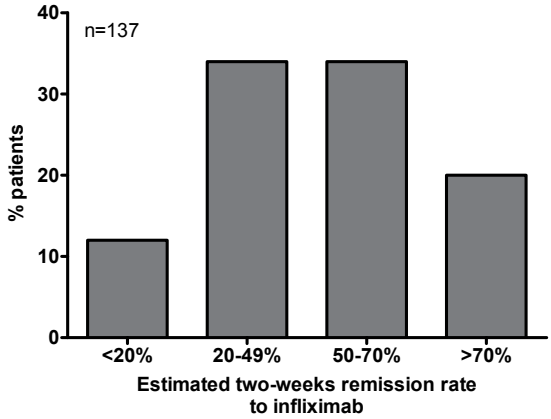


**Figure 1.** Patients' estimates of the chance of remission from infliximab after 2 weeks (n = 137).

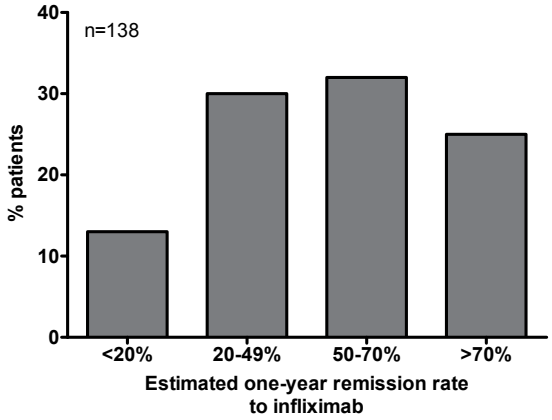


**Figure 2** .Patients' estimates of the chance of remission from infliximab after 1 year (n = 138).

### Low perceived treatment-associated risks of infliximab

The estimated chances of serious side-effects like lymphoma and dying of a serious infection are shown in Figures 3 and 4. Sixty-nine percent of patients that answered this question (93/135) assessed the infliximab-associated risk of lymphoma to be the same or no higher than twice that of the general population. Concerning the risk of dying from a serious side-effect of infliximab, 43% (60/138) answered that infliximab-use was not associated with a

higher mortality risk and 36% of patients (49/138) estimated that this chance of dying was not more than two-times the mortality risk of the general population.

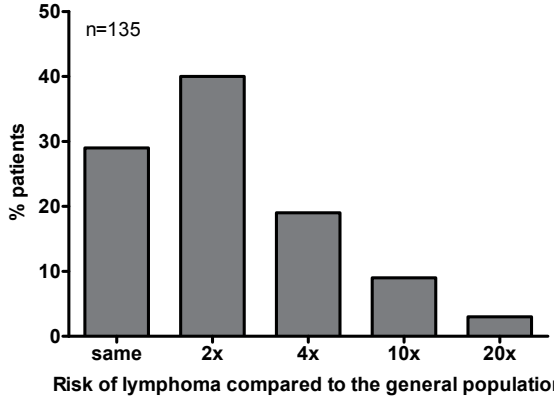


**Figure 3.** Patients' estimates of the risk of lymphoma associated with infliximab compared to the general population (n = 135).

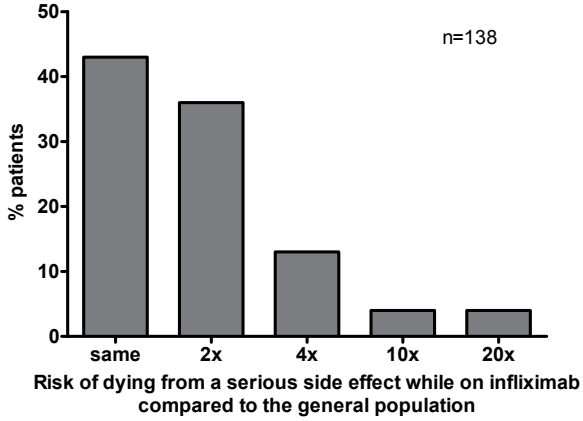


**Figure 4.** Patients' estimates of the risk of dying from a serious side effect of infliximab as compared to the general population (n =138).



### Minimal demanded benefit is a 75% remission rate

Seventy-one percent of patients (104/146) would demand at least a 75% chance of remission before considering taking such a high-risk drug. Forty-seven percent of these patients (69/146) would even demand at least a 95% remission rate (Figure 5). Fifty percent (52/104) of the patients demanding at least a 75% remission rate and 45% (31/69) of the patients demanding a 95% remission rate were currently using infliximab or had used infliximab in the past. Patients demanding at least a 75% remission rate estimated the 2-week remission rate higher than patients that demanded a remission rate < 75% (p=0.006). Of the patients demanding a

75% remission rate, 69% (76/111) assessed the infliximab-associated risk of lymphoma to be the same or no higher than twice that of the general population and 77% (86/112) perceived the mortality risk to be the same or not higher than twice that of the general population. There was no significant difference in estimates of risks and benefits of infliximab among the different categories of minimal demanded benefits of a hypothetical drug.

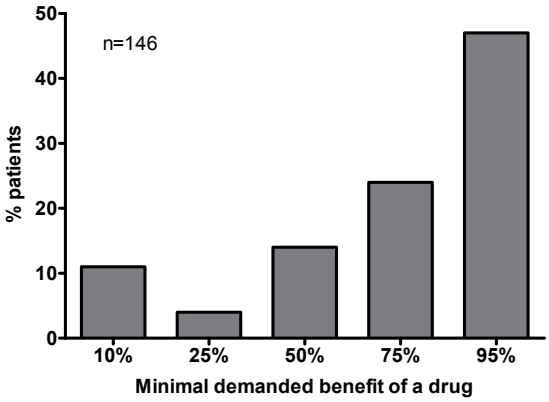


**Figure 5.** Patients' minimal demanded benefit of a drug with a death rate of 1/250 (n = 146).

### Past or current infliximab use significantly influences patients' perceptions

Ever use of infliximab, either in the past or at present, significantly influenced the perception of the 2-week remission rates due to infliximab (p=0.012). Eighteen percent of ever users of infliximab (11/62) compared to 7% of non-users (5/75) estimated the 2-week remission rate to be $\leq$ 20%. Current users of infliximab gave higher perceptions of the 2-week remission rate (p=0.016) and the 1-year remission rate (p=0.008) than those who were not currently treated with infliximab (p=0.016). Forty-eight of 97 non-users (49%) compared with 28 out of 37 users (76%), estimated remission rate $\geq$ 50% (p=0.04). This estimation of the 1-year remission rate was also higher in current users compared to past users (p=0.05). There was no significant difference between past and current users of infliximab with regard to the other estimations of benefits/risks.

### CD and prior counselling lead to higher perceptions of benefits

Patients with CD estimated the 1-year remission rate due to infliximab higher than patients with UC (p=0.03). Patients that recalled a discussion regarding the risks and benefits of infliximab also estimated this 1-year remission rate higher than those who did not recall such a discussion (p=0.03).

### Males estimate treatment associated risks of infliximab higher than females

With regard to the risks of lymphoma while taking infliximab, 80% of the females (67/84) compared with 51% of the males (26/51) predicted this chance to be the same or not higher than twice that of the general population ($p < 0.001$). Concerning the mortality risk, 89% percent of females (67/85) compared with 62% of the males (33/53) estimated the mortality risk of infliximab to be the same or not more than twice the baseline risk ($p = 0.001$). Patients' estimates were not significantly different when comparing groups of respondents based on age or duration of disease.

## DISCUSSION

This study demonstrates a wide range of estimates of the risks and benefits of infliximab. As compared to the large randomized maintenance trials for CD and UC [3, 4] and a systematic risk analysis [8], the majority of patients are overestimating the remission rates and may be underestimating the risks of infliximab. This optimistic view may be explained by various reasons. Firstly, patients that recalled having spoken with their physician about the risks of infliximab had higher estimates of the 1-year remission rate compared with people who did not recall such a conversation. This suggests that treating physicians may have conveyed an optimistic view, possibly due to the physicians' own positive perception of the available data, lack of time to adequately discuss the benefits and risks, or because physicians wanted to encourage the patient to accept the treatment. A second reason for patients' optimism may be that they discount concerning news and want to stay hopeful for their future.

In addition to the high estimations of the remission rates, patients also demand a high remission rate before willing to accept treatment-associated risks. Seventy-one percent of the patients would only consider taking a high-risk drug when associated with a 1-year remission rate of at least 75% and almost half of them would even demand at least a 95% remission rate. Long-term remission rates approaching 75% have only been achieved using infliximab early in the disease course (early aggressive treatment).[6] Conventional therapies have not been able to prevent complications or surgery in IBD, nor did the implementation of immunosuppressants change the course of disease. In addition to the Belgian and Dutch open randomised trial on early combined immunosuppression, a group of French investigators also demonstrated that treatment with infliximab plus azathioprine led to better response in CD patients not treated previously with azathioprine/6-MP compared with those who had previously received azathioprine/6-MP.[6,13] Therefore, changing the course of disease might only be feasible early in the disease. Our study demonstrates that patients are willing to accept treatment-associated risks as long as the remission rates are high, which up till today have solely been achieved with early aggressive treatment.

Of our patients demanding such a high remission rate of > 75% before willing to accept the associated risks, 50% were currently using infliximab or had used it in the past. Since these risks were in fact mirroring the risks associated with the use of infliximab, these results suggest a lack of proper understanding of the risks and benefits of infliximab. A possible explanation is that the precise risks are lacking due to controversy in literature, or that patients are not informed correctly. Another possibility is that the patients have problems interpreting the information accurately and cannot put them in perspective. To interpret available information accurately, patients should be able to comprehend percentages and very small numbers and should in addition have an understanding of probabilities. Furthermore, patients were put in a hypothetical scenario. This is in fact an effective method for standardization, but it is still possible that patients would answer differently when put in an actual situation in which they are suffering from a severe disease and have to decide on their therapy. However, our results are indeed based on patients from a referral center, reflecting those with a chronic severe disease that are often difficult to treat.

Our study confirms the results of a similar questionnaire distributed to 165 IBD patients and parents of IBD patients in the United States.[12] Other data concerning IBD patients' perceptions of treatment-associated risks and benefits as well as the minimal demanded benefit of therapy are lacking.

In summary this study firstly demonstrates that IBD patients misperceive the effectiveness of infliximab and may misunderstand its risks. In addition, patients are making treatment choices without adequate information. Better communication to patients concerning the risks and benefits of treatment is necessary in order to appropriately involve patients in the decision-making process. Secondly, this study demonstrates that patients demand a high remission rate before they are willing to accept treatment related risks. Early aggressive treatment is the only treatment strategy that approaches patients' minimal demands of treatment-related benefits in exchange for the risks of side-effects. Therefore, based on its high response rate, early aggressive treatment may be more acceptable to patients than other treatment algorithms.

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# Chapter XIV

# High therapy adherence but substantial limitations to daily activities amongst members of the Dutch inflammatory bowel disease patients' organization: a patient empowerment study

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## ABSTRACT

**Background and aims:** Adherence is important for successful treatment in inflammatory bowel disease (IBD) patients. Previous studies demonstrated high prevalence of non-adherence. We aimed to assess IBD patients' perceptions of therapy adherence and disease-related functional status in members of the Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN).

**Methods:** IBD patients anonymously completed a survey at the website of the CCUVN. Statistical analysis was performed using principal component analysis, univariate and multivariate logistic regression.

**Results:** The questionnaire was completed by 1067 patients (617 (58%) Crohn's disease (CD) and 450 (42%) ulcerative colitis (UC)). Mean age was 43 years (SD 13.7); women (66%). Of 920 patients currently using medication, 797 (87%) were adherent. Of the patients using 5-ASA, 91% were adherent (527/582), versus 96% using corticosteroids (316/330) and 97% (414/425) using immunosuppressives. CD patients (OR 1.54; 95% CI 1.05-2.27), patients with duration of disease $\leq$ 8 years (OR 2.25; 95% CI 1.49-3.39) were more adherent. Fifty percent of patients reported a low functional status and were limited in daily activities.

**Conclusions:** This population-based study shows high therapy adherence, but low functional status in Dutch CCUVN-related IBD patients. The high adherence rate in this present study could be an effect of CCUVN membership.

## INTRODUCTION

Inflammatory bowel diseases (IBD), which are classically subdivided into ulcerative colitis (UC) and Crohn's disease (CD), represent chronic diseases characterized by periods of remission and unpredictable flare-ups. Several therapeutic strategies are available, including long-term drug therapies to induce and maintain remission.[1] The chronic nature of the disease dictates that therapy is usually continued for prolonged periods of time.

Adherence to therapy is generally defined as the extent to which patients take medications as prescribed by their health-care providers.[2] Non-adherence to long-term medical therapy is common in chronic diseases. In many disorders (e.g. HIV infection, hypertension and psychiatric diseases) lack of adherence has been identified as a main cause of treatment failure.[2, 3] Non-adherence is also one of the many possible reasons for relapsing disease in IBD [4], and has consequently also been associated with higher healthcare costs.[5, 6] Non-adherence to 5-ASA may also be associated with a higher risk of colorectal cancer.[7]

However, the data available on adherence in IBD patients are contradictory. Clinical trials reported high adherence rates varying between 70% and 97%.[8-10] In contrast, studies in daily clinical practice reported adherence rates ranging from 28% to 82%.[4, 11-19]

Several risk factors for non-adherence have been identified, in particular young age, multiple concomitant medications, a short duration of disease and high education levels. Disease activity and gender have also been linked to treatment adherence, but data on these factors were inconsistent.[4, 11, 13, 16-18] A Canadian longitudinal population-based study demonstrated that predictors of adherence differed remarkably between men and women.[16]

The majority of the reports on therapy adherence in IBD focus on UC and the use of 5-ASA products. Data on CD and other drugs for IBD are scarce.

Patient empowerment is becoming increasingly important for management of chronic diseases.[20] It includes that patients are being responsible for their choices and also the consequences of their choices. As a result of empowerment, patients may develop greater sense of self-efficacy regarding various disease and treatment-related behaviours, and may express changes in life priorities and values. As a result of empowerment, patients are also expected to better self-manage not only their disease, but also their lives.[21]

We assessed adherence in IBD patients from the patients' point of view in patients related to Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN). In addition, we aimed to assess patients' perceptions of health-related functional status, and its potential

influence on therapy adherence. In this patient empowered population-based study, IBD patients were asked to anonymously fill out a patient-based survey. This survey focused on patients' perceptions of therapy adherence and disease related functional status.

## MATERIALS & METHODS

### Questionnaire

This patient empowerment study was performed in collaboration with the Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN). A questionnaire was developed by members of the CCUVN working in close collaboration with a panel of IBD patients not associated with the CCUVN. During several meetings, the most important problems patients experience in their life with IBD including therapy adherence and limitations in daily life activities were discussed. The questionnaire mirrors the outcome of these discussions. After the questionnaire had been framed, an independent physician advised the panel on the scientific and medical content of the questionnaire. The questionnaire focused on patients' medication use and medication-taking behaviour, asking directly how often patients took their medication as prescribed by their physician. The questionnaire assessed reasons for non-adherence, the side-effects of medication, the characteristics of the disease, the impact of the disease on daily life and limitations that patients experience as a consequence of their disease. Questions on limitations in daily life were framed on a four point scale ranging from "not limited" to "extremely limited". In addition, questions were included on coping behaviour and patients' perceptions of their personal healthcare. Duration of the disease was categorized into four categories (0-2 years, 3-8 years, 9-15 years, >15 years). After pilot-testing on a panel of IBD patients, the questionnaire was further adjusted accordingly.

### Study population

The definitive questionnaire was placed on the website of the CCUVN from December 2006 to January 2007. The CCUVN has approximately 10,250 members, of whom 9,509 have registered their gender and age. Of these 9,509 registered CCUVN members, 65% are women and 66% are $\leq$ 50 years old. IBD patients were asked to fill out the questionnaire anonymously. A randomly selected group of patients from our outpatient IBD clinic was used to extent our questionnaire and representativeness of the internet population. The questionnaires were filled in during an outpatient visit before patients visited their physician. Patients who already cooperated in the online questionnaire were excluded.

### Therapy adherence

Therapy adherence was defined as taking medication according to prescription. Adherence to medication was established and analyzed for each type of medication separately.

Overall adherence was defined as taking at least 80% of medications as prescribed. Patients who did not take their medications according to the prescription were analyzed as being non-adherent. This group comprised patients who forgot to take their medication as well as patients who refused to take the medication advised by their physician. Multiple-drug users who reported being adherent to only one of multiple prescribed drugs were analyzed as being non-adherent in the overall medication group.

### Functional status

Functional status was defined as the ability to perform daily activities without impairment due to the disease. Identified daily activities were work, education, family life, activities with partner and/or children, getting pregnant/pregnancy and delivery, eating and dining out, sports, going out and holidays.

### Statistical analysis

Differences between adherent and non-adherent patients regarding age, gender, type of disease, disease duration, functional status, use of medication and relationship with treating physicians were analyzed statistically using univariate and multivariate logistic regression. Multivariate logistic regression was performed stepwise-forward in which all variables were included. Therapy adherence between patients from the online group and the patients from the outpatient clinic group was compared using independent *t*-test. We performed a power analysis to see what difference between an internet group of 1000 and an outpatient group of 180 can be detected. We found that a fraction of 80% in the internet group versus 88% in the outpatient group will be significantly detected ($\alpha = 0.05$) with a probability of 80%.

Principal component analysis (PCA) was performed to determine the pattern of responses concerning the impact of the disease on daily activities in the online group only. The percentage of the variance explained by this analysis is expressed by the eigenvalue. The results are represented on two axes in a biplot [22, 23], provided that the first two eigenvalues are large enough.

## RESULTS

### Study population

In total, 1,093 patients completed the questionnaire online. Twenty-six patients were excluded from analysis because of lack of information on their type of IBD (n=24) or on their gender (n=2). Patient characteristics are shown in Table 1. Of the remaining 1,067 patients, 617 had CD (58%) and 450 had UC (42%). Their mean age was 42.9 years (SD 13.7), duration of disease was $\geq$ 9 years in 575 patients (54%), and 703 patients (66%) were women.

**Table 1.** Patient characteristics

| | Online group (%) | Outpatient clinic group (%) |
|---|---|---|
| **No. of patients** | 1067 | 169 |
| **Disease** | | |
| Crohn's disease | 617 (58) | 125 (74) |
| Ulcerative colitis | 450 (42) | 41 (24) |
| Indeterminate colitis | - | 3 (2) |
| **Female gender** | 703 (66) | 84 (50) |
| **Mean age (SD)** | 42.9 (±13.7) | 38.7 (±14.4) |
| **Duration of disease ≥ 9yrs** | 575 (54) | 93 (55) |
| **Decreased functional status** | 531 (50) | 100 (59) |
| **Overall adherence to therapy** | 797 (87) | 125 (82) |
| **Positive perception of relationship with physician** | 949 (89) | 156 (93) |
| **Member CCUVN** | 1001 (94) | 61 (36) |

### Therapy adherence

Univariate analyses on factors influencing therapy adherence are listed per medication group in Table 2. Multivariate analyses are listed in Table 3. Overall, 920 patients (86%) were currently on medication. Among them, 797 patients (87%) reported taking all medications as prescribed by their treating physician. Univariate analysis showed that high therapy adherence was associated with a shorter duration of disease (0-8 years) ($p < 0.001$). Of the 431 patients with a short duration of disease, 393 were therapy adherent (91%), against 404 out of 489 patients with a longer duration of disease (83%). After correcting for potential confounders, CD (OR 1.54; 95% CI 1.05-2.27; p=0.027) and a short duration of disease (OR 2.25; 95% CI 1.49-3.39; p<0.001) were associated with a higher chance of adherence to therapy.

### Adherence to 5-ASA

Of the 920 patients using medication, 582 used 5-ASA, to which 527 (91%) reported being completely adherent. CD was independently associated with higher therapy adherence to 5-ASA (p=0.005); 94% of CD patients (258/274) were adherent, against 87% of UC patients (269/308). Of the patients using 5-ASA, 269 patients reported to have functional impairments. Of these 269 patients, 251 patients (93%) were therapy adherent, against 276 out of 313 patients (88%) reporting a normal functional status (p=0.035). In addition, older age was an independent predictor for therapy adherence, with an Odds Ratio (OR) of 1.33 for 10 years older age (p=0.011). After correcting for potential confounders, the following covariates were associated with adherence to 5-ASA products: CD (OR 2.64; 95% CI 01.41-4.94; p=0.002), a short duration of disease (OR 1.93; 95%CI 1.02-3.67; p=0.046), 10 years older age (OR 1.57; 95% CI 1.22-2.02; p=0.001), and a decreased functional status (OR 1.88; 95% CI 1.02-3.44;

**Table 2.** High level of therapy-adherence in online group (univariate logistic analysis)

| | Overall | 5-ASA | Corticosteroids | Immuno-suppressives | Anti-diarrhoeals |
|---|---|---|---|---|---|
| | *n=920* | *n=582* | *n=330* | *n=423* | *n=144* |
| **Adherence (%)** | 797 (87) | 527 (91) | 316 (96) | 414 (98) | 101 (70) |
| **Gender (%)** | | | | | |
| Male | 267 (86) | 187 (91) | 104 (94) | 123 (98) | 34 (76) |
| Female | 530 (87) | 340 (90) | 212 (97) | 291 (98) | 67 (68) |
| | *p=0.99* | *p=0.89* | *p=0.19* | *p=0.63* | *p=0.34* |
| **Disease (%)** | | | | | |
| CD | 469 (88) | 258 (94) | 189 (97) | 270 (98) | 84 (72) |
| UC | 328 (84) | 269 (87) | 127 (93) | 144 (97) | 17 (63) |
| | *p=0.050* | ***p=0.006**** | *p=0.084* | *p=0.55* | *p=0.37* |
| **Duration of disease (%)** | | | | | |
| 0-8 years | 393 (91) | 227 (92) | 155 (98) | 213 (99) | 31 (79) |
| ≥ 9 years | 404 (83) | 300 (90) | 161 (94) | 201 (97) | 70 (67) |
| | ***p <0.001**** | *p=0.49* | *p=0.056* | *p=0.29* | *p=0.14* |
| **Age (OR for 10 years older)** | 1.04 | 1.33 | 0.79 | 0.90 | 1.17 |
| **95% CI** | (0.91;1.19) | (1.08;1.65) | (0.54;1.17) | (0.54-1.49) | (0.87-1.57) |
| | *p=0.55* | ***p=0.011**** | *p=0.25* | *p=0.67* | *p=0.31* |
| **Decreased functional status (%)** | | | | | |
| Yes | 431 (88) | 251 (93) | 223 (97) | 248 (98) | 70 (71) |
| No | 366 (85) | 276 (88) | 93 (92) | 166 (97) | 31 (67) |
| | *p=0.67* | ***p=0.037**** | ***p=0.036**** | *p=0.36* | *p=0.62* |
| **Relationship with physician (%)** | | | | | |
| positive | 709 (87) | 473 (91) | 286 (96) | 368 (98) | 93 (70) |
| negative | 88 (85) | 54 (86) | 30 (97) | 46 (96) | 8 (73) |
| | *p=0.67* | *p=0.17* | *p=0.77* | *p=0.3* | *p=0.85* |

p=0.042). The change in p-value for duration of disease in univariate and multivariate logistic regression was caused by a strong relation with age.

### Adherence to corticosteroids and immunosuppressives

In total, 330 patients used corticosteroids, to which 316 (96%) reported being completely adherent. Ninety-seven percent (223/229) of the patients with functional impairments were adherent to corticosteroids against 92% of patients (93/101) with a normal functional status (p=0.028). In multivariate analysis, the sole predicting factor for adherence to corticosteroids was a decreased functional status (OR 3.2; 95% CI 1.08-9.47; p=0.036). In the immunosuppressives group (n=423), 414 patients (98%) reported to be adherent to therapy. None of the factors were significant for therapy adherence in this group. In the anti-TNF group (n=111),

**Table 3.** Multivariate logistic analysis of therapy adherence in online group

| | Overall *OR (95% CI)* | 5-ASA *OR (95% CI)* | Corticosteroids *OR (95% CI)* | Immunosuppressives *OR (95% CI)* | Anti-TNF *OR (95% CI)* |
|---|---|---|---|---|---|
| **Gender** | - | - | - | - | - |
| **Crohn's disease** | 1.54 (1.05;2.27) | 2.64 (1.41;4.94) | - | - | - |
| **Duration of disease < 9 yrs** | 2.25 (1.49;3.39) | 1.93 (1.02;3.67) | - | - | - |
| **Age (OR for 10 yrs older)** | - | 1.57 (1.22-2.02) | - | - | - |
| **Decreased Functional status** | - | 1.88 (1.02;3.44) | 3.2 (1.08;9.47) | - | - |
| **Positive relationship physician** | - | - | - | - | - |

110 patients (99%) were adherent to therapy. In the antibiotics group, 100% of the patients (12/12) were adherent to therapy.

### Daily activities

In total, 531 patients (50%) reported a decreased disease-related functional status. Patients' perceptions on the impact of their disease on functional status were analyzed using principal component analysis (PCA). The results are demonstrated in Figure 1. Our PCA demonstrated that the 11 factors that were presented to the respondents were all positively correlated with an eigenvalue (% of variance explained) of 48.7 (first component, shown on *x*-axis). The second eigenvalue (*y*-axis) is 10.6, which means that 60% of the total variation is represented in the biplot. We decided this to be enough to produce the biplot and refrain from extracting more axes. The first component (*x*-axis) represents the extent to which patients are troubled by their disease in daily activities. The second component (*y*-axis) provides information on the distribution of answers among the respondents, and shows which patients have an impaired quality of life and in which activities their disease is particularly bothersome. In the biplot, all the arrows point to the right, and are therefore positively correlated, i.e. patients are in general troubled in each activity. The horizontal axis can be interpreted as the overall level of limitations, regardless the kind. That aspect is represented in the vertical dimension, with a much lower eigenvalue. The group of respondents was limited in eating and going out for a restaurant meal, and the other group of respondents was limited in other aspects. The overall impact of the disease on pregnancy and education was smaller than on other activities, because these activities were not applicable to all respondents. CD patients were less restricted in daily activities (mean = –0.09) than UC patients (mean = 0.14, $p<0.001$). No correlation was found between the first component and overall therapy adherence (p=0.56).

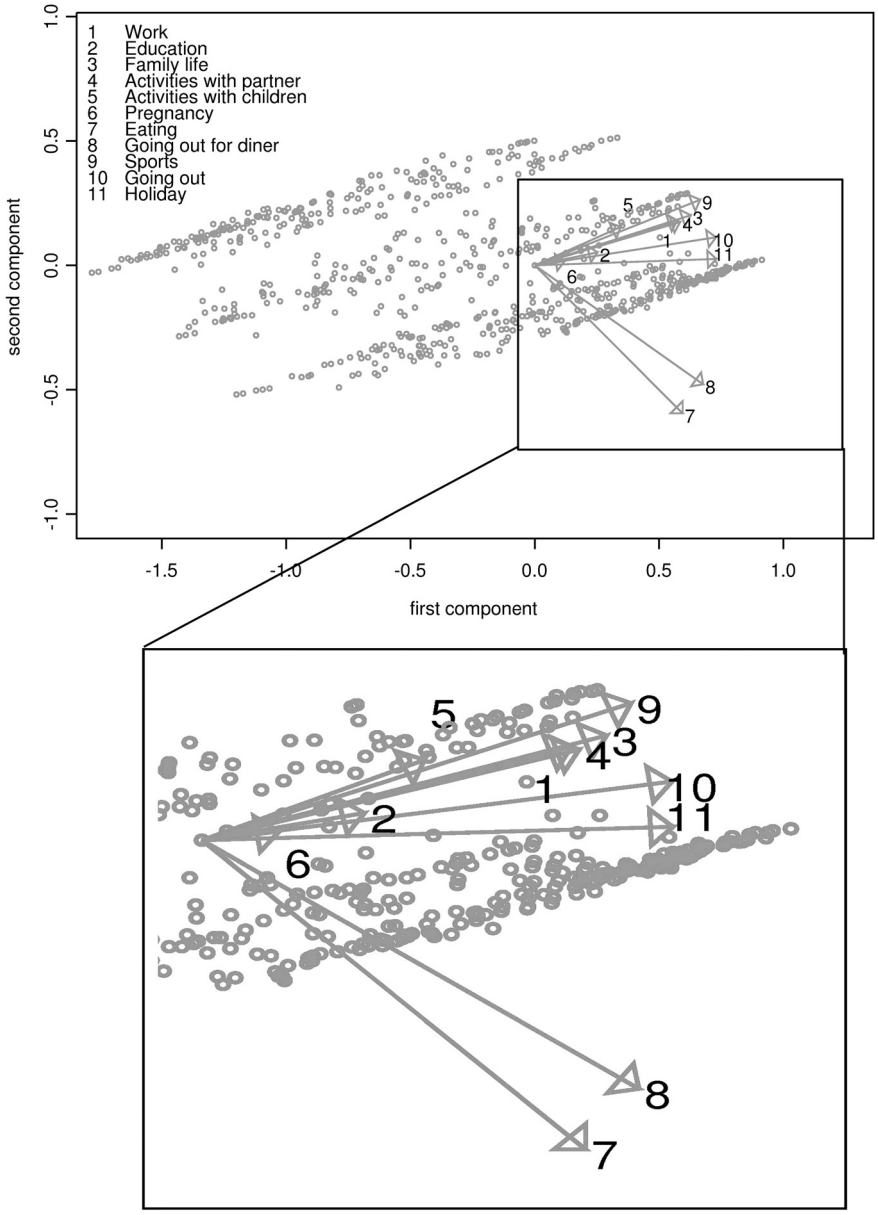


**Figure 1.** The negative influence of IBD on daily activities.

The x-axis represents the extent to which patients are troubled by their disease in daily activities (mean = 0). The y-axis provides information on the distribution of answers among the respondents: it shows which patients have a decreased functional status and in which activities their disease is particularly bothersome. Each dot represents one respondent. The eleven arrows represent the daily activities. The length and direction of the arrow explains the correlation between the arrows. At first sight, the length and direction of the arrows are similar. This shows that patients are troubled in each activity.

### Outpatient clinic group

In total, 169 patients from our outpatient IBD clinic completed the questionnaire: 125 had CD (74%), 41 had UC (24%) and three had indeterminate colitis (2%). Their mean age was 38.7 years (SD 14.4), duration of disease was $\geq$ 9 years in 93 patients (55%), and 84 patients (50%) were women. Of this group 36 patients were member of the CCUVN. Overall adherence in the outpatient clinic group (82%) was comparable to overall adherence in the online group (87%) (p=0.06). There was no difference in answers between patients from the online group and patients from the outpatient clinic concerning functional status.

## DISCUSSION

This patient empowerment study in The Netherlands reveals patients' perceptions of high therapy adherence in patients with inflammatory bowel disease related to Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN).

The level of adherence required for effective treatment will vary according to the medical condition and the type of treatment. A gold standard for assessment of adherence has not yet been agreed upon. As we wanted to obtain unbiased information on patients' perceptions of therapy adherence we used a self-reporting system. Although this method has been contested for reasons of reliability and truthfulness of the given answers, it has been successfully tested against actual drug levels in blood.[13, 24] In addition, it has been proven to correlate well with pill counts, electronic monitoring, and pharmacy refill records.[25, 26] The validity of the method is reinforced by the fact that we included nearly 1100 patients in our analysis, who gave their perceptions anonymously, knowing that their answers could not influence their disease, treatment or relationship with their treating physician.

Crohn's disease patients reported to be more therapy adherent than patients with ulcerative colitis. There are four possible reasons for this. First, this might be explained by a difference in counselling: unlike CD patients, UC patients have the option of colectomy in the final treatment-strategy of their disease. Second, UC patients are more likely to achieve complete remission than CD patients.[27, 28] Third, the presence of fistulas and strictures may contribute to higher adherence-rates in CD patients. Fourth, as demonstrated in a Canadian study, CD patients have greater healthcare utilization than UC patients.[29]

Contrary to previous studies, this study demonstrates that patients with a short duration of disease demonstrate a higher adherence rate than those with a longer duration of disease. In general, it is known that patients with a chronic disease are more likely to be non-adherent.[2, 11] In CD, the first phase of the disease is known to be the active phase with mucosal inflam-

mation; later in the disease, patients are more likely to develop a stricturing or penetrating disease.[30] In the active phase of their disease, patients will most likely have more symptoms and are therefore more willing to take their medication in order to reduce their complaints. It is more difficult to get patients to take their medication when they feel well, because the rationale for the continued need of medication is unclear.[4] This could also be an explanation why patients report high adherence to corticosteroids and immunosuppressives, since these drugs are usually prescribed to treat active and more severe disease. In our large group of patients we could not confirm gender as an effect-modifier for therapy adherence as was earlier demonstrated in a smaller Canadian population-based study of 326 patients.[16]

Patients report to be less adherent to 5-ASA than to all other types of medications. This can be explained by the fact that 5-ASA is the first therapeutic strategy in IBD and is therefore used to treat patients with less severe disease. Why patients with CD were more adherent to 5-ASA we could not explain and seems in contrast with reports that demonstrated the lack of effectiveness of this drug in CD.

Using the internet, we were able to reach a large, nationwide patient group and also to obtain information anonymously without intentional or unintentional interference by the healthcare providers. This enabled us to obtain sincere information on patients' perceptions on therapy adherence and quality of life. In addition, we asked for adherence per medication group, identifying patients as adherent to one drug, but simultaneously non-adherent to another. We acknowledge the lacking of other important factors influencing therapy adherence such as anxiety, depression and hospitalization. Although these factors were considered to be important for the survey, the panel decided not to include these and other factors because of the length of the questionnaire. However, even though we are well aware of the limitations of this online survey, the design of this study was carefully chosen to fit our main aim. In addition, the high adherence rates were confirmed in a representative sample from our outpatient IBD clinic.

This is the first patient empowerment study to report patients' perceptions of disease-related limitations in daily life. Previous studies have demonstrated an impaired quality of life in IBD patients, in which CD patients generally experience a worse quality of life than UC patients.[1, 12, 31-34] This study confirms that many IBD patients are impaired in daily activities. Contrary to previous studies, this study reveals that CD patients experience fewer restrictions in daily activities than UC patients. This could be explained by the fact that UC patients generally have more bloody diarrhoea, which might impair their functioning in daily activities. In extending the current knowledge about IBD-related quality of life, this study maps out both the degree to which patients are bothered by their disease in daily activities and the individual correlations between these activities. It is known from literature that internet respondents report a

significantly lower quality of life than patients recruited from the hospital.[35] However, in our study the poor patients' perceived quality of life in our internet respondents is confirmed in the control group from our outpatient IBD clinic.[12] For further research, this questionnaire needs validation and therefore the current results cannot be compared with the healthy population.

A known limitation of an internet survey is the lack of information it provides on response rate and generalizability. The CCUVN has approximately 10,250 members, of whom 9,509 have registered their gender and age. Comparison of the 1,026 patients who filled out our questionnaire with the 10,250 members shows that our response rate was approximately 10%, with the respondents being fully representative of all CCUVN members with regard to age, and gender. Furthermore, we recognize that these patients are all members of the CCUVN and therefore are not representative for all Dutch IBD patients.

In conclusion, unlike previous studies, this patient empowerment study demonstrates a high adherence rate amongst IBD patients who are member of the Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN), even in those with non-active disease. It therefore gives a new insight into therapy adherence and functional status among patients with inflammatory bowel disease in this specific patient group. Results of adherence of this study imply that being member increases therapy adherence; furthermore, this study emphasizes the poor quality of life that patients experience and the negative influence of IBD on their functioning in daily life.

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# Chapter XV - i

## General discussion and summary

## INTRODUCTION

Inflammatory bowel disease (IBD), which is classically subdivided into ulcerative colitis (UC) and Crohn's disease (CD), represents a chronic disease characterized by periods of remission and unpredictable flare-ups, and the development of many complications, such as fistulas and colorectal cancer (CRC). These complications have a large impact on patients' quality of life. Clinical practice is evolving rapidly, with increasing understanding of the pathogenesis of IBD and its complications. Consequently, patients are also confronted with these new insights into their disease, the treatment and the prevention of complications, including intense CRC screening programs, and medications with often unknown side-effects. Research in this patient group is therefore in need of a multidisciplinary approach. Adherence to treatment is an important aspect in preventing the relapsing course of disease and the development of complications. Patients' perceptions of their disease, effect of medication and the associated risks are an important aspect in assessing grounds of adherence and disease management. Patients' perceptions may therewith form an important step towards improving the management of complications in IBD. The aim of this dissertation was to investigate the diverse complications of IBD from a multidisciplinary perspective (**chapter I**). This thesis addressed in the first place the risks of malignancy in IBD including the role of CRC surveillance colonoscopy. Secondly, we addressed the patients' perceptions of their disease and the associated risks.

## PART 1: (PRE) MALIGNANT COMPLICATIONS OF IBD

### Cancer in fistulas

One third of CD patients develops a fistulizing disease.[1] Two major types of fistulas in CD patients are perianal- and enterocutaneous fistulas. Cancer may originate from these fistulas. To emphasize the difficulty of diagnosing these tumors we presented in **chapter II** a case report of a CD patient who presented with a persistent enterocutaneous fistula. Colonoscopy showed no abnormalities in the terminal ileum and cecum. The patient was treated with corticosteroids and azathioprine for CD, but the fistula responded only partially to therapy. Surgery was performed and revealed a well-differentiated adenocarcinoma, originating from the fistula tract. We conclude that there should be awareness of the risk of developing cancer in persistent enterocutaneous fistulas and that surgery is indicated early in these particular cases.

This case report led us to the question whether there is indeed an increased risk of developing cancer in enterocutaneous or perianal fistulas. We therefore performed a retrospective cohort study on the prevalence of cancer in fistulas in nine large medical centers in The Netherlands (**chapter III**). In this chapter, we demonstrated that adenocarcinoma complicating perianal

or enterocutaneous fistulas is a rare phenomenon. Out of 2,324 patients with a fistula, only four patients developed an adenocarcinoma in the fistula tract during an observation-period of 17 years. This implies that the estimated prevalence is unlikely to exceed 0.17% in case of patients with any manifestation of a fistula. The total IBD population in this study comprised 6,058 CD patients. Only four out of these 6,058 CD patients developed a fistula-associated adenocarcinoma which is by approximation calculated to be a prevalence of 0.004%. We could not identify any malignant transformations in non-CD related fistulas. Although it remains a rare complication, caution is needed since the diagnosis of concomitant adenocarcinoma formation in already established fistulas is difficult to make.

### Small bowel cancer

Although the literature mainly focuses on the development of CRC in IBD patients, it is also known that CD patients have an increased risk of small bowel cancer (SBA).[2-4] **Chapter IV** elucidated this with a case series of three CD patients. This case series underlined the necessity of performing full work up in the diagnosis of CD and considering SBA in patients with small bowel CD who failed medical therapy. Based on this case series we concluded that a firm diagnosis of CD, preferably with endoscopy and histological biopsies, is important for clinical practice. Moreover, in a patient followed for ileal CD with unusual symptoms, especially with subocclusive syndrome, cancer should be considered.

### IBD-related CRC

#### *Epidemiology*

CRC is among the most feared long-term complications of IBD and accounts for approximately 10-15% of all deaths in IBD patients.[2] The exact magnitude of the CRC risk remains a matter of debate. Initial reports mainly originated from tertiary referral centers, which generally include patients with a more severe disease. A well-cited meta-analysis from 2001 estimated the cumulative incidence of CRC in UC patients at 2% after 10 years of disease, 8% after 20 years and 18% after 30 years of disease. **Chapter V** gave an overview and critical appraisal of the recent literature regarding the risk of IBD-related CRC. Due to various biases and methodological errors in published studies, the actual risk remains debated and it is unsure whether we are over-, or underestimating the actual IBD-related CRC risk. Geographical differences as well as differences in local treatment policies and methodological errors complicate a correct interpretation of published studies. Moreover, the recently reported lower incidence rates might be a result from successful treatment-strategies, including 5-ASA maintenance-therapy and dysplasia surveillance programs. A sound knowledge of the overall epidemiology of CRC in IBD patients is important if we are to improve clinical practice and strengthen the basis of surveillance guidelines.

*Risk analyses*

Surveillance colonoscopy is used as the foundation of a prevention strategy, with colectomy being reserved for IBD patients in whom dysplasia or CRC are discovered. The cost effectiveness of surveillance depends on the actual risk of developing IBD-related CRC. If the IBD-related CRC risk is indeed low, we should question whether we should continue performing surveillance in all IBD patients. Therefore, we performed a nationwide nested case-control study in The Netherlands (**chapter VI**). In this study we demonstrated that the risk of developing CRC in IBD patients is limited in general hospitals (0.04% per year). Additionally, we demonstrated that the annual population rate for IBD-related CRC in The Netherlands was 0.05%. Moreover, we identified several strong risk factors for IBD-related CRC in this cohort, including older age, longer duration of IBD, longer duration of primary sclerosing cholangitis (PSC), and co-presence of pseudopolyps. We found a protective role for thiopurines and anti-Tumor Necrosis Factor alpha (anti-TNFα). Since the population rate was very low despite the fact that only 12% underwent surveillance, it is uncertain from our results whether surveillance colonoscopy is necessary for all IBD patients. Parameters which lead to early CRC in both referral and non-referral centers are needed to identify patients in need of earlier start of surveillance.

## Surveillance

**Chapter VII** assessed the patient-, and disease characteristics of IBD-related CRC in a nationwide cohort of IBD patients from general hospitals. Our results emphasized the problem of a high proportion of IBD-associated CRCs developing before the recommended start of surveillance. Older age at diagnosis of IBD was proven to be associated with this early development of IBD-related CRC. Moreover, the patients who were included in a surveillance program had significantly better tumor characteristics compared with those who were not included in such a program. Based on our results, we suggested that older age at onset of IBD could be an additional factor to start surveillance in IBD patients. Accordingly, we would recommend earlier start of surveillance and an immediate start at time of IBD diagnosis for patients diagnosed with IBD above the age of 45 years. Moreover, better registration of start of symptoms is needed. Adapting the surveillance guidelines and identifying patients in need of earlier start of surveillance will detect CRC at an earlier stage and may therewith improve prognosis.

*The burden of CRC surveillance*

In **chapter VIII** we elucidated further on the improvement of surveillance guidelines. Surveillance for all IBD patients is associated with unnecessary burden and costs. Based on the risk factors that were found in our nested case-control study (**chapter VI)** we developed a risk prediction tool for individually tailored CRC surveillance in general hospitals. This model is a first step towards individualized surveillance for IBD patients in general hospitals. According

to our results we proposed to start surveillance every 3 years in IBD patients with a predicted risk of 0.2% or higher. After further validation, this model may support physicians in deciding on timing of start of surveillance.

*Mucosal inflammation while the patient is clinically in remission*

Inflammation is a well-accepted risk factor for the development of CRC. However, clinical symptoms are not an accurate measurement for disease activity and mucosal inflammation may be present without any clinical symptoms. Data are lacking on whether it is necessary to change the therapeutic strategy when a patient in clinical remission shows endoscopic inflammation and whether or not intervening leads to a better disease course. **Chapter IX** demonstrated that a large proportion of mucosal inflammation is found in IBD patients in clinical remission. Additionally, we showed that in a large proportion of patients histological inflammation was diagnosed without any signs of active disease during endoscopy. The incentive to treat patients in clinical remission but with inflammation found during endoscopy was low in clinical practice. In 39% of the patients inflammation spontaneously recovered. Nonetheless, endoscopic or histological inflammation without any symptoms was associated with more severe mucosal inflammation at two years follow-up. However, we could not demonstrate a worse disease course, including the development of dysplasia, during long-term follow-up in patients with inflammation found during endoscopic or at histological examination. We conclude that the clinical benefit of unconditionally treating all patients with mucosal inflammation in order to improve long-term prognosis needs to be further investigated as we could not show a beneficial effect of active treatment and moreover we found spontaneous recovery in one third of the patients.

*Asymptomatic inflammation as a pitfall for surveillance colonoscopy*

Active inflammation is one of the pitfalls during surveillance colonoscopy in IBD patients. By histology, low-grade dysplasia is difficult to distinguish from regenerative changes as a result of inflammation.[6] Moreover, there is a large degree of interobserver disagreement among pathologists for the detection and grading of dysplasia in the presence of active inflammation.[7, 8] Therefore, the interpretation of biopsies can be seriously hampered when active mucosal inflammation is present. **Chapter X** described the results from a prospective randomized controlled study that defined the effectiveness of treating patients with a low dose of corticosteroids prior to surveillance to decrease mucosal inflammation. Firstly, in line with the results from chapter IX, we confirmed that two third of patients in clinical remission has mucosal inflammation. We demonstrated that a short course of corticosteroids does indeed lower the disease activity in individual biopsies. Moreover, there was a trend of diminished disease severity and extent of disease on endoscopy and histology per individual patient. Contrary to previous studies, corticosteroids might be able to decrease inflammation and may subsequently induce mucosal healing in IBD patients. Further research is needed to

assess the optimal dosage and duration of medication use to optimize the circumstances for histological analysis of dysplasia during surveillance colonoscopy.

## PART 2: PATIENTS' PERCEPTIONS OF DISEASE AND ASSOCIATED RISKS

### Patient empowerment and shared decision-making

Patients' perceptions as a part of patient empowerment and shared decision-making are becoming increasingly important in therapeutic strategies of chronic diseases like IBD.[9-14] It has been suggested that patients show better adherence when they are actively involved in the decision-making process.[15, 16] Non-adherence is an important reason for relapsing disease in IBD.[17] Shared decision-making can therefore be used to educate patients about the utmost importance of adherence to medication and the necessity to commit and follow-through on their treatment. **Chapter XI** described a large patient empowerment study assessing IBD patients' preferences with regard to their involvement in the decision of treatment choices. This patient empowerment study demonstrated that IBD patients prefer active involvement in the decision-making process concerning the treatment of their disease. It is therefore a challenge to implement shared decision-making in the healthcare of IBD in the future. Further research is needed on physicians' perspectives on shared decision-making and on developing a model to implement shared decision-making in clinical practice using predictive factors. Nonetheless, our results demonstrated that most IBD patients are ready to implement shared decision-making to improve their treatment strategy.

### Patients' knowledge of disease and associate risks

Patients' perceptions and their accurate knowledge of their disease and associated risks are of utmost importance to make appropriate decisions regarding the management of their disease. However, limited data are available on IBD patients' knowledge of the basic characteristics of their disease, the management of their disease and the associated risks. In **chapter XII** we therefore mapped out IBD patients' knowledge of disease, perceived risks of CRC and colonoscopy, and their perspectives on the current recommendations for colectomy when low-grade dysplasia is found. This nationwide survey demonstrated that IBD patients are insufficiently informed about their disease. Although they knew which medication they take and what kind of IBD they suffer from, many patients were unaware of the localization of their disease and misperceive their life expectancy, CRC risk and the possible benefits of colonoscopy. Most patients perceived that they are at a higher risk of developing CRC than has been reported in the literature and only few seemed prepared to follow current recommendations for colectomy if dysplasia were detected. In general, they would tolerate a high risk of cancer before agreeing to colectomy. Our findings imply that improvement of patient education is necessary in order to appropriately involve patients in the decision-

making process. An IBD patients' organization can support patient education and may help patients in the process of shared decision-making. Our results indicate that a model needs to be developed to implement shared decision-making in clinical practice using predictive factors and detailed guidelines for patient education. Future research is needed to assess the practical issues of implementing shared decision-making in clinical practice, including the role of nurse practitioners in this paradigm.

In **chapter XIII** we assessed IBD patients' perspectives of the treatment-associated risks and benefits of anti-TNFα. This study firstly demonstrated that IBD patients misperceive the effectiveness of anti-TNFα and may misunderstand its risks. In addition we demonstrated that patients are making treatment choices without adequate information. Better communication to patients concerning the risks and benefits of treatment is necessary in order to appropriately involve patients in the decision-making process. Strikingly, patients demanded a high remission rate before they are willing to accept treatment related risks. Early aggressive treatment is the only treatment strategy that approaches patients' minimal demands of treatment-related benefits in exchange for the risks of side-effects. Therefore, based on its high response rate, early aggressive treatment may be more acceptable to patients than other treatment algorithms.

### Therapy adherence and disease-related functional status

To elucidate further on the impact of IBD we describe in **chapter XIV** the results from a nationwide patient empowerment study on disease-related functional status and therapy adherence in IBD patients. In conclusion, unlike previous studies, this patient empowerment study demonstrates a high adherence rate amongst IBD patients who are member of the Dutch patients' association of Crohn's disease and ulcerative colitis (CCUVN), even in those with non-active disease. Results of adherence from this study implied that being a member increases therapy adherence; furthermore, this study emphasized the poor quality of life that patients experience and the negative influence of IBD on their functioning in daily life.

## CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, this dissertation presents a revisited approach to complications in IBD. Firstly, we demonstrate a limited risk of IBD-related CRC and indicate that surveillance guidelines are in need of adjustments. We propose to implement individually tailored surveillance and an immediate start of surveillance for patients > 45 years old at time of IBD diagnosis. Given the high rate of mucosal inflammation found during surveillance colonoscopy, a short course of corticosteroids prior to surveillance could be considered to decrease disease mucosal inflammation in order to optimize the histological assessment of low-grade dysplasia.

Secondly, we demonstrate that patients are ill-informed about their disease, treatment, and associated risks. Patients should be included in the decision-making process of their disease more actively. Membership of an IBD patients' organization is therefore recommended for all IBD patients to improve patient education, to aid patients in the decision-making process of the management of their disease, and to improve therapy adherence. Moreover, physicians need to be trained in including patients in the decision-making process in clinical practice. Future research should focus on improving patient education and could assess the role of nurse practitioners in the paradigm of shared decision-making.

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# Chapter XV - ii

## Algemene discussie en samenvatting

## INTRODUCTIE

Inflammatoire darmziektes (IBD) zijn chronische ontstekingsziektes van de darm. IBD is een verzamelnaam voor twee chronische darmziektes, te weten colitis ulcerosa en de ziekte van Crohn. In het geval van colitis ulcerosa bevindt de ontsteking zich in de dikke darm, dit in tegenstelling tot de ziekte van Crohn waarbij het gehele spijsverteringskanaal, van mond tot anus, aangetast kan zijn. IBD wordt gekarakteriseerd door periodes van onvoorspelbare opvlammingen en is geassocieerd met diverse complicaties, zoals de ontwikkeling van darmkanker. Deze complicaties hebben een grote invloed op de kwaliteit van leven van IBD-patiënten. De inzichten in de pathogenese van IBD zijn de laatste jaren snel toegenomen. Hierdoor worden naast artsen, ook patiënten geconfronteerd met snel veranderende inzichten met betrekking tot de behandeling van de ziekte en het voorkomen van complicaties. Een voorbeeld hiervan is de richtlijnen die nu gelden voor intensieve surveillance van IBD geassocieerde darmkanker, maar ook de implementatie van nieuwe medicatie met nog ongekende bijwerkingen op de lange termijn. Wetenschappelijk onderzoek naar IBD is dan ook gebaat bij een multidisciplinaire benadering. Therapietrouw is een belangrijk aspect in het voorkomen van terugkerende opvlammingen en de ontwikkeling van complicaties. De kennis en visie van patiënten wat betreft hun ziekte, medicatiegebruik en de bijbehorende risico's vormen een belangrijke basis om de redenen voor therapietrouw en het omgaan met de ziekte te kunnen doorgronden. Dit kan daarom een belangrijke stap vormen in het verbeteren van het behandelen van complicaties van IBD.

In dit proefschrift worden vanuit verschillende invalshoeken de diverse complicaties onderzocht die bij IBD kunnen optreden (**hoofdstuk I**). Allereerst waren we geïnteresseerd in het risico op kanker bij IBD-patiënten en de interpretatieproblemen die geassocieerd zijn met surveillance colonoscopieën (kijkonderzoek van de dikke darm). In de tweede plaats hebben we gekeken naar de kennis en mening van patiënten met betrekking tot hun ziekte en de bijbehorende risico's.

## DEEL 1: (PRE) MALIGNE COMPLICATIES VAN IBD

### Kanker in fistels

De ziekte van Crohn wordt in een derde van de gevallen gecompliceerd door de ontwikkeling van fistels.[1] De twee voornaamste types bij Crohn patiënten zijn perianale fistels en enterocutane fistels. In deze fistels kan kanker zich ontwikkelen. Om te benadrukken dat deze tumoren moeilijk te diagnosticeren zijn, presenteren we in **hoofdstuk II** een casus van een patiënt met de ziekte van Crohn, die een enterocutane fistel ontwikkelde. Een colonoscopie liet geen afwijkingen zien in het terminale ileum en het coecum. De patiënt werd behandeld

met corticosteroïden en azathioprine, maar de fistel reageerde slechts matig op de therapie. De patiënt werd vervolgens geopereerd waarbij een goed gedifferentieerd adenocarcinoom werd gevonden die uitging van de fistel. We concluderen dat men bij moeilijk behandelbare enterocutane fistels alert moet zijn op de ontwikkeling van kanker en dat chirurgie vroegtijdig is geïndiceerd in deze specifieke gevallen.

Deze casus bracht ons bij de vraag of er een verhoogd risico is op het ontwikkelen van kanker in enterocutane of perianale fistels. Daarom hebben we een retrospectieve cohortstudie uitgevoerd in negen grote Nederlandse ziekenhuizen naar de prevalentie van kanker in fistels. In **hoofdstuk III** laten we zien dat adenocarcinomen als een complicatie van perianale of enterocutane fistels een zeldzaam fenomeen zijn. Van de 2.324 patiënten met een fistel ontwikkelden slechts vier patiënten een adenocarcinoom in de fistelgang gedurende een periode van 17 jaar. Dit impliceert dat de geschatte prevalentie van fistel-geassocieerde kanker in een willekeurige patiënt hoogstwaarschijnlijk niet hoger is dan 0,17%. De totale IBD-populatie in deze studie omvatte 6.058 Crohn patiënten. Slechts vier van deze 6.058 Crohn patiënten ontwikkelden een adenocarcinoom in de fistel. Dit staat ongeveer gelijk aan een geschatte prevalentie van 0,004%. We hebben geen maligniteiten kunnen vinden in niet Crohn-gerelateerde fistels. Aangezien de diagnose van een bijkomend adenocarcinoom in een al vastgestelde fistel lastig te stellen is, moet men er ondanks het feit dat het een zeldzame complicatie is toch op bedacht zijn.

### Dunne darm kanker

Het focus in de literatuur ligt voornamelijk op het ontwikkelen van dikke darm kanker bij IBD-patiënten. Minder bekend is dat Crohn-patiënten daarnaast ook een verhoogd risico hebben op het ontwikkelen van dunne darm kanker.[2-4] **Hoofdstuk IV** licht dit nader toe aan de hand van drie patiënten met de ziekte van Crohn. Dit hoofdstuk benadrukt het belang van volledige diagnostiek om een verdenking op de ziekte van Crohn te bewijzen. Indien er onvoldoende reactie is op de ingestelde therapie dient tevens de diagnose dunne darm kanker overwogen te worden in de differentiaal diagnose. Op basis van deze serie patiënten concluderen we dat in een patiënt die onder behandeling is voor Crohn in het terminale ileum en persisterende symptomen heeft ondanks adequate therapie, men bedacht moet zijn op kanker. Daarnaast stellen we ook vast dat een Computed Tomography (CT)-scan niet de aangewezen methode is voor het vaststellen van de ziekte van Crohn en dunne darm kanker. Endoscopie met histologische biopten is de gouden standaard voor patiënten die verdacht worden van de ziekte van Crohn. Tevens dient bij deze patiënten zelfs explorerende chirurgie overwogen te worden om dunne darm kanker uit te sluiten.

## IBD-gerelateerde darmkanker

*Epidemiologie*

Darmkanker is een van de meest gevreesde complicaties van IBD en is verantwoordelijk voor ongeveer 10-15% van alle sterfgevallen in IBD.[2] De exacte omvang van het risico op darmkanker blijft een punt van discussie. Initiële studies komen voornamelijk vanuit tertiaire verwijzingscentra, die in het algemeen patiënten met een ernstigere ziekte behandelen. De frequent geciteerde meta-analyse uit 2001 laat een cumulatieve incidentie van darmkanker bij colitis ulcerosa patiënten zien van 2% na 10 jaar, 8% na 20 jaar en 18% na 30 jaar ziekteduur.[2] Recente populatiestudies laten echter een veel lager risico zien variërend van 1/500 tot 1/1600 patiënten per jaar.[5] **Hoofdstuk V** geeft een overzicht en werpt een kritische blik op de recente literatuur met betrekking tot het risico op IBD-gerelateerde darmkanker. Wegens inconsistenties in de gepubliceerde studies, blijft het daadwerkelijke risico een discussiepunt en is het onzeker of we het daadwerkelijke risico op IBD-gerelateerde darmkanker nu juist onder-, of overschatten. Geografische verschillen, alsmede verschillen in locale behandelingsstrategieën en methodologische fouten bemoeilijken een correcte interpretatie van gepubliceerde studies. Bovendien kunnen de lagere incidentie getallen een gevolg zijn van succesvolle behandelstrategieën, zoals 5-ASA onderhoudstherapie en dysplasie surveillance programma's. Degelijke kennis van de algemene epidemiologie van darmkanker in IBD-patiënten is belangrijk als we de klinische praktijk willen verbeteren en de basis van de surveillance richtlijnen willen versterken om darmkanker-gerelateerde morbiditeit en mortaliteit te verminderen.

*Risico analyses*

Surveillance colonoscopieën vormen momenteel de basis van een preventiestrategie voor darmkanker, en het verwijderen van de dikke darm (=colectomie) wordt achter de hand gehouden voor patiënten bij wie dysplasie of darmkanker wordt ontdekt. De kosteneffectiviteit van surveillance hangt af van het daadwerkelijke risico op IBD-gerelateerde CRC. Als het risico op IBD-gerelateerde darmkanker inderdaad laag is, dan moeten we ons afvragen of we wel door moeten gaan met het screenen van alle IBD-patiënten. Met deze gedachte hebben we een case-control studie uitgevoerd in Nederland (**hoofdstuk VI**). In dit onderzoek laten we zien dat het risico op het ontwikkelen van IBD-gerelateerde darmkanker erg laag is in algemene ziekenhuizen (0,04% per jaar). Bovendien tonen we aan dat dit risico voor de hele IBD-populatie in Nederland 0,05% per jaar bedraagt. Tevens hebben we verschillende sterke risicofactoren voor IBD-gerelateerde darmkanker aangetoond, waaronder oudere leeftijd, langere ziekteduur van IBD, langere ziekte duur van primaire scleroserende cholangitis, en de aanwezigheid van pseudopoliepen. Daarnaast vonden we een beschermende rol voor het gebruik van immunosuppressiva en anti-Tumor Necrosis Factor Alpha (anti-TNFα).

Gezien het lage risico op darmkanker in deze IBD-populatie, ondanks het feit dat slechts 12% van de patiënten deelnam aan een surveillance programma, is het op basis van onze resultaten onzeker of surveillance wel noodzakelijk is voor alle IBD-patiënten. Parameters die leiden tot vroegtijdige ontwikkeling van darmkanker in zowel tertiaire verwijzingsziekenhuizen als in algemene ziekenhuizen moeten onderzocht worden om patiënten te kunnen selecteren bij wie vroegtijdig met surveillance gestart dient te worden.

### Surveillance

In **hoofdstuk VII** hebben we de patiënt-, en ziekte-karakteristieken van IBD-gerelateerde darmkanker onderzocht in een nationaal cohort van IBD-patiënten in 78 algemene ziekenhuizen. Onze resultaten laten zien dat een groot aantal IBD-gerelateerde darmkankers reeds ontstaat voor de aanbevolen start van surveillance. Oudere leeftijd ten tijde van de diagnose van IBD was een risicofactor voor snelle ontwikkeling van colorectale kanker na het ontstaan van de IBD. Patiënten die deelnamen aan een surveillance programma bleken significant betere tumoreigenschappen te hebben vergeleken met patiënten die niet opgenomen waren in een dergelijk programma. Dit benadrukt allereerst het belang om surveillance te verrichten. Bovendien zou een subgroep van patiënten geïdentificeerd moet worden, die behoefte heeft aan een eerdere start van surveillance. Dienovereenkomstig raden wij aan om eerder te starten met surveillance. In patiënten boven de leeftijd van 45 jaar ten tijde van IBD diagnose raden wij aan direct met surveillance te starten. Bovendien is een betere registratie van het begin van IBD-gerelateerde symptomen noodzakelijk. Het aanpassen van de surveillance richtlijnen en het identificeren van patiënten die eerder moeten starten met surveillance kan leiden tot een eerdere diagnose van darmkanker en een betere prognose.

#### *De zware last van darmkanker surveillance*

In **hoofdstuk VIII** zijn we nader ingegaan op de verbetering van surveillance richtlijnen. Surveillance voor alle IBD-patiënten gaat gepaard met onnodige lasten en kosten. Op basis van de risicofactoren die we in onze case-control studie hebben aangetoond (**hoofdstuk VI**), hebben we een predictiemodel ontwikkeld voor individueel gerichte risicostratificatie voor het starten van surveillance in IBD-patiënten in algemene ziekenhuizen. Naar aanleiding van onze resultaten raden we aan om in patiënten met een risico van 0,2% of hoger elke 3 jaar een surveillance colonoscopie te doen. Na verdere validatie kan dit model artsen ondersteunen in de beslissing wel of niet te starten met surveillance.

#### *Mucosale ontsteking terwijl de patiënt klinisch in remissie is*

Ontsteking is een bekende risicofactor voor het ontwikkelen van darmkanker. Echter, klinische symptomen vormen geen goede maatstaf voor de ziekteactiviteit en mucosale ontsteking kan aanwezig zijn zonder aanwezigheid van enige klinische symptomen. Het is onbekend of de behandelstrategie aangepast dient te worden als een patiënt, die klinisch in remissie is,

mucosale ontsteking blijkt te hebben. Bovendien is het onbekend of wel of niet ingrijpen tot een beter ziekteverloop leidt. **Hoofdstuk IX** laat zien dat een groot aantal patiënten, ondanks klinische remissie, toch ontsteking van de mucosa heeft. Aanvullend laten we zien dat een groot gedeelte van de patiënten zonder enige teken van activiteit tijdens endoscopie, toch histologische inflammatie heeft. De drijfveer om inflammatie te behandelen in patiënten die klinisch in remissie zijn is laag in de praktijk. In 39% van de patiënten geneest de mucosale ontsteking spontaan. Desondanks is asymptomatische ontsteking, hetzij endoscopisch hetzij histologisch, geassocieerd met een ernstigere mucosale ontsteking bij controle twee jaar later. Echter, we konden geen slechter beloop van de ziekte aantonen voor deze patiënten gedurende onze onderzoeksperiode van 7 jaar. We concluderen dat verder onderzocht moet worden of het klinisch van belang is alle patiënten met mucosale ontsteking te behandelen voor verbetering van de lange termijn prognose. Dit aangezien we geen voordeel van actieve behandeling konden aantonen en een groot gedeelte spontaan leek te genezen.

*Asymptomatische ontsteking als een valkuil van surveillance colonoscopieën*

Actieve mucosale ontsteking is één van de valkuilen van surveillance colonoscopieën. Laaggradige dysplasie is histologisch moeilijk te onderscheiden van regeneratieve veranderingen ten gevolge van inflammatie met als gevolg een grote mate van verschil in mening tussen de diverse pathologen.[6-9] Daarom kan de histologische beoordeling van surveillance biopten zeer moeilijk zijn wanneer er een actieve ontsteking van de mucosa is. In **hoofdstuk IX** hebben we aangetoond dat twee derde van de IBD-patiënten die in klinische remissie is toch mucosale ontsteking heeft. **Hoofdstuk X** beschrijft de resultaten van een prospectief gerandomiseerde studie, die het effect van het behandelen van patiënten met een lage dosis corticosteroïden voorafgaand aan surveillance colonoscopieën heeft onderzocht. Het doel van de studie was om inflammatie van de mucosa te proberen te verminderen, hetgeen een positief effect zou kunnen hebben op de histologische beoordeling van dysplasie. Allereerst, in overeenstemming met de resultaten van hoofdstuk IX, bevestigen we dat twee derde van de patiënten in klinische remissie mucosale ontsteking heeft. We tonen aan dat een korte kuur corticosteroïden inderdaad de ziekteactiviteit in de individuele biopten vermindert. Bovendien was er een trend dat corticosteroïden leiden tot een verminderde maximale ernst en uitbreiding van de ontsteking per patiënt. In tegenstelling tot voorgaande studies, lijken corticosteroïden in staat om ontsteking te verminderen. Verder onderzoek is noodzakelijk om de juiste dosis en duur van de behandeling te bepalen ter optimalisering van de histologische beoordeling van dysplasie in surveillance biopten.

## DEEL 2: DE VISIE VAN PATIËNTEN OP HUN ZIEKTE EN DE GEASSOCIEERDE RISICO'S

### Patient empowerment en gezamenlijke besluitvorming

De visie van patiënten als een onderdeel van patient empowerment (= het mondiger maken van patiënten) en gezamenlijke besluitvorming ("shared decision-making"), worden steeds belangrijker in de behandelstrategieën van chronische ziektes zoals IBD.[10-15] Het is bekend dat patiënten meer therapietrouw zijn als ze actief betrokken worden in de besluitvorming omtrent hun ziekte en de behandeling daarvan.[16,17] Therapieontrouw is een belangrijke oorzaak voor opvlammingen van de ziekte in IBD-patiënten.[18] Gezamenlijke besluitvorming kan daarom gebruikt worden om patiënten voor te lichten over het belang van therapietrouw. **Hoofdstuk XI** beschrijft een grootschalige patient empowerment studie om de voorkeur van IBD-patiënten met betrekking tot hun rol in de besluitvorming van hun behandelingsopties te bepalen. Deze patient empowerment studie laat zien dat IBD-patiënten graag een actieve rol hierin spelen. Het is daarom een uitdaging om deze gezamenlijke besluitvorming in de toekomst te implementeren in de zorg van IBD-patiënten. Verder wetenschappelijk onderzoek is noodzakelijk om de visie van artsen hierop te onderzoeken en een model te ontwikkelen voor implementatie hiervan in de dagelijkse praktijk. Ons onderzoek toont aan dat IBD-patiënten klaar zijn om gezamenlijke besluitvorming in te voeren ter verbetering van hun behandelingstrategie.

### Wat patiënten weten van hun ziekte en de geassocieerde risico's

De mening van IBD-patiënten en adequate kennis van hun ziekte, de behandeling en de geassocieerde risico's en complicaties zijn van groot belang om weloverwogen beslissingen te kunnen nemen over de behandeling van hun ziekte. Echter, er is slechts beperkte data beschikbaar over de kennis van IBD-patiënten betreffende hun ziekte, het risico op darmkanker, het risico van colonoscopieën en hun visie op de huidige aanbevelingen om een colectomie te ondergaan wanneer laaggradige dysplasie is gevonden bij een surveillance coloscopie. Met een landelijke onderzoek tonen we in **hoofdstuk XII** aan dat IBD-patiënten onvoldoende geïnformeerd zijn over hun ziekte. De meerderheid van de IBD-patiënten bleek zich niet bewust van de lokalisatie van de ziekte in de darm. Daarnaast bleek men een verkeerd beeld te hebben van hun levensverwachting, risico op darmkanker en de mogelijke voordelen van colonoscopieën. Veel patiënten dachten dat ze een hoger risico op darmkanker hebben dan in de literatuur staat beschreven en slechts een paar patiënten leken bereid om de huidige aanbevelingen op te volgen (i.e. colectomie) als er premaligne afwijkingen worden gevonden. Over het algemeen vinden patiënten dat er een hoog risico op het ontwikkelen van kanker moet zijn voordat ze bereid zijn een colectomie te ondergaan. Onze bevindingen impliceren dat de voorlichting van patiënten verbeterd dient te worden om hen op een juiste manier te kunnen betrekken in de besluitvorming rondom hun ziekte. Een IBD-patiëntenvereniging

kan daarbij een belangrijke rol spelen. Deze resultaten rechtvaardigen de ontwikkeling van een model voor gezamenlijke besluitvorming in de klinische praktijk van IBD-patiënten zoals in het vorige hoofdstuk is beschreven.

In **hoofdstuk XIII** hebben we de visie van IBD-patiënten met betrekking tot behandelingsgeinduceerde risico's en voordelen van anti-TNFα onderzocht. Samenvattend was dit de eerste studie die laat zien dat IBD-patiënten een verkeerd beeld hebben van de doeltreffendheid van anti-TNFα en dat ze mogelijk de daarbij behorende risico's verkeerd inschatten. Bovendien tonen we opnieuw aan dat patiënten beslissingen over hun behandeling dienen te nemen zonder te beschikken over de juiste informatie. Opvallend is dat patiënten pas bij een zeer hoge kans op remissie bereid zijn de behandelingsgeïnduceerde risico's van anti-TNFα te accepteren. Vroegtijdige start met anti-TNFα is de enige behandeloptie met een succespercentage waarbij patiënten bereid zijn de risico's op bijwerkingen te accepteren.

### Therapietrouw en de invloed van de ziekte op het dagelijks leven

In **hoofdstuk XIV** worden de resultaten van een landelijk patient empowerment onderzoek naar de therapietrouw van IBD-patiënten en de invloed van de ziekte op het dagelijks leven beschreven. In tegenstelling tot voorgaande studies, laat deze studie een hoge therapietrouw zien onder IBD-patiënten die lid zijn van de patiëntenvereniging voor Crohn en Colitis Ulcerosa Nederland (CCUVN). De resultaten met betrekking tot de therapietrouw impliceren dat lidmaatschap van een patiëntenvereniging de therapietrouw bevordert. Daarnaast wordt duidelijk dat IBD-patiënten hun kwaliteit van leven als slecht beoordelen.

## CONCLUSIES EN AANBEVELINGEN VOOR DE TOEKOMST

In conclusie presenteert dit proefschrift een herziene benadering van complicaties in IBD. Allereerst tonen we aan dat het risico op IBD-gerelateerde darmkanker laag is en we laten zien dat de surveillance richtlijnen toe zijn aan verandering. We stellen voor om te starten met individueel gerichte surveillance en een onmiddellijke start van surveillance in patiënten > 45 jaar ten tijde van het stellen van de IBD diagnose. Gezien het grote aantal patienten met mucosale ontsteking tijdens surveillance colonoscopieën, zou een korte kuur met een lage dosis corticosteroïden voorafgaand aan de surveillance colonoscopie overwogen kunnen worden. Dit om de mucosale ontstekingsactiviteit te verminderen en de histologische beoordeling van biopten ten aanzien van laaggradige dysplasie te verbeteren.

Ten tweede tonen we aan dat IBD-patiënten slecht op de hoogte zijn van hun ziekte, de behandeling en de geassocieerde risico's. Patiënten moeten actiever in de besluitvorming van hun ziekte betrokken worden. Lidmaatschap van een IBD-patiëntenvereniging is daarom

aanbevolen voor alle IBD-patiënten om de patiëntenvoorlichting te verbeteren, patiënten te helpen bij de besluitvorming omtrent hun ziekte, en de therapietrouw te bevorderen. Bovendien moeten artsen getraind worden om patiënten in het besluitvormingsproces te betrekken. Verder wetenschappelijk onderzoek dient zich te richten op het verbeteren van de voorlichting van patiënten en zou eveneens de rol van verpleegkundigen in het proces van de gezamenlijke besluitvorming kunnen onderzoeken.

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# Curriculum Vitae
# Bibliography
# PhD Portfolio

# Curriculum Vitae

The author of this dissertation was born on January 21st, 1985 in Mijnsheerenland, The Netherlands. After graduating from high school (gymnasium) at the Chr. S.G. Johannes Calvijn, Rotterdam in 2003, Judith started medical school at the Erasmus University Medical Center, Rotterdam. In 2005, Judith was invited to join a Master of Science (MSc) Program in Clinical Research at the Netherlands Institute for Health Sciences (NIHES), Rotterdam. As a part of this MSc-program she studied a summer at Harvard School of Public Health, Harvard, Boston, MA, USA. In November 2005, she started a research project at the Department of Gastroenterology and Hepatology of the Erasmus Medical Center, Rotterdam under supervision of prof. dr. E.J. Kuipers and dr. C.J. van der Woude. Among others she did a voluntary internship at the Department of Gastroenterology and Hepatology at Dartmouth-Hitchcock Medical Center, Lebanon, NH and White River Junction VAMC, VT, USA. In 2007, she received the Mark van Blankenstein award for best student of the Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam. In September 2007, she received her masters' degree in medicine and continued her research in a PhD-program. In August 2008, she graduated as Master of Science in clinical research and was consequently registered as Master of Science in epidemiology (Epidemiologist degree A) in 2009. Judith started her clinical rotations in February 2010 and is expected to graduate from medical school in 2011.

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Siegel CA, Schwartz LM, Woloshin S, Cole EB, Rubin DT, Vay T, Baars JE, Sands BE. When Should Ulcerative Colitis Patients Undergo Colectomy for Dysplasia? Mismatch Between Patient Preferences and Physician Recommendations Inflamm Bowel Dis. 2010; Feb 23 [Epub ahead of print]

Baars JE, Siegel CA, van 't Spijker A, Markus T, Kuipers EJ, van der Woude CJ. Inflammatory bowel disease patients are insufficiently educated about the basic characteristics of their disease and the associated risk of colorectal cancer. Digestive and liver disease 2010; May 15 [Epub ahead of print]

Baars JE, van der Woude CJ. Are colorectal cancer rates in IBD lower than we think? Accepted for publication in: Clinical Dilemma's in Inflammatory Bowel Disease 2, Irving P, Ramptom D, Shanahan F, Siegel C (ed), chapter 46, Wiley-Blackwell England

Baars JE, Vogelaar L, Wolfhagen FHW, Biermann K, Kuipers EJ, van der Woude CJ. A short course of corticosteroids prior to surveillance colonoscopy to decrease mucosal inflammation in inflammatory bowel disease patients: results from a randomized controlled trial. Journal of Crohn's and Colitis (2010), doi:10.1016/j.crohns.2010.07.011

Baars JE, van der Woude CJ, Colorectal carcinoma complicating inflammatory bowel disease. The Annals of Gastroenterology & Hepatology, *in press*

Baars JE, Nuij VJAA, Oldenburg B, Kuipers EJ, van der Woude CJ. Two third of patients with inflammatory bowel disease in clinical remission has asymptomatic mucosal inflammation. *Submitted for publication*

Baars JE, Kuipers EJ, Erkelens GW, van Haastert M, Nicolaï JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early occurrence of colorectal cancer in inflammatory bowel disease patients; a nationwide long-term survey. *Submitted for publication*

Baars JE, Looman CWN, Steyerberg EW, Beukers R, Tan ACITL, Weusten BLAM, Kuipers EJ, van der Woude CJ. The risk of inflammatory bowel disease related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Submitted for publication*

Baars JE, Looman CWN, Steyerberg EW, Beukers R, Tan ACITL, Weusten BLAM, Kuipers EJ, van der Woude CJ. A colorectal cancer-risk prediction model for inflammatory bowel disease patients in general hospitals: a first step towards individualized surveillance-strategies. *Submitted for publication*

Baars JE, Thijs JC, Bac DJ, Kuipers EJ, van der Woude CJ. Small bowel carcinoma mimicking Crohn's disease: a case series. *Submitted for publication.*

Baars JE, Kuipers EJ, Dijkstra G, Hommes DW, de Jong DJ, Stokkers PCF, Oldenburg B, Pierik M, Wahab PJ, van Bodegraven AA, van der Woude CJ, and the initiative for Crohn and Colitis. Malignant transformation of perianal- and enterocutaneous fistulas occurs rarely: Results of 17 years of follow-up from The Netherlands. *Submitted for publication*

# PhD Portfolio

## Summary of PhD training and teaching

| | |
|---|---|
| Name PhD student: Judith E. Baars | PhD period: 2007-2010 |
| Erasmus MC Department: | Promotor: prof.dr. E.J. Kuipers |
| Gastroenterology and hepatology | Supervisor: dr. C.J. van der Woude |

### 1. PhD training

| | Year | Workload |
|---|---|---|
| **General courses** | | |
| - Biomedical English Writing and Communication | 2008 | 112 hours |
| - English presentation course (Erasmus University, Rotterdam) | 2008 | 10 hours |
| **Specific courses** | | |
| - Master of Science Program in Clinical Research at the Netherlands Institute for Health Sciences (NIHES), Rotterdam | 2005-2008 | |
| **Attended seminars and workshops** | | |
| - "Regionale themabijeenkomst over gastro-enterologie en hepatologie voor huisartsen", March 14, 2007, Rotterdam | 2007 | 4 hours |
| - 2nd Young ICC research meeting, September 26, 2007, Utrecht | 2007 | 7 hours |
| - The 6th Erasmus Endoscopy Day, September 6-7, 2007 Rotterdam | 2007 | 16 hours |
| - Young Investigator Workshop, ASNEMGE, UEGW, October 28, 2007, Paris, France | 2007 | 8 hours |
| - Department seminars (weekly) | 2007/2008 | 60 hours |
| - Department journal club | 2007/2008 | 18 hours |
| - Erasmus Gastroenterology Day, January 17, 2008, Rotterdam | 2008 | 8 hours |
| - Consultatieavond "interessante Crohn casuïstiek", January 22, 2008, Rotterdam | 2008 | 4 hours |
| - Regionale themabijeenkomst over gastro-enterologie en hepatologie voor huisartsen, March 4, 2008, Rotterdam | 2008 | 4 hours |
| - ICC minisymposium, "zorg rond zwangerschap bij patiënten met een inflammatoire darmziekte", September 23, 2008, Amersfoort | 2008 | 6 hours |
| - The 7th Erasmus Endoscopy Days, september 25-26, 2008, Rotterdam | 2008 | 16 hours |
| - Autumn symposium CPO "Quality of Life and Quality of Care"", December 2, 2008, Rotterdam | 2008 | 4 hours |

| Oral Presentations | | |
|---|---|---|
| - The Incidence of IBD-associated Colorectal Carcinoma in non-academic hospitals in the Netherlands. IBDay symposium on IBD for (pediatric) Gastroenterologists and internists, November 15, 2007, Rotterdam, The Netherlands. | 2007 | 10 hours |
| - The risk of colorectal carcinoma in IBD patients is limited in non-tertiary cohorts: preliminary results of a nationwide long-term survey. Dutch society of Gastroenterology & Hepatology (NVGE), March 14, 2008,Veldhoven, The Netherlands | 2008 | 18 hours |
| - The risk of Colorectal Carcinoma in IBD patients. Department of Gastroenterology & Hepatology, Erasmus MC, July 4, 2008, Rotterdam, The Netherlands | 2008 | 12 hours |
| - Early occurrence of colorectal carcinoma in IBD patients in non-tertiary cohorts: results of a nationwide long-term survey. Dutch society of Gastroenterology & Hepatology (NVGE), October 3, 2008, Veldhoven, The Netherlands | 2008 | 12 hours |
| - Low frequency of Inflammatory Bowel Disease-related colorectal carcinoma (CRC) in non-tertiary centers: final results of a nationwide long-term survey. ECCO, February 6, 2009, Hamburg, Germany (oral poster presentation) | 2009 | 14 hours |
| - A short course of corticosteroids prior to surveillance colonoscopy to diminish mucosal inflammation in inflammatory bowel disease patients: results from a randomized controlled trial. Gastroenterology & Hepatology (NVGE), October 8, 2010, Veldhoven, The Netherlands | 2010 | 12 hours |
| - Two third of patients with inflammatory bowel disease in clinical remission has asymptomatic mucosal inflammation. Gastroenterology & Hepatology (NVGE), October 8, 2010, Veldhoven, The Netherlands | 2010 | 12 hours |
| - Malignant transformation of perianal- and enterocutaneous fistulas occurs rarely: Results of 17 years of follow-up from The Netherlands. Gastroenterology & Hepatology (NVGE), October 8, 2010, Veldhoven, The Netherlands | 2010 | 12 hours |
| **Poster presentations** | | |
| - International differences in patient perceptions of the benefits and risks of infliximab. United European Gastroenterology Week, October 29, 2007, Paris, France | 2007 | 32 hours |
| - High level of adherence to therapy in Dutch patients with inflammatory bowel disease. United European Gastroenterology Week, October 29, 2007, Paris, France | 2007 | 28 hours |

| | | |
|---|---|---|
| - Patients with decreased quality of life are insufficiently educated about their disease and associated risks. ECCO, February 27, 2008, Lyon, France | 2008 | 29 hours |
| - Impact of decreased quality of life in inflammatory bowel disease patients on disease-related behavior. ECCO, February 27, 2008, Lyon, France | 2008 | 34 hours |
| - High level of adherence to therapy in Dutch patients with inflammatory bowel disease. ECCO, February 27, 2008, Lyon, France | 2008 | 24 hours |
| - The risk of colorectal carcinoma in IBD patients is limited in non-tertiary cohorts: preliminary results of a nationwide long-term survey. ECCO, February 27, 2008, Lyon, France | 2008 | 30 hours |
| - Impact of decreased quality of life in inflammatory bowel disease patients on disease-related behavior. Digestive Disease Week, May 21, 2008, San Diego, CA, USA | 2008 | 24 hours |
| - High level of adherence to therapy in Dutch patients with inflammatory bowel disease. Digestive Disease Week, May 18, 2008, San Diego, CA, USA | 2008 | 24 hours |
| - The risk of colorectal carcinoma in IBD patients is limited in non-tertiary cohorts: preliminary results of a nationwide long-term survey. Digestive Disease Week, May 19, 2008, San Diego, CA, USA | 2008 | 28 hours |
| - Patients with decreased quality of life are insufficiently educated about their disease and associated risks. Digestive Disease Week, May 18, 2008, San Diego, CA, USA | 2008 | 24 hours |
| - Early occurrence of colorectal carcinoma in IBD patients in non-tertiary cohorts: results of a nationwide long-term survey. United European Gastroenterology Week,October 20, 2008, Vienna, Austria (poster of distinction) | 2008 | 34 hours |
| - Patients' perspectives on current guidelines of surveillance colonoscopy in IBD. United European Gastroenterology Week October 20 2008, Vienna, Austria | 2008 | 28 hours |
| - Low frequency of Inflammatory Bowel Disease-related colorectal carcinoma (CRC) in non-tertiary centers: final results of a nationwide long-term survey. ECCO, February 6, 2009, Hamburg, Germany (highly commended poster) | 2009 | 34 hours |

| Other accepted abstracts on scientific conferences | | |
|---|---|---|
| - Zelinkova Z, Baars JE, Markus T, Kuipers EJ, van der Woude CJ. Female perception of the quality of life differs from male inflammatory bowel disease patients. United European Gastroenterology Week, October 2007, Paris, France (poster presentation) | 2007 | 8 hours |
| - Siegel CA, Schwartz LM, Woloshin S, Cole E, Rubin D, Bunnag A, Vay T, Baars JE, Sands BE. When should ulcerative colitis patients undergo colectomy for dysplasia? Mismatch between patient preferences and physician recommendations. Digestive Disease Week, May 2008, San Diego, CA, USA (poster presentation) | 2008 | 12 hours |
| - Zelinkova Z, Baars JE, Markus T, Kuipers EJ, van der Woude CJ. Female perception of the quality of life differs from male inflammatory bowel disease patients. Digestive Disease Week, May 2008, San Diego, CA, USA (poster presentation) | 2008 | 7 hours |
| - Baars JE, Kuipers EJ, Beukers R, Tan A, Weusten B, Casparie MK, van der Woude CJ. Low frequency of Inflammatory Bowel Disease-related Colorectal Carcinoma (CRC) in non-tertiary centers: final results of a nationwide long-term survey. Dutch society of Gastroenterology & Hepatology (NVGE), March 2009, Veldhoven, The Netherlands (oral presentation) + Digestive Disease Week, May 2009, Chicago, IL, USA (oral presentation) | 2009 | 24 hours |
| - Mooiweer E, Baars JE,Lutgens MW, Siersema PD, Kuipers EJ, Oldenburg B, van der Woude CJ. Colorectal cancer in Inflammatory Bowel Disease: a comparison between large cohorts from referral centers and general hospitals. Dutch society of Gastroenterology & Hepatology (NVGE), March 2010, Veldhoven, The Netherlands (oral presentation) + Digestive Disease Week, May 2010, New Orleans, LA, USA (poster presentation) | 2010 | 8 hours |
| **National conferences** | | |
| - Dutch society of Gastroenterology & Hepatology (NVGE), March 22-23, 2007, Veldhoven, The Netherlands | 2007 | 20 hours |
| - Dutch society of Gastroenterology & Hepatology (NVGE), March 13-14, 2008, Veldhoven, The Netherlands | 2008 | 22 hours |
| - Dutch society of Gastroenterology & Hepatology (NVGE), October 2-3, 2008, Veldhoven, The Netherlands | 2008 | 22 hours |
| - Dutch society of Gastroenterology & Hepatology (NVGE), October 7-8, 2010, Veldhoven, The Netherlands | 2010 | 30 hours |

| | | |
|---|---|---|
| International conferences | | |
| - 15th United European Gastroenterology Week "UEGW 2007", October 17-31, 2007, Paris, France | 2007 | 28 hours |
| - 3rd congress of ECCO- Inflammatory bowel diseases 2008, February 28 - March 1, 2008, Lyon, France | 2008 | 24 hours |
| - Digestive Disease Week, May 17-22, 2008, San Diego, CA, USA | 2008 | 40 hours |
| - 16th United European Gastroenterology Week "UEGW 2008" October 18-22 2008, Vienna, Austria | 2008 | 28 hours |
| - 4th congress of ECCO- Inflammatory bowel diseases 2009, February 5-7, 2009, Hamburg, Germany | 2009 | 24 hours |
| Other<br>Peer review activities: | | |
| - Annals of Internal medicine | 2009 | 20 hours |
| - European Journal of Gastroenterology & Hepatology | 2009/2010 | |
| - Digestive and liver disease | 2010 | |
| Editorial board: | | |
| - World Journal of Gastrointestinal Pharmacology & Therapeutics | 2010 | 12 hours |

## 2. Teaching

| | **Year** | **Workload** |
|---|---|---|
| Tutoring | | |
| - Supervising medical students (2nd - 4th year) in extracurricular research activities | 2008-2010 | 90 hours |

# Acknowledgements

# Dankwoord

Het schrijven van een proefschrift gaat met vallen en opstaan. Ik ben dan ook veel dank verschuldigd aan de mensen die hierin met mij zijn meegegaan en mij telkens weer hebben geholpen bij het opstaan. Ik kijk met veel plezier terug naar mijn leerzame, maar vooral ook geweldige tijd als onderzoeker op de afdeling Maag-, Darm-, en Leverziekten (MDL) in het Erasmus MC, Rotterdam. Een aantal personen wil ik hieronder graag in het bijzonder bedanken:

**Promotor: prof.dr. E.J. Kuipers**

Beste Ernst, al vroeg in mijn studie nam je mij onder je hoede als mijn tutor in het kader van mijn MSc-programma en liet je me vroegtijdig kennis maken met het vakgebied van de MDL. Na een uitgebreide kennismaking met alle subafdelingen van de MDL, was ik al snel verkocht en ben ik voortijdig van start gegaan met mijn onderzoek. Ik wil je graag hartelijk bedanken voor je enthousiasme en je betrokkenheid bij al mijn studies. Met een kritische blik wist je de diverse onderzoeken altijd weer naar een hoger niveau te tillen. Daarnaast heb ik je motiverende woorden, je vaak vaderlijke adviezen en de hulp die je me geboden hebt om ervaring in het buitenland op te doen zeer gewaardeerd. Het was fijn dat ik altijd bij je terecht kon voor raad en daad! Ik hoop in de toekomst nog veel van je te mogen leren.

**Copromotor: dr. C.J. van der Woude**

Beste Janneke, zonder jou was dit proefschrift er uiteraard nooit gekomen. Jarenlang heb ik als een "waakhond" voor je deur gezeten en de nodige sociale controle over en weer kon daardoor dan ook niet ontbreken. Vanaf het begin af aan heb je me veel vrijheid en vertrouwen gegeven en me mijn eigen gang laten gaan. Naast alle zakelijke besprekingen, was er ook voldoende tijd voor gezelligheid en vooral ook voor persoonlijke interesse. Je overgrote enthousiasme, maar vooral ook je werklust en klinische blik werkten zeer aanstekelijk! Ik heb ontzettend veel van je geleerd en heb veel bewondering voor de manier waarop je de IBD-groep binnen het Erasmus MC de afgelopen jaren hebt opgezet en uitgebreid. Dank je wel voor alles en ik kijk erg uit naar verdere samenwerkingsprojecten!

**Promotiecommissie**

De leden van de kleine commissie: prof.dr. J.F. Lange, prof.dr. D.W. Hommes, en prof.dr. E.W. Steyerberg, wil ik hartelijk bedanken voor het beoordelen van mijn proefschrift. De overige leden van de grote commissie: prof.dr. D.J. van Leeuwen, prof.dr. J.L.C.M. van Saase, prof.dr. J.J. van Busschbach, en dr. B. Oldenburg, wil ik graag danken voor het plaatsnemen in mijn promotiecommissie.

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