Colorectal Cancer in Inflammatory Bowel Disease:
Towards an improved surveillance guideline

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“The Road goes ever on and on
Down from the door where it began.
Now far ahead the Road has gone,
And I must follow, if I can,
Pursuing it with eager feet,
Until it joins some larger way
Where many paths and errands meet.
And whither then? I cannot say”

J.R.R. Tolkien

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CHAPTER 1

General Introduction

BACKGROUND AND AIM

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, are chronic disorders with varying phenotypes and disease severity. The worldwide incidence and prevalence are rising[1]. In the Western world, the incidence and prevalence are up to 8-14/100,000 and 120-200/100,000 persons, respectively, for ulcerative colitis and 6-15/100,000 and 50-200/100,000 persons, respectively, for Crohn's disease[2]. The incidence in the Netherlands is 8-10/100,000 person years for ulcerative colitis and 6-7/100,000 person years for Crohn's disease[3,4]. It is estimated that around 90,000 Dutch inhabitants had IBD by the end of 2003[5], which makes IBD, in order of magnitude, comparable to diseases such as breast cancer, sporadic colorectal cancer and dementia.

One of the most feared long-term complications of IBD is colorectal cancer. Arnold Bargen was one of the first to recognize the association between "chronic ulcerative colitis" and malignant disease[6]. In his paper published in 1928 in the *Archives of Surgery*, he reported 20 cases from the Mayo Clinic with colorectal cancer and "chronic ulcerative colitis". A condition that he believed was caused by a microbial infection. Strikingly, he already reported characteristics of the disease that are presently known as risk factors for IBD-associated colorectal cancer. He went into detail on polyposis of the colon. It is unlikely that he meant adenomatous polyps, which were at that time not yet considered as precursor lesions for sporadic colorectal cancer, but it appears that he described post-inflammatory polyps, which were first associated with colorectal cancer in IBD by Rutter et al. almost eight decades later[7]. Others, including us, subsequently reproduced this result, which will be discussed in **Chapter 6**. Bargen also reported that patients were young when diagnosed with colorectal cancer, which has frequently been reproduced in the recent literature, including our own data. The final paragraph of Bargen's paper strikes the essence of this thesis: "*Malignant disease superimposed on chronic ulcerative colitis offers a grave prognosis. Operation, even if the malignant condition is discovered fairly early, yields discouraging results. One must then consider medical treatment. The only hope, it seems, is preventive treatment, that is, the cure of the colitis and the removal of the polyps.* This sentence was written almost 90 years ago and, despite medical advances, the prognosis of IBD-associated colorectal cancer still is worse than that of sporadic CRC[8].

Moreover, the first part of the last sentence also holds true 85 years after publication. It is current best medical practice to prevent colorectal cancer in IBD by colonoscopic surveillance to detect asymptomatic cancer or precancerous dysplastic lesions, and to treat patients with chemopreventive measures. When our group started studies on IBD-related CRC in 2006, the focus was on IBD patients for whom surveillance guidelines had failed. Data were collected on all IBD-associated CRC cases in 7 academic hospitals in The Netherlands and we found that approximately 20% of patients developed cancer at an earlier time than official guidelines recommended starting surveillance. In an attempt to explain this shortcoming, the evidence for these guidelines was evaluated. This showed us that most guideline recommendations were based on expert opinion. The main reason for this was that a randomized controlled trial demonstrating the benefit of colonoscopic surveillance had not and will not be performed because it is generally believed that colonoscopic

surveillance is the most optimal tool to detect neoplasia in IBD patients. Therefore, medical ethical committees are unlikely to approve study designs in which surveillance is withheld from individuals at risk of IBD-associated CRC. Furthermore, neoplasia takes years to develop and only in a minority of patients. Thus, a large number of unselected patients should be followed-up for decades in order to reach endpoints such as neoplastic lesions. Therefore, our evidence is derived from non-randomized cohort studies, retrospective data and case-control series. The guidelines and expert opinions that drive them are based on these data.

The aim of this thesis is to provide better evidence for colonoscopic surveillance in IBD in order to improve guidelines. In the following, this will be outlined in more detail.

1.Surveillance efficacy

The guidelines by the British Society of Gastroenterology (BSG)[9] and the American Gastroenterological Association (AGA)[10] advice starting colonoscopic surveillance after 8 or 10 years of disease symptoms in all IBD patients with evidence of prior colitis. The goal is to detect neoplasia in a pre-invasive phase or invasive cancer at an early stage to prevent colorectal cancer related mortality. Over the years, we have encountered several patients at the University Medical Center Utrecht, who developed CRC shortly after IBD diagnosis. For these patients the start of surveillance after 8 years of disease symptoms was clearly too late. In **Chapter 2** we report a cohort of 149 patients with IBD-associated colorectal cancer from 7 university medical centers in The Netherlands in which surveillance guidelines as they were published in 2006 were applied[11,12]. We looked critically at time intervals between onset of symptoms or IBD diagnosis as starting point, and colorectal cancer as endpoint. We detected a significant proportion of patients who developed cancer before the start of surveillance[13].

In general, it is important to establish the effectiveness of cancer surveillance in any disorder prior to launching a surveillance program. However, the evidence for the effectiveness of colonoscopic surveillance in IBD patients is limited. A Cochrane systematic review[14] published in 2006 concluded that no clear evidence was available that surveillance indeed prolongs survival in patients with extensive colitis. Nonetheless, there is indirect evidence that surveillance detects cancer at an early stage. The latter is mainly based on the paper by Choi et al.[15] In **Chapter 3** we present additional evidence that surveillance could benefit colitis patients.[16]

2. Colorectal cancer risk and high-risk groups

An often-cited reason for not following guidelines is that cost-effectiveness is unproven, the yield compared to committed resources is thought to be low and recent studies have suggested that the incidence of colorectal cancer in IBD in the past decade is decreasing[17] . The landmark study by Eaden et al published in 2002 in *Gut* reported cumulative risks of colorectal cancer in ulcerative colitis patients of 2%, 8%, and 18% after 10, 20, and 30years of disease[18]. These numbers are substantial compared to the 5% lifetime risk of sporadic colorectal cancer in the general population and were the basis for the surveillance guidelines of the BSG and the AGA published in 2002-2003[11,12]. However, in 2006, both Rutter[19] et al. and Jess et al.[20] independently reported cumulative risks of colorectal cancer of 8% and 2%,

respectively, after 30 years of disease. Obviously, these are much lower risks when compared to the meta-analysis by Eaden et al.[18] The same lower risk of developing CRC in IBD was seen in studies that reported standardized incidence ratios, which are ratios of observed colorectal cancer in the investigated cohort divided by the number of colorectal cancer cases that could be expected in the general population of the same gender, age and person years. In 1990, Ekbom et al. published a standardized incidence ratio of 5.7 for colorectal cancer in ulcerative colitis[21]. They also reported a standardized incidence ratio of 5.6 for Crohn's colitis patients[22]. However in 2009, in an update of the ulcerative colitis and Crohn's disease cohorts combined, Soderlund et al.[17] reported a standardized incidence ratio of only 2.3. These trends prompted us to investigate the risk of colorectal cancer in Crohn's and ulcerative colitis over the past decades in a new meta-analysis that is reported in **Chapter 4**. We pooled results of all patients with colitis (both ulcerative colitis and Crohn's colitis) and found a standardized incidence ratio of 1.7 [1.2-2.3; 95%CI] when we included the newest population based studies (*Lutgens et al. 2013, IBD; in press*). We also calculated cumulative risks of 1%, 2% and 5% at 10, 20 and 30 years of disease, respectively. These risks are comparable to the above-mentioned studies of Jess and Rutter, but also shows that the standardized incidence ratios and cumulative risks that are being reported in the last decade are lower than those which were found in reports from the 1980's, 1990's and the meta-analysis by Eaden et al. Nonetheless, in subgroups of IBD patients significantly higher risks of developing CRC are observed. In our meta-analysis we were able to estimate standardized incidence ratios and cumulative risks in patients with extensive colitis. The standardized incidence ratio in patients with extensive ulcerative colitis was found to be 6.9 [1.9-11.9; 95%CI] and cumulative risks in this subset were 2%, 12% and 21% at 10, 20 and 30 years of disease duration, respectively. IBD patients with concomitant primary sclerosing cholangitis also have an increased risk of CRC. Our group previously reported a cumulative risk of 31% after 20 years of disease in these patients[23]. Thus, the risks are substantially higher in individuals with extensive IBD and concomitant primary sclerosing cholangitis. Recent studies have provided various risk and protective factors for colorectal cancer in IBD. Longer disease duration[18,24], extensive disease[21,22,24], severity of histologic inflammation[25,26], primary sclerosing cholangitis[24,27], family history of CRC[28--31], post-inflammatory polyps[7,31] and colonic stenosis in ulcerative colitis[7] have all been associated with a higher colorectal cancer risk, while using 5-ASA[32], thiopurines[33], NSAIDS[31], and a normal colono-scopic appearance[7] have been reported to be protective factors for colorectal cancer in Crohn's and ulcerative colitis.

The updated BSG guideline from 2009 has already incorporated some of these factors to determine surveillance intervals[9]. We fully support this approach, but also feel that more studies are needed to collect evidence that the currently used stratification with corresponding different surveillance intervals for low, intermediate and high-risk groups are indeed justified. In **Chapter 5 and 6**, we report two studies in which high-risk patients are identified and we provide a risk score to differentiate between low and high-risk IBD patients. In collaboration with the University Hospital Leuven we developed a prediction model for high-risk patients and propose a modification of the BSG risk stratification from 2009.

3. Cost-Effectiveness

The evidence for the cost-effectiveness of colonoscopic surveillance in IBD is thin and based on data that predates current updated surveillance guidelines[34]. As mentioned above, the BSG took a risk profiling approach in the latest update of their surveillance guideline. They stratified patients into low, medium and high-risk groups with corresponding surveillance intervals of 5-yearly, 3-yearly and annual surveillance. We performed a Markov analysis to compare this risk profiling approach of the BSG guideline to that of the AGA guideline. The AGA recommends annual surveillance only for patients with primary sclerosing cholangitis and leaves the choice to do surveillance every 1-3 years to each individual gastroenterologist based on known risk factors. **Chapter 7** reports our results and discusses the various concerns, e.g. the increased occurrence of interval cancers when longer intervals are employed.

Finally, in **Chapter 8** we summarize all our results, which can be found in Dutch as **Chapter 9**. The overall aim of this thesis was to provide evidence for the fine-tuning of colonoscopic surveillance in patients with colitis. We started with the observation that colorectal cancer may occur before the start of surveillance. We then assessed the risk of colorectal cancer in the patients with colitis, and discussed the effects of surveillance when survival is the endpoint. Finally, we identified patients at a high risk of developing colorectal cancer in IBD and ended with testing cost-effectiveness of the risk profiling approach.

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CHAPTER 2

High Frequency of Early Colorectal Cancer in Inflammatory Bowel Disease

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ABSTRACT

Background & Aim: To detect precancerous dysplasia or asymptomatic cancer, patients suffering from inflammatory bowel disease often undergo colonoscopic surveillance based on American or British guidelines. It is recommended to initiate surveillance after 8-10 years of extensive colitis, or after 15-20 years for left-sided disease. These starting points, however, are not based on solid scientific evidence. Our aim was to assess the time-interval between onset of inflammatory bowel disease (IBD) and colorectal carcinoma (CRC), and subsequently evaluate how many patients developed cancer before their surveillance was recommended to commence.

Methods: A nationwide automated pathology database (PALGA) was consulted to identify patients with IBD-associated colorectal carcinoma in 7 university medical centres in the Netherlands between January 1990 and June 2006. Data were collected retrospectively from patient charts. Time-intervals between onset of disease and cancer diagnosis were calculated in months.

Results: 149 patients were identified with confirmed diagnoses of IBD and CRC (ulcerative colitis n=89 / Crohn's disease n=59 / indeterminate colitis n=1). Taking *date of diagnosis* as entry-point, 22% of patients developed cancer before the 8 or 15-year starting points of surveillance, and 28% if surveillance would commence 10 or 20 years after diagnosis for extensive or left-sided disease respectively. Using *onset of symptoms* to calculate the time-interval, 17%-22% of patients would present with cancer prior to surveillance starting points.

Conclusions: These results show that the diagnosis of colorectal cancer is delayed or missed in a substantial number of patients (17-28%) when conducting surveillance strictly according to formal guidelines.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC). Eaden et al. showed cumulative risks of 2%, 8% and 18% after 10, 20 and 30 years of disease, respectively, for patients with ulcerative colitis[1]. Jess et al. found an increased standardized incidence ratio of 1.9 for CRC in Crohn's disease[2]. Although IBD-associated CRC only constitutes 1-2% of all colorectal carcinomas, it is a frequent cause of death in IBD patients[1].

IBD-associated colorectal carcinogenesis is characterized by an "inflammation-dysplasia-carcinoma" sequence[3] which differs from the "adenoma-carcinoma" sequence in sporadic CRC. High-grade or multifocal low-grade dysplasia indicate that the entire mucosal lining of the colon, exposed to chronic inflammation, is at increased risk of developing cancer[3;4], thereby heralding the rigorous advice of proctocolectomy. In order to prevent development of CRC, IBD patients are advised to undergo colonic surveillance aimed at detection of dysplasia or asymptomatic early CRC at a surgically curable stage. Surveillance guidelines currently most often followed are those defined by the American Gastroenterological Association (AGA)[5] and the British Society for Gastroenterology (BSG)[6].

These guidelines recommend to start surveillance after 8-10 years of disease in case of Crohn's disease or extensive ulcerative colitis, and after 15-20 years of disease in case of left-sided ulcerative colitis. Starting surveillance before these time intervals is not recommended. The evidence, however, on which this is based is poor. The aim of the present study was to assess the time intervals between the occurrence of IBD and CRC and to evaluate how often IBD-associated CRC occurred before the first surveillance colonoscopy is advised.

MATERIALS & METHODS

Study Population

PALGA, the nationwide network and registry of histo- and cytopathology[7] containing pathology reports generated in The Netherlands dating back to 1971, was used to search for patients with IBD-associated CRC. These reports are concluded with diagnostic terms in line with SNOMED® terminology. The PALGA database has complete nationwide coverage since 1990. Therefore a PALGA search for the time period of January 1990 until June 2006 in all Dutch university medical centres for synchronous or metachronous diagnoses of IBD and CRC was performed. The following combinations of search terms were used: ulcerative colitis AND adenocarcinoma, Crohn's disease AND adenocarcinoma, colon AND colitis AND adenocarcinoma, colon AND inflammation AND adenocarcinoma, colon AND chronic inflammation AND adenocarcinoma, colon AND idiopathic colitis AND adenocarcinoma, colon AND adenocarcinoma AND active inflammation.

Data collection

The following data were collected from patient charts: type of IBD, sex, age at IBD diagnosis, age at CRC diagnosis, date of IBD diagnosis, date of onset of symptoms attributable to IBD, date of CRC diagnosis, maximum extent of disease as seen on colonoscopy, maximum histological extent of disease, tumour location, tumour stage, history of colonic surgery or surgery during follow-up, history of 5-ASA medication,

concomitant primary sclerosing cholangitis (PSC). Charts were additionally scrutinized on whether or not patients had undergone surveillance colonoscopies based on formal guideline protocols[5;6] prior to diagnosis of CRC.

AGA and BSG colonic surveillance guidelines for patients with IBD

The differences between the AGA and BSG guidelines (Table 1) are small. In the British guidelines shorter colonoscopy intervals are recommended with every subsequent decade of disease, while in the American guidelines colonoscopy is advised every one to two years with no increment in frequency for longer disease duration. Initiation of surveillance after 15 years of left-sided colitis instead of 15 to 20 years is another small difference between the AGA and BSG guidelines, respectively.

Table 1. British Society of Gastroenterology Guidelines

1	Surveillance colonoscopies should be performed when the disease is in remission
2	All patients should have a screening colonoscopy after 8-10 years that will also clarify disease extent
3	Regular surveillance should begin after 8-10 years (from onset of symptoms) for pancolitis and after 15-20 years for left sided disease
4	As the risk of cancer increases exponentially with time, there should be a decrease in the screening interval with increasing disease duration. For patients with pancolitis, in the 2nd decade of disease a colonoscopy should be conducted every three years, every two years in the 3rd decade, and yearly by the 4th decade of disease
5	Two to four random biopsies specimens every 10 cm from the entire colon should be taken with additional samples of suspicious areas
6	Patients with primary sclerosing cholangitis (including those with an orthotropic liver transplant) represent a subgroup at higher risk of cancer and they should have annual colonoscopy

Statistical analysis

As entry point of follow-up the date of diagnosis of IBD as well as the date of onset of symptoms attributable to IBD were analysed separately. Intervals between these starting points and the date of diagnosing CRC were measured in months. From these data the percentages of patients were calculated that developed CRC before 8 or 15 years of disease duration for extensive or left sided colitis, respectively, or before 10 or 20 years of disease duration for extensive or left-sided colitis, respectively. Intervals of patients with Crohn's colitis were only compared with the 8 and 10 year intervals as there is no explicit distinction for extent of disease in the AGA and BSG guidelines for these patients. A similar approach was chosen for patients with unknown disease extent. Statistical analysis was done with SPSS for Windows software version 12.0.1.

RESULTS

Patients

Our search resulted in 166 patients, of which 17 were excluded, leaving 149 patients with IBD-associated CRC for analysis (Table 2). The reasons for exclusion were: no definite diagnosis of IBD (n=11), diagnosis of adenocarcinoma in the biopsy sample that could not be reproduced in the colectomy specimen (n=2), a focus of micro-carcinoid instead of adenocarcinoma (n=2), unknown date of IBD-diagnosis (n=1) and occurrence of CRC before IBD was diagnosed (n=1).

Table2. Patient characteristics

	IBD-CRC (n=149)	UC (n=89)	CD (n=59)	IC (n=1)
Male	89 (60%)	58 (65%)	29 (49%)	1 (100%)
Median age at diagnosis of IBD	29 (6-83)	30 (10-71)	29 (6-83)	70
Median age at onset of symptoms	28 (6-83)	28 (10-71)	29 (6-83)	67
Median age at diagnosis of CRC	49 (21-85)	49 (21-83)	50 (27-85)	77
Disease Extent				
Unknown (UC)		9 (10%)		0 (0%)
left-sided disease (UC)		14 (16%)		1 (100%)
extensive disease (UC)		66 (74%)		0 (0%)
Disease Extent				
unknown (CD)			10 (17%)	
<50% segmental colitis (CD)			17 (29%)	
>50% segmental colitis (CD)			14 (24%)	
pancolitis (CD)			18 (30%)	
PSC	19 (13%)	16 (18%)	3 (5%)	0 (0%)

IBD-CRC = Inflammatory Bowel disease associated colorectal cancer; UC = Ulcerative colitis; CD = Crohn's disease; IC = Indeterminate colitis; IBD = Inflammatory bowel disease; CRC = Colorectal cancer; PSC = Primary Sclerosing Cholangitis

Males were more frequently affected than females (male:female ratio of 3:2). Ulcerative colitis, (ileo)colonic Crohn's disease or indeterminate colitis were the underlying types of IBD in 60%, 39% and 1% of patients, respectively (Table 2). The median age at diagnosis of IBD-associated CRC was 49 years (range 21-85) and did not differ between ulcerative colitis and Crohn's disease patients. Concomitant PSC was found in 19 (13%) patients. In the majority of these patients (n=15) PSC occurred after IBD was diagnosed. Extensive disease (inflammation extending proximal of the splenic flexure) was found in 74% of patients with ulcerative colitis. In more than half (53%) of the patients with Crohn's disease more than 50% of the colonic mucosa was involved at one moment during follow-up.

Colorectal cancers

Multiple synchronous primary colorectal cancers were found in 9% of patients (n=14). In total 166 carcinomas were identified in 149 patients; 11 patients had two carcinomas and in three patients three tumours were found. The initial cause of diagnosis of CRC was surveillance colonoscopy in 25 (17%) cases of which 2 were index colonoscopies, thus only 23 patients were part of a surveillance program prior to CRC-diagnosis. All other diagnoses of CRC were made incidentally due to various causes (Table 3).

Table 3. Initial cause of CRC Diagnosis

	N	(%)
Surveillance colonoscopy	25	(17)
Non-surveillance colonoscopy	35	(23)
Increase of symptoms*	61	(41)
Incidental finding in colectomy specimen	20	(13)
Refractory disease	10	(7)
Proctectomy in IPAA procedure	1	(1)
Toxic Megacolon	1	(1)
Stenosis	1	(1)
Perforation after colonoscopy	1	(1)
Dysplasia	6	(4)
Suspected appendicitis**	1	(1)
Suspected acute cholecystitis**	1	(1)
Abnormal laboratory findings	4	(3)
Unknown***	2	(1)

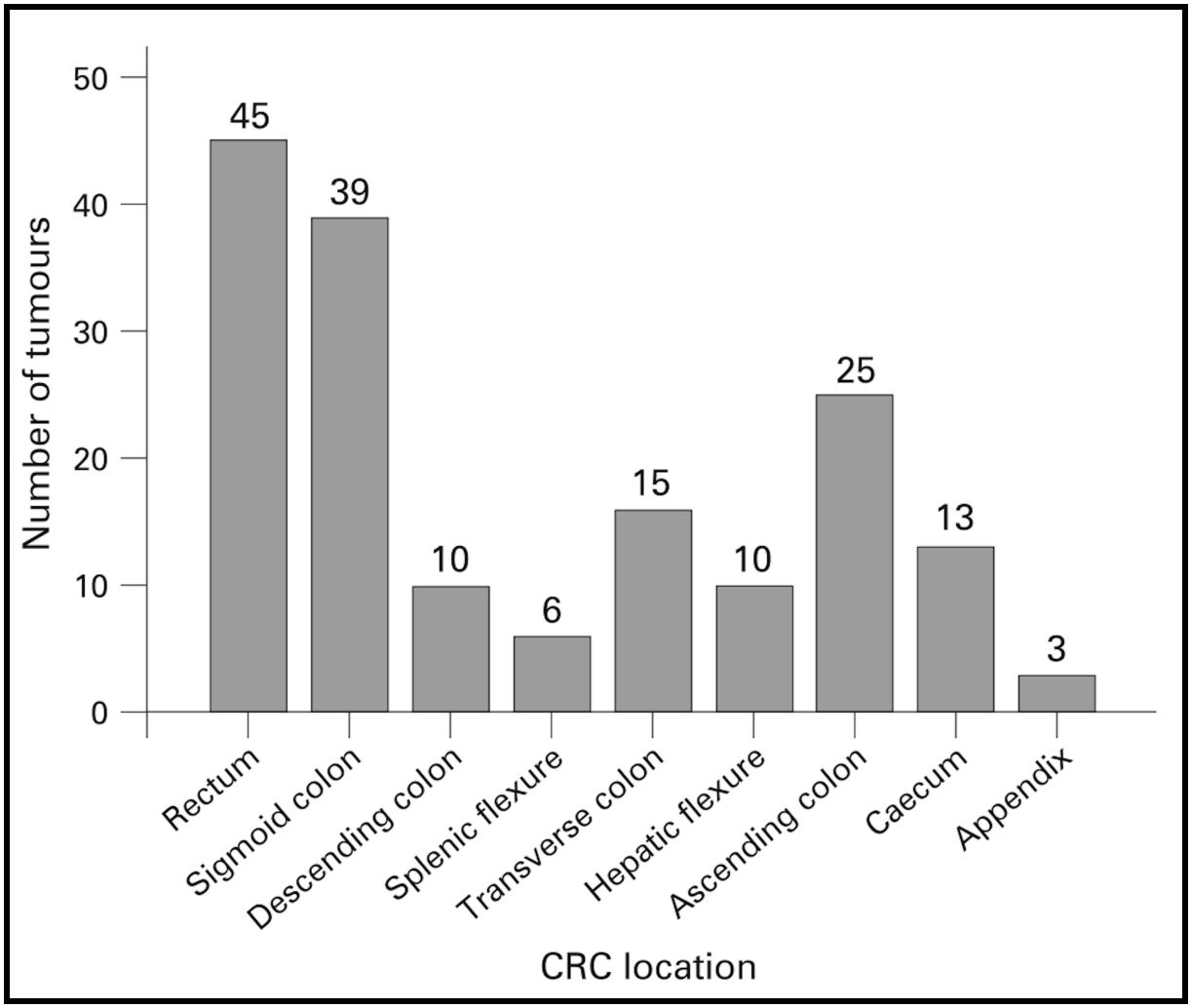
* symptoms include increase of abdominal pain, altered bowel habits with or without rectal blood loss

** CRC detected during laparotomy

*** referrals for proctocolectomy of which the initial cause of CRC diagnosis was irretrievable

Most cancers (51%) were located in the left colon (Figure 1), mainly rectum (27%) and sigmoid colon (24%). There was no difference between ulcerative colitis and Crohn's disease concerning left or right-sided tumour location (p=0.89). Almost all tumours, 160 out of 166, were found in colonic mucosa that was or had been inflamed. More than half of the patients (53%) had T3 tumours and 31 (18.6%) patients already had metastases when CRC was diagnosed (Table 4).

Figure 1 Colorectal cancer location and distribution throughout the colon



Tumour location in the colon of all 166 carcinomas in 149 patients. Bars represent number of tumours in corresponding region of the colon on the x-axis.

Table 4. Tumour Stage

	N	%
T stage		
Tis	13	7.8%
T1	19	11.4%
T2	21	12.7%
T3	89	53.6%
T4	11	6.6%
Tx	13	7.8%
Total	166	100.0%
N Stage		
N0	102	61.4%
N1	26	15.7%
N2	29	17.5%
Nx	9	5.4%
Total	166	100.0%
M Stage		
M0	103	62.0%
M1	31	18.7%
Mx	32	19.3%
Total	166	100.0%
AJCC stage		
0	13	7.8%
I	34	20.5%
II	50	30.1%
III	33	19.9%
IV	31	18.7%
unknown	5	3.0%
Total	166	100,0%

NOTE. 5 tumours not classifiable under AJCC Stage: 2 TxNoMo, 2 TxNxMx, 1 TxNxM0

Intervals between IBD and CRC

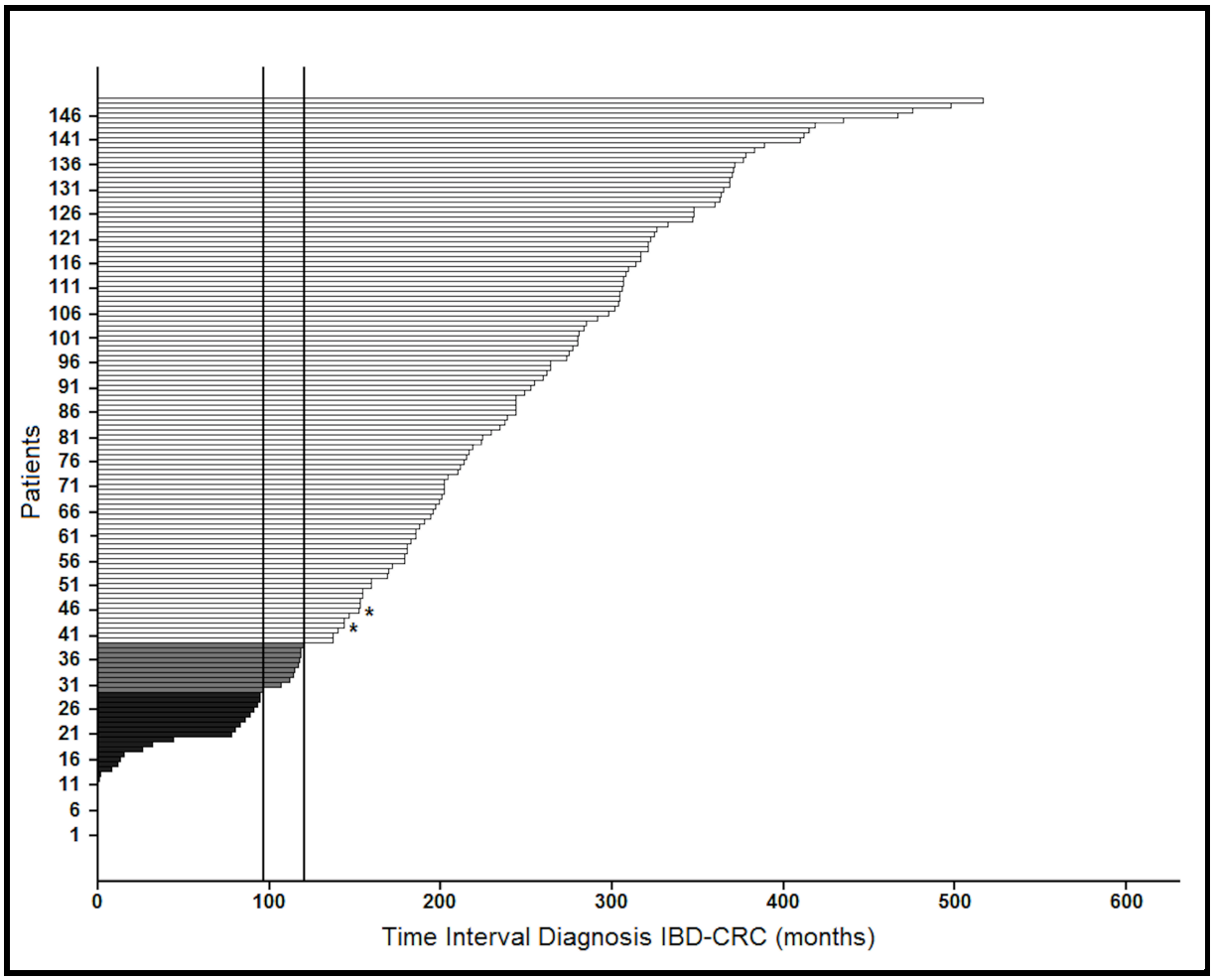
The intervals between diagnosing IBD and CRC varied from 0 to 45 years (Figure 2). We observed that 33 of 149 (22%) patients developed CRC before the first surveillance colonoscopy is recommended to take place when the surveillance guidelines of 8 or 15 years duration of disease are followed (Table 5). Ulcerative colitis, Crohn's disease and indeterminate colitis was the underlying type of IBD in 19, 13 and 1 patients, respectively. If the starting points of 10 or 20 years had been used, 41 CRCs in 149 patients (28%) would have developed CRC before surveillance (ulcerative colitis, Crohn's disease and indeterminate colitis in 25, 15 and 1 patients, respectively). If the *onset of symptoms* instead of *the moment of diagnosing* IBD is used as starting point of disease duration, as advocated by the BSG, 25 out of 149 (17%) patients would have developed CRC before 8 or 15 years of disease. Thirty-three of 149 patients (22%) would have developed CRC if the starting points of surveillance (10 and 20 years) had been used. In 11 patients IBD and CRC were diagnosed simultaneously. Seven of these patients had Crohn's disease and four had ulcerative colitis. If these 11 patients are excluded from analysis, then 15% of patients developed CRC before 8 or 15 years of disease duration, and 20% of patients before 10 or 20 years of disease duration. These percentages are 9% and 15% respectively with onset of symptoms as entry point.

Table 5. Analysis of IBD-CRC intervals in different subgroups

	8 l 15yr IBD-CRC interval	10 l 20yr IBD-CRC interval	8 l 15yr OoS-CRC interval	10 l 20yr OoS-CRC interval
All Cases				
CRC Before SPoS	33 (22%)	41 (28%)	25 (17%)	33 (22%)
CRC After SPoS	116 (78%)	108 (72%)	124 (83%)	116 (78%)
Total	149 (100%)	149 (100%)	149 (100%)	149 (100%)
Ulcerative Colitis				
CRC Before SPoS	19 (21%)	25 (28%)	14 (16%)	19 (21%)
CRC After SPoS	70 (79%)	64 (72%)	75 (84%)	70 (79%)
Total	89 (100%)	89 (100%)	89 (100%)	89 (100%)
Crohn's disease				
CRC Before SPoS	13 (22%)	15 (25%)	10 (17%)	13 (22%)
CRC After SPoS	46 (78%)	44 (75%)	49 (83%)	46 (78%)
Total	59 (100%)	59 (100%)	59 (100%)	59 (100%)

NOTE. All numbers for 8 l 15 IBD-CRC interval and 10 l 20 OoS-CRC interval are the same which is purely coincidental. Abbreviations used are SPoS, starting point of surveillance; OoS, onset of symptoms; IBD, inflammatory bowel disease; CRC, colorectal cancer

Figure 2 Time Intervals between Diagnosis of IBD and CRC



Bars represent time intervals between diagnosis of IBD and CRC in months for all individual 149 patients. The left vertical line indicates the starting point of surveillance at 8 years disease duration. The right vertical line indicates the starting point of surveillance at 10 years disease duration. Black bars represent the patients with "early" CRC before 8 years disease duration. Grey bars represent additional "early" CRC's before 10 years disease duration. An asterisk indicates a patient with left-sided colitis who developed CRC before 15 or 20 years disease duration.

DISCUSSION

This study demonstrates that a substantial part of all IBD-associated colorectal cancers occur before colonic surveillance should start according to BSG and AGA guidelines. Strict adherence to these guidelines will therefore lead to late detection of these "early" cancers, which may reduce the efficacy of colonic surveillance in IBD.

How were starting points of surveillance determined in the AGA and BSG guidelines? In the AGA surveillance guidelines[5] no specific reference to publications is given that support abstaining from surveillance during the first decade of IBD, thus we must assume this was based on expert opinion. The BSG guidelines[6] are to a large extent a derivative of the results of a meta-analysis performed by Eaden et al. Based on data of 19 studies[8-26], IBD-associated CRC risks of 2%, 8% and 18% for the respective disease durations of 10, 20 and 30 years were found. Furthermore,

Eaden and Mayberry state in the BSG surveillance guideline that CRC is rarely encountered when disease duration is less than 8-10 years. This statement is based on data dating back as far as the 60's[23;24;27-29]. Although relatively large numbers of carcinomas and person-years were included in the British meta-analysis, this study still has limitations. Two studies[9;10] in the meta-analysis included patients who had undergone subtotal colectomy for non-malignant indications, thereby eliminating the risk of cancer in the colon except the rectum. Moreover, 3 of 19 studies[12;17;22] excluded explicitly those patients who developed CRC within 5, 7 or 10 years of IBD duration. Despite these drawbacks, which artificially reduce the risk of CRC in the first 10 years after the onset of IBD, 73 of 394 colorectal cancers (19%) found in 16 of the 19 aforementioned studies[8;11-13;15-17;20-26] occurred within an IBD duration of less than 10 years. This percentage fits remarkably well in our range of 17-28%. However, this aspect of the meta-analysis is not taken into account in the BSG surveillance guidelines. The authors might have considered CRC in recent-onset IBD not related to the chronic inflammatory condition. Another possibility is that the cumulative risk of 2% in the first 10 years of disease was regarded too low for initiating colonic surveillance when seen from a cost-effectiveness point of view. Still, both our data and those of the meta-analysis show that approximately 20% of IBD-associated colorectal carcinomas occur in the first decade of IBD.

The AJCC tumour stage distribution (fifth edition) in our study population (table 3) did not differ from those in a population based cohort of more than 119000 patients of all types of colon cancer[30] and a population based cohort of more than 1300 sporadic colon carcinomas[31]. Hence, our data does not support the general notion of a more advanced stage of cancer at diagnosis in IBD patients.

Information about medication history was collected for this group of patients. This is especially interesting with regard to the possible antineoplastic effect of 5-ASA treatment[32]. However, the retrospective design of our data collection warrants us to be prudent with its interpretation. Not all physicians meticulously registered the exact duration of medication usage. Despite this drawback and the lack of a proper control group, it is interesting to note that 119 out of 139 (10 cases unknown) patients (86%) have used a 5-ASA preparation during the course of their disease. Of these 119 patients, 64 (54%) used 5-ASA medication for more than three-quarters of their disease duration. Nevertheless, all these patients developed CRC.

According to AGA and BSG guidelines IBD patients with concomitant PSC should have annual surveillance colonoscopy starting the day PSC is diagnosed. In our study population PSC was diagnosed in 19 cases (13%). These patients would have undergone immediate surveillance after diagnosing PSC so their first colonoscopy may have been performed earlier than 8/15 or 10/20 years. Correction of our data for PSC leads to small decreases in the percentages of patients with early CRC that would be missed if surveillance guidelines are followed. Instead of 22% of all patients, 20% would be missed when 8 and 15 year starting points had been applied.

The main clinical difference between sporadic and IBD-associated colorectal cancer is that the last occurs in patients with concurrent IBD. Other distinguishing clinical features are CRC development in individuals at a younger age and a higher rate of synchronous primary colorectal carcinomas[3]. A potential argument against our findings may be that the colorectal cancers, diagnosed within 10 years of onset of IBD, were in fact sporadic colorectal carcinomas. This seems very unlikely however,

because the median age of patients when CRC was diagnosed did not differ between the “early” and “late” carcinoma groups (47 years [21-83] vs. 49 years [28-85]) and almost all (38 of 41) “early” tumours were found in mucosa that was or had been inflamed endoscopically and/or histologically. Of three tumours data were lacking to fully ascertain inflammation of the surrounding mucosa. This was also the case in three of the “late” tumours.

In 11 of 149 patients (6.7%) IBD and CRC were diagnosed simultaneously. We decided to include these patients in the analysis for three reasons. Firstly, we believe that it is imprudent to exclude the possibility of developing CRC within 10 years of disease duration. Too much is still unknown about inflammation induced carcinogenesis to firmly assume that colorectal cancer does not develop within this time period. Secondly, the existence of asymptomatic colitis may have put a patient at risk without the patient or physician ever knowing. This could lead to an underestimation of disease duration. Finally, although we acknowledge that immediate surveillance would not have advanced the CRC-diagnosis in patients with synchronous diagnoses of CRC and IBD, it does support our notion that disease duration is not reliable to base surveillance guidelines on.

Onset of IBD-associated symptoms, instead of the actual diagnosis, may provide a better estimation of years at risk and therefore is advised by the BSG to use as starting point. Unfortunately, the date of onset of symptoms cannot always be retrieved and may give rise to recall bias. In the present study, the date of onset of IBD-associated symptoms was equal to the actual date of diagnosing IBD in little over half of our patients (52%). Furthermore, date of onset of IBD-associated symptoms and the date of the actual diagnosis differed less than one year in 74% of our patients. So, in only a quarter of our patients this had had some impact on timing of surveillance.

We must stress that our study was not designed to obtain data on prevalence and risk of CRC in the entire IBD population. The required population based cohort to answer this question is near impossible to obtain in the Netherlands due to a lack of defined health care districts and a large number of patients that remain under primary care at their general practitioner. This is especially the case for mild cases of IBD. A part of these patients never undergoes endoscopy with biopsies to confirm the diagnosis. Because our search was restricted to patients with confirmed diagnoses of IBD and CRC treated at university medical centres, our study group is not population-based. All our patients were primarily treated in, or were referred to, tertiary referral centres and therefore it is possible that our group of patients represents a subset of IBD patients with more severe disease than the general IBD population. Nevertheless, the present study provides important information on this particular subset of patients and identified all IBD patients who developed cancer over the past 15 years in this setting.

Well aware of the limitations of a retrospective study design, this design of this study was carefully chosen to fit our main aim. We were primarily interested in the time span between diagnosis of IBD and the diagnosis of CRC, and evaluate how often cancer occurred in the first decade of disease. This was found to be the case in approximately one-fifth of the patients in this study.

Current AGA and BSG guidelines are solely based on duration and extent of colitis, and the presence of PSC. The structure of surveillance guidelines after a fixed period of time seems to be somewhat rigid. The results of this study show that the

diagnosis of cancer is sometimes delayed when fixed starting points of surveillance are used. Not all IBD patients develop cancer though, and therefore annual or biannual colonoscopy might be overreaching for some. We advocate a structure that stratifies patients according to the risk of developing CRC. Of interest are other risk factors for IBD-associated CRC, such as severity of disease[33], early age of onset of IBD[15;20], family history of CRC[34-36] and pseudopolyps[37;38] which have not (yet) been incorporated in surveillance guidelines, but could help in predicting patients that have a higher risk than others. Very intriguing in this respect is a publication by Rutter et al[38]. which concludes that macroscopically normal looking mucosa on colonoscopy reduces the cancer risk to that of the general population. In this case surveillance could be reduced for this subset of patients. At present no predictive test exists for IBD-associated neoplasia with high positive and negative predicting values just using clinical and endoscopic features of IBD patients. Integration of these features with biomarkers of colorectal neoplasia may prove to be a fruitful approach for the future. A large prospective trial is needed in which all of these features are evaluated so that surveillance guidelines can be adjusted accordingly.

In summary, we identified 149 patients with IBD-associated CRCs. Implementation of the current BSG and AGA entry points for surveillance in our patient population may lead to delay in diagnosing colorectal cancer in approximately 20% of patients. Surveillance guidelines largely based upon disease duration therefore seem to be insufficient and need to be expanded.

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CHAPTER 3

Colonoscopic Surveillance Improves Survival after Colorectal Cancer Diagnosis in Inflammatory Bowel Disease

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ABSTRACT

Background: Colonoscopic surveillance provides the best practical means for preventing colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients. Strong evidence for improved survival from surveillance programs is sparse.

Objective: The aim of this study was to compare tumor stage and survival of IBD patients with CRC who were part of a surveillance program with those who were not.

Design & Setting: A nationwide pathology database (PALGA) was consulted to identify IBD patients with CRC seen in all eight university hospitals in The Netherlands over a period of 15 years.

Patients: Patients were assigned to the surveillance group when they had undergone one or more surveillance colonoscopies prior to a diagnosis of CRC. Patients who had not undergone surveillance served as controls.

Main outcome measurements: Tumor stage and survival were compared between the two groups.

Results: A total of 149 patients with IBD-associated CRC were identified. Twenty-three had had colonoscopic surveillance before CRC was discovered. The 5-year CRC-related survival rate of patients in the surveillance group was 100% compared to 74% in the non-surveillance group (p=0.042). In the surveillance group, only 1 patient died as a consequence of CRC compared to 29 patients in the control group (p=0.047). In addition, more early tumor stages were found in the surveillance group (p=0.004).

Conclusions: These results provide evidence for improved survival from colonoscopic surveillance in IBD patients by detecting CRC at a more favorable tumor stage.

INTRODUCTION

The increased risk of colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD) has been well documented [1,2] In an effort to detect dysplasia or early stage cancer, it is advised that patients should enter a surveillance program according to guidelines of the American Gastroenterological Association (AGA) [3] or the British Society of Gastroenterology (BSG) [4] . While not flawless, it is currently the best tool available to detect early stage neoplasia or prevent CRC in patients with IBD. The level of evidence for its effectiveness, however, is low and has only been studied in patients with ulcerative colitis (UC) [5] . The ideal setup to evaluate effectiveness of surveillance programs would be a randomized trial with CRC-related mortality as primary endpoint. Unfortunately, such a trial does not exist and probably never will be performed because of practical and ethical considerations [6] . Therefore, retrospective studies are probably the best alternative to assess effectiveness of colonoscopic surveillance.

A recent review by the Cochrane Collaboration [5] identified three studies that presented indirect evidence for improved survival from colonoscopic surveillance in UC patients [7-9] . These studies either had a low number of patients with IBD-associated CRC or a low number of patients in a surveillance program, which prevented the outcomes to reach statistical significance.

We recently reported on time intervals between the diagnosis of IBD and CRC in a large cohort of patients with IBD-associated CRC, collected in all university medical centers in The Netherlands using a nationwide pathology database [10] . The aim of the present retrospective study was to compare tumor stage and survival in this cohort between patients that were part of a surveillance program with those who were not.

MATERIALS & METHODS

Search Strategy

PALGA, the nationwide network and registry of histo- and cytopathology [11] , contains pathology reports generated in the Netherlands dating back to 1971. These reports are concluded with diagnostic terms in line with SNOMED® terminology and were used to search for patients with IBD-associated CRC. PALGA achieved nationwide coverage in 1990. For that reason, a search for the time period of January 1990 until July 2006 in all eight Dutch university medical centers for synchronous or metachronous diagnoses of IBD and CRC was conducted. The following combinations of search terms were used: ulcerative colitis AND adenocarcinoma, Crohn's disease AND adenocarcinoma, colon AND colitis AND adenocarcinoma, colon AND inflammation AND adenocarcinoma, colon AND chronic inflammation AND adenocarcinoma, colon AND idiopathic colitis AND adenocarcinoma, colon AND adenocarcinoma AND active inflammation. Only patients with a confirmed histological diagnosis of inflammatory bowel disease and CRC were included.

The PALGA search engine ensures patient privacy by supplying anonymous data. Only the patient's own physician was able to link PALGA identification codes to real patient identification codes. The treating physician in each university medical center subsequently supplied only first author with anonymous data. No personal patient data were recorded.

Data extraction

The following data were collected from patient charts by one investigator (ML): type of IBD, gender, age at IBD diagnosis, age at CRC diagnosis, date of onset of symptoms, date of IBD diagnosis, date of CRC diagnosis, date of start of surveillance, intervals between surveillance colonoscopies, date of end of follow-up, cause of death, tumor stage in the resection specimen or by radiological imaging if the patient was not operated, concurrent primary sclerosing cholangitis (PSC), existing co-morbidity, history of smoking and alcohol use, history of 5-ASA medication. A diagnosis of PSC had to be made with retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), or liver biopsy. Co-morbidity was defined as severe cardiac, severe pulmonary, severe renal, severe liver dysfunction, or malignancy other than CRC.

Surveillance criterion

A patient was assigned to the surveillance group when prior to CRC diagnosis at least one or more surveillance colonoscopies at regular intervals (every 1-3 years) had been performed. The remainder of the patients were assigned to the non-surveillance group and served as controls. The surveillance quality had to meet the standard which is described by current guidelines [3,4] . This entails the intent to detect neoplasia by taking 4 random biopsies every 10 cm of the colon in addition to targeted biopsies of suspicious areas during that colonoscopy. No attempt was made to compare surveillance colonoscopies with each other based on frequency or number of biopsies.

Patients who were under regular surveillance for multiple years, but for some reason had skipped one colonoscopy, were only assigned to the surveillance group if the longest lapse since the last colonoscopy was 3 years or less. In order to minimize selection bias, patients in whom the diagnosis of CRC was made by colonoscopy according to surveillance protocol for the first time (thus not yet enrolled in a surveillance programme), were not assigned to the surveillance group when the reason for this first surveillance colonoscopy was new or recurrent symptoms of disease.

Statistical Analysis

The chi-squared test, Fisher's exact test and student's *t* test were used where appropriate to compare patient characteristics between the two groups. Kaplan-Meier and Cox-regression analyses were employed for survival calculations. The primary study endpoints were CRC-related or overall death. The end of follow-up was either the end of study date (1st of July 2006) or date of death. When a patient was lost to follow-up, the date of the last visit to the hospital was recorded as end of follow-up. The Tarone-Ware test of equality of survival distributions was used to compare differences between survival curves. Tumor stages were grouped according to the sixth edition staging system of the American Joint Committee on Cancer (AJCC) [12,13] . The chi-squared test and Fisher's exact test were used where appropriate to compare tumor stages between the surveillance and non-surveillance groups. P-values <0.05 were considered statistically significant. SPPS software for windows version 14.0 was used for all statistical analyses.

RESULTS

Our search identified 166 patients, of which 17 were excluded. The reasons for exclusion were: no histological confirmed diagnosis of IBD (n=11), suspected adenocarcinoma in the biopsy sample that could not be reproduced in the colectomy specimen (n=2), a focus of micro-carcinoid instead of adenocarcinoma (n=2), unknown date of IBD-diagnosis (n=1) and occurrence of CRC before IBD was diagnosed (n=1). This left 149 cases for analysis. Twenty-three patients had undergone one or more surveillance colonoscopies prior to the diagnosis of CRC and were analyzed as the surveillance group. Surveillance was started after a median of 14.3 [std 8.0] years after histological diagnosis of IBD. CRC developed after a median of 6.4 years [range 1-21] after initiation of surveillance. The remaining 126 patients were assigned to the non-surveillance control group. Patient characteristics are shown in Table 1. No statistically significant differences were found between the two groups for any of the variables.

Table 1 Patient Characteristics

	Surveillance group N=23	Non-surveillance group N=126	p-value
IBD			
ulcerative colitis	18 (78%)	71 (56%)	0.053
Crohn's disease	5 (22%)	54 (43%)	
indeterminate colitis	0 (0%)	1 (1%)	
Gender			
male	17 (74%)	72 (57%)	0.132
female	6 (26%)	54 (43%)	
Co-morbidity	3 (13%)	29 (23%)	0.410
Median age at IBD-diagnosis	26 [9-50]	30 [6-83]	0.148
Median age at CRC-diagnosis	48 [38-71]	49 [21-85]	0.986
PSC	2 (9%)	17 (14%)	0.739
Mean interval between onset of IBD symptoms and diagnosis of CRC (months)	273 [15-541]	231 [0-536]	0.143
Mean follow-up time after CRC (months)	57 [0-188]*	51 [0-235]*	0.635

IBD = Inflammatory bowel disease; CRC = Colorectal cancer; PSC = Primary Sclerosing cholangitis
4 patients were lost to follow-up immediately after diagnosis of CRC and were not included in survival analyses

Follow-up after a diagnosis of CRC was complete for 114 (79%) patients until the study end date or death. Thirty-one (21%) patients were lost to follow-up. Four of these 31 patients, two in the surveillance group and two in the non-surveillance group were lost to follow-up immediately after diagnosis of CRC and were therefore excluded from the survival analyses.

Table 2 Multivariate Cox regression analysis: Mortality by CRC

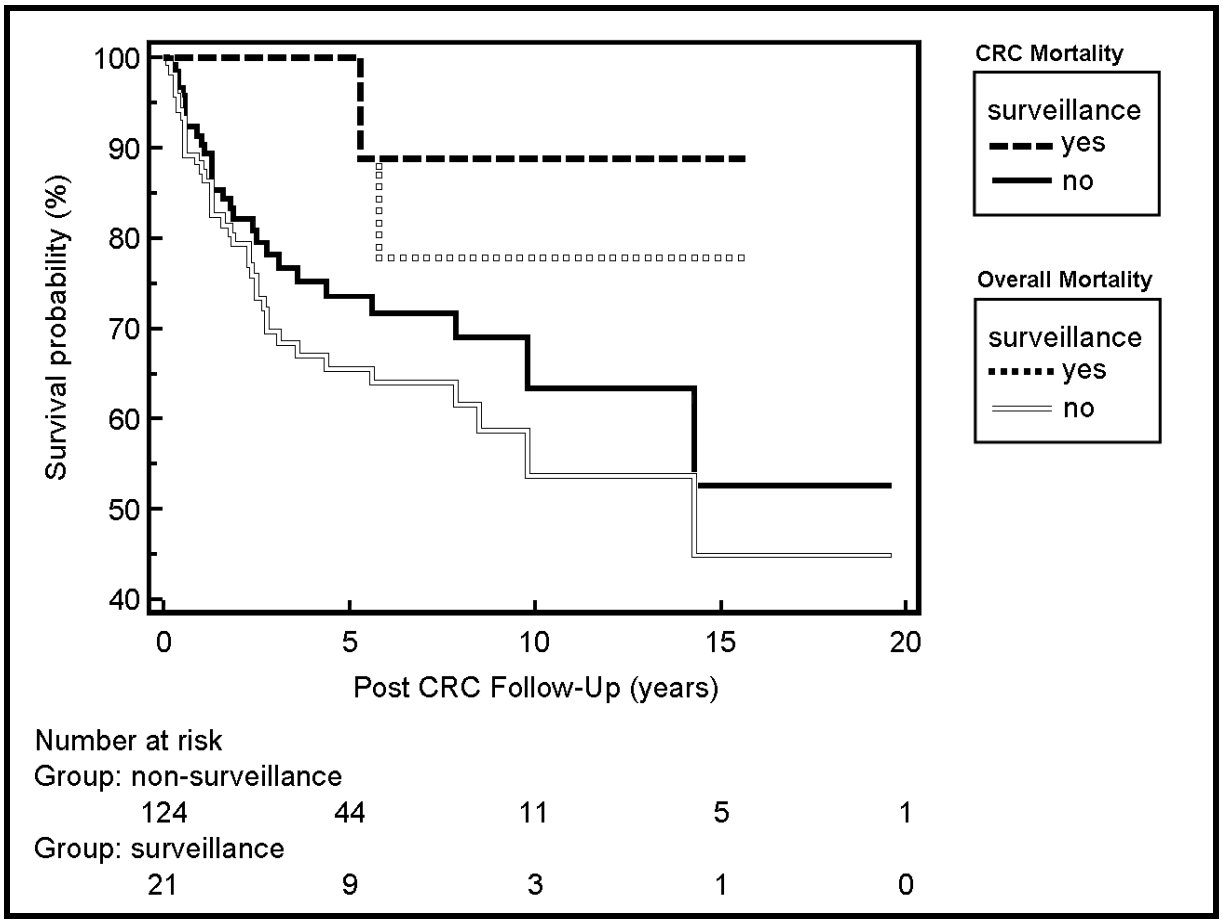
Variable	P-value	P-value*
Type of IBD	0.80	0.74
Age at CRC-diagnosis	0.55	0.71
Co-morbidity	0.74	0.64
Primary sclerosing cholangitis	0.16	0.10
Surveillance	0.10	0.08

CRC = Colorectal cancer; IBD = Inflammatory bowel disease;
*Exclusion of 11 patients with simultaneous diagnoses of IBD and CRC

Overall, 42 of 145 (29%) patients died. The cause of death was directly related to metastasized CRC in 30 patients. Of the remainder, six patients died from metastasis of a different primary tumor (cholangiocarcinoma (n=3), renal cell

tumor (n=1), urothelial carcinoma (n=1), primary tumor of the stomach (n=1)), and another six patients died after complications related to colectomy. In the surveillance group, only one patient died due to CRC compared to 29 patients in the non-surveillance control group (p=0.047). The overall 5-year survival rates in the surveillance group and the non-surveillance control group were 100% and 65%, respectively (p=0.029) (Figure 1). CRC-related 5-year mortalities were 0% and 26% in the surveillance and non-surveillance groups, respectively (p=0.042) (Figure 1).

Figure 1 Survival analysis for CRC-related and overall mortality



The Tarone-Ware test of equality of survival distribution was used to compare survival between the two groups. CRC-related mortality is presented by the solid squares and line. Overall mortality is presented by the outlined squares and line.
For CRC-related mortality the 5-year survival in the surveillance group (solid squares) was 100% compared to 74% in the non-surveillance group (solid black line) (P=0.029); the primary endpoint was date of death by CRC; cases were censored for date of end of study, date of death related to any other primary malignancy, date of death related to colectomy; date of death by any other cause, and date of lost to follow-up.
For overall mortality the 5-year survival in the surveillance group (outlined squares) was 100% compared to 65% in the non-surveillance group (outlined line) (P=0.042); the primary endpoint was date of death; cases were censored for date of end of study period and date of lost to follow-up.

Additionally, a multivariate Cox-regression analysis including type of IBD, concurrent PSC, age at CRC diagnosis, and co-morbidity as co-variables confirmed the association between colonoscopic surveillance and improved survival with reduced CRC-related mortality, however this did not reach statistical significance (p=0.10) (Table 2).

Eleven patients in the non-surveillance group were diagnosed with IBD and CRC simultaneously. Exclusion from analysis of these patients strengthens the

effect. The 5-year overall mortality remains 0% in the surveillance group and is 36% in the non-surveillance group (p=0.02). For CRC-related mortality these percentages are 0% compared to 29% (p=0.03). This effect also remains visible in the multivariate analysis, although again it is not statiscally significant (Table2).

In 10 out of 149 patients (7%) we did not have information about 5-ASA prescription. This leaves 139 for analysis of which 119 (86%) have used a 5-ASA preparation during the course of their disease. Of these 119 patients, 64 (54%) used 5-ASA medication for more than three quarters of their disease duration. Nevertheless, all these patients developed CRC despite 5-ASAs chemopreventive nature. As mentioned earlier, 4 out of 149 patients were excluded when evaluating survival because they were lost to follow-up directly after CRC diagnosis. Therefore, 135 patients remain for 5-ASA analysis between groups. Twenty patients were in the surveillance group and 115 in the non-surveillance group. All 20 patients (100%) in the surveillance group had used 5-ASA preparations during their disease. In the non-surveillance group, 96 out of 115 (77%) had used 5-ASA preparations. This difference showed a trend but was not statiscally significant (p=0.08). Furthermore, when included in the multivariate cox-regression analysis it is of no influence on survival (p=0.96) while the effect of surveillance (p=0.098) remains unchanged.

Tumor stages of the two groups are separately shown in Table 3. Tumors were staged by a pathologist on the resection specimen in 138 patients (93%) according to the TNM classification. Information on TNM stage could not be retrieved in 11 patients (7%) for the following reasons: not operated on because of metastatic disease (n=6), or fully detailed pathology report of resection specimen not retrievable (n=5). In patients from the surveillance group the observed number of lower stage tumors was higher than the expected number. This effect was statistically significant when Stage 0 and 1 tumors were compared to all higher stages between the two groups. In the surveillance group 12 patients (52%) had stage 0 and 1 tumors compared to 28 patients (24%) in the non-surveillance group (p=0.004). Moreover, the same effect was also observed in the opposite direction with a statistically significantly lower number of patients with Stages 3B-C and 4 tumors: four patients (17%) in the surveillance group compared to 48 patients (42%) in the non-surveillance group (p=0.049).

Table 3 Tumor Stages

AJCC	Tumor Stage	Non-surveillance N=121	Surveillance N=23	P-value
0	T in situ	9	2	0.689
1	T1, T2, N0, M0	19	10	0.008
2A	T3, N0, M0	40	4	0.135
2B	T4, N0, M0	2	1	0.409
3A	T1, T2, N1, M0	3	2	0.180
3B	T3, T4, N1, M0	14	2	1.000
3C	Any T, N2, M0	12	0	0.215
4	M1	22	2	0.367

NOTE. 5 tumors not classifiable under AJCC Staging: 2 TxNoMo, 2 TxNxMx, 1 TxNxM0

Despite surveillance, four cancers in the surveillance group were diagnosed as a consequence of new or altered symptoms of disease. These so called interval cancers had varying tumour stages: T1N0M0, T2N1M0, T3N0M0 and T4N0M0. The interval since last surveillance colonoscopy was 10, 14, 8 and 7 months respectively and the patients were on 1, 2, 1, and 3 yearly intervals of surveillance colonoscopies.

DISCUSSION

This series shows an improved survival in IBD patients who developed CRC and in whom colonoscopic surveillance was performed. It provides evidence showing the efficacy of surveillance on CRC-related mortality with sufficient numbers of patients with IBD-associated CRC. CRC-related mortality was significantly lower in the surveillance group, with a 5-year survival rate of 100% in the surveillance group and 74% in the non-surveillance group. This effect can be explained by the detection of earlier stage CRC in the surveillance group, which translates into a better prognosis.

This report adds to the relatively small body of evidence, indicating survival benefit through a surveillance strategy in ulcerative colitis. We feel that it is prudent to join the ulcerative colitis and Crohn's colitis data, because there is increasing evidence that the pathogenesis and natural behavior of inflammation-associated dysplasia in UC and CD does not differ, and the risk of CRC is increased in both [1,2] . A recent systematic review [5] by the Cochrane collaboration detected only three papers [7-9] that properly addressed the question of surveillance effectiveness for patients with ulcerative colitis. Other surveillance studies lacked valid control groups[14-20] or were not designed to answer this question [21] . The reviewers of the Cochrane paper concluded that all three publications pointed towards a beneficial effect of surveillance on survival, but that the evidence was indirect. Lashner and colleagues [7] showed an improved overall survival in the surveillance group, but were unable to show that this was secondary to a reduced CRC-related mortality. Likewise, they could not find a difference in tumor stage between the two groups. Choi and colleagues [8] published a small series of 41 patients who developed CRC associated with ulcerative colitis, of whom 19 were in a colonoscopic surveillance program and 22 were not. In their series, as in ours, CRC was detected at a significantly earlier stage in patients who had undergone colonoscopic surveillance. Karlen and colleagues [9] identified a trend towards a protective effect of colonoscopic surveillance.

The strength of the current series lies in the high number of cases with IBD-associated CRC available for analysis and the strict criteria for inclusion in the surveillance group. Moreover, no differences between the two groups in age at cancer diagnosis, length of follow-up, and interval between onset of IBD and CRC-diagnosis were found, eliminating confounding from differences in these variables (Table 1). The multivariate analysis confirmed the association between colonocopic surveillance and improved survival, but failed to reach statistical significance most likely due to a type II error resulting from multiple variables in the analysis (table 2). The putative additional effect of smoking or alcohol could not be evaluated in this analysis because of high percentages of missing values.

Selection is a potential bias that needs consideration. Patients who presented with diarrhea or rectal bleeding and subsequently were diagnosed with both IBD and CRC could very well have affected the observed results. These patients would not have participated in an endoscopic surveillance program and were probably only detected with IBD due to their CRC-related symptoms. Eleven patients in our series were simultaneously diagnosed with IBD and CRC. However, our results for CRC-related tumor stage and mortality between groups did not change when patients whose interval between diagnosis of IBD and CRC was less than one year were excluded from the analysis. This does not come as a surprise since these patients

were probably not different from the patient group that did not undergo surveillance. It seems likely that these individuals did not seek medical care for their condition because of absence of symptoms and presented some years after the start of the disease because of symptoms that were found to be (at least partly) CRC-related.
It is well recognized that 5-ASA is thought to be chemopreventive for neoplasia. We collected data on medication use in all patients. However the retrospective design of our data collection warrants us to be careful with its interpretation. Not all physicians meticulously registered the exact duration of medication usage, nor did we have insight into medication adherence.

Lead-time bias is known to influence screening and surveillance data [22] . However, lead-time bias only occurs if the intervention (in this case earlier tumor detection) does not affect the terminal event (in this case mortality by CRC). In the case of CRC, lead-time bias is probably not a significant problem, as earlier diagnosis of CRC at a more favorable stage does improve survival in a beneficial way [23,24] . Others have questioned the importance of lead-time bias in CRC screening studies as well [25] .

Because of the lack of randomization, volunteer bias might have influenced results. The patients in the surveillance group could have been more health conscious leading to an earlier diagnosis of CRC. In our study, however, the mean duration of disease until CRC detection was longer in the surveillance group (22.7 versus 19.3 years). Therefore, it is not very likely that volunteer bias played a major role in this study.

Four cancers in the surveillance group were found to be interval cancers. This has been observed by others as well [8] . We did not extract information on the exact number of biopsies for each surveillance colonoscopy separately and therefore cannot comment upon whether these interval cancers may be attributable to sub-optimal practice during the previous surveillance colonoscopy. The occurrence of altered bowel symptoms may lead to a diagnosis of CRC. Whether interval cancers are due to a failure of detection during previous colonoscopy or to a rapid progression of cancer is difficult to determine. Back-to-back colonoscopy in patients without IBD has shown that the miss rate for adenomas is 6-27%, which is, amongst others, depending on adenoma size [26] . In addition, in all four of these patients unifocal low grade dysplasia (LGD) had been diagnosed prior to the diagnosis of CRC in a part of the colon close to the location where subsequently CRC was detected. Therefore, either the CRC was missed at the previous colonoscopy or LGD had progressed towards CRC between the two colonoscopies. Most clinicians recommend colectomy for high grade dysplasia, however management for LGD is controversial. Only 5% of Dutch gastroenterologists recommend colectomy for unifocal LGD. A little under 30% of Dutch gastroenterologists recommend colectomy in case of multifocal LGD [27] .

Finally, referral center bias deserves attention. All included cases in this study were primarily treated in or referred to tertiary university medical centers, which may have lead to the introduction of bias towards patients with more severe disease. Regarding the level of risk of CRC in IBD patients, this kind of bias might be of major importance, but it is less clear how this may affect the main outcome of the present study since index and control patients all originate from referral hospitals. While it is true that the results from this study cannot be translated to the general IBD population unequivocally, to date no study exists comparing survival outcome

between IBD patients from referral centers and population based cohorts undergoing surveillance.

In conclusion, the patients in the surveillance group showed statiscally significant lower CRC related mortality and more favorable tumor stages. The evidence for improved survival in this paper strengthens the notion that colonoscopic surveillance in patients with longstanding IBD is beneficial and should be performed in patients with a presumed high risk profile.

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CHAPTER 4

Declining Risk of Colorectal Cancer in Inflammatory Bowel Disease: An Updated Meta-Analysis of Population Based Cohort Studies

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ABSTRACT

Background: Recently reported risks of colorectal cancer (CRC) in inflammatory bowel disease (IBD) have been lower than those reported before 2000. The aim of this meta-analysis was to update the CRC risk for ulcerative and Crohn's colitis, investigate time trends and identify high-risk modifiers.

Methods: The MEDLINE search engine was used to identify all published cohort studies on CRC risk in IBD. Publications were critically appraised for study population, Crohn's disease localization, censoring for colectomy, and patient inclusion methods. The following data was extracted: Total and stratified personyears at risk, number of observed CRC, number of expected CRC in background population, time period of inclusion, and geographical location.
Pooled standardized incidence ratios and cumulative risks for 10-year disease intervals were calculated. Results were corrected for colectomy and isolated small bowel Crohn's disease.

Results: The pooled standardized incidence ratio of CRC in all IBD patients in population-based studies was 1.7 [1.2-2.2 95%CI]. High-risk groups were patients with extensive colitis and an IBD diagnosis before age 30 years with standardized incidence ratios of 6.4 [2.4-17.5] and 7.2 [2.9-17.8], respectively. Cumulative risks of CRC were 1%, 2% and 5% after 10, 20 and more than 20 years disease duration, respectively.

Conclusions: The risk of CRC is increased in IBD patients, but not as high as previously reported and not in all patients. This decline could be the result of aged cohorts. The risk of CRC is significantly higher in patients with longer disease duration, extensive disease, and IBD diagnosis at young age.

INTRODUCTION

The association between inflammatory bowel disease (IBD) and colorectal carcinoma (CRC) is well documented, but reported risk estimates vary widely[1,2]. This is most likely due to differences in study design, study population and patient selection. The first meta-analysis on the risk of IBD-associated CRC calculated a cumulative risk of 2% at 10 years, 8% at 20 years and 18% at 30 years disease duration in ulcerative colitis patients[3]. Although these risks were based on studies with considerable differences in design and quality, they were used to justify surveillance strategies in patients with long-standing ulcerative colitis. Other meta-analyses haven been published since, all three on Crohn's disease[4-6]. These studies consistently reported an increased risk in patients with colitis, but all had weaknesses, such as combining results from population-based studies with referral centers[3,5], inclusion of case series[3], combining studies that were mainly updates of the same cohort (thus including the same patients twice)[5,6], inclusion of studies with Crohn's patients that only had ileal disease[4-6] or inclusion of patients after proctocolectomy[3-6]. Recently, new population-based data have been published suggesting that the risk of CRC is decreasing[7] or is not increased at all when compared to the general population[2,8]. These studies were not included in any of these meta-analyses.

The primary aim of the present study was to conduct an updated meta-analysis that minimized study heterogeneity with carefully selected studies on the risk of colorectal cancer in ulcerative and Crohn's colitis, and to investigate time trends and potential modifiers of the cancer risk.

MATERIALS & METHODS

Article search, inclusion and exclusion criteria

For this meta-analysis, we followed published guidelines for systematic reviews and meta-analyses as outlined by the PRISMA Statement[9]. The MEDLINE search engine was queried from 1949 till July 2011. Search terms and queries are listed in Table 1. Cross-reference searching in Web of Science was used for selected publications to identify additional studies. Finally, reference lists were manually screened.

We only included cohort studies that reported on the occurrence of CRC in patients with ulcerative colitis, Crohn's disease or both. For population-based studies the patient cohort had to be selected from a well defined geographical area and time period of inclusion. For referral centers all patients treated in a predefined time period had to be included. Eligible studies had to contain published data that allowed calculation of personyears at risk for CRC or had to report observed versus expected CRC numbers.

We excluded from the main risk analyses studies that did not censor personyears at risk for total or subtotal colectomy, studies that did not stratify personyears for isolated small bowel and colonic Crohn's disease, studies that based patient selection only on hospital discharge records, studies that focused on dysplasia progression exclusively, studies reporting on surveillance programs that excluded patients with short-disease duration, cancer mortality studies, survival studies after a diagnosis of CRC, case-control studies, case reports, case series, reviews, editorials and letters.

Table1 Search terms and query

Type of Search	Search Terms
TIAB	("carcinoma"[Title/Abstract] OR "cancer"[Title/Abstract] OR "malignancy"[Title/Abstract] OR "neoplasia"[Title/Abstract] OR "adenocarcinoma"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal cancer"[Title/Abstract] OR "colorectal malignancy"[Title/Abstract] OR "colorectal neoplasia"[Title/Abstract] OR "colorectal adenocarcinoma"[Title/Abstract] OR "intestinal carcinoma"[Title/Abstract] OR "intestinal cancer"[Title/Abstract] OR "intestinal malignancy"[Title/Abstract] OR "intestinal neoplasia"[Title/Abstract] OR "intestinal adenocarcinoma"[Title/Abstract] OR "rectal carcinoma"[Title/Abstract] OR "rectal cancer"[Title/Abstract] OR "rectal malignancy"[Title/Abstract] OR "rectal neoplasia"[Title/Abstract] OR "rectal adenocarcinoma"[Title/Abstract] OR colon carcinoma[Title/Abstract] OR colon cancer[Title/Abstract] OR colon malignancy[Title/Abstract] OR colon neoplasia[Title/Abstract] OR colon adenocarcinoma[Title/Abstract] OR rectum carcinoma[Title/Abstract] OR rectum cancer[Title/Abstract] OR rectum adenocarcinoma[Title/Abstract] OR "CRC"[Title/Abstract]) AND ("inflammatory bowel disease"[Title/Abstract] OR "IBD"[Title/Abstract] OR "ulcerative colitis"[Title/Abstract] OR "Crohn's disease"[Title/Abstract] OR "Crohn's"[Title/Abstract] OR "Crohn"[Title/Abstract] OR "Crohns disease"[Title/Abstract] OR "Crohns"[Title/Abstract] OR "Crohn"[Title/Abstract] OR "colitis ulcerosa"[Title/Abstract] OR "Morbus Crohn"[Title/Abstract])
MeSH	("colorectalneoplasms"[MeSH Terms] AND "inflammatory bowel diseases"[MeSH Terms]) AND "colorectal neoplasms"[MeSH Terms]

TIAB=Title / Abstract; MeSH=Medical Subject Headings

Quality Assessment

Three authors (ML, FV and BO) independently read all selected publications. A simplified study scoring form was used, including three criteria: 1) type of population: population-based or referral center 2) censoring personyears at risk for colectomy 3) stratifying personyears at risk for disease localization in Crohn's disease. These criteria were used to stratify the data analyses. All discrepancies between reviewers were resolved in a consensus meeting.

One author (ML) gathered the following information from selected publications: year of publication, time period of inclusion and follow-up, geographical region of the cohort, type of IBD, and extent of disease activity.

Abovementioned data helped us to ensure that only data from cohorts with comparable internal and external validity were pooled, thereby minimizing heterogeneity between pooled studies. To achieve this, we employed several approaches: First, we separated analyses for population based and referral center studies because the latter are prone to select patients with more severe disease and are not representative for the entire IBD population. Second, by excluding data that did not censor personyears for (sub)total colectomy or stratify for pure ileal Crohn's disease, we ensured that no personyears were included from patients without an

increased CRC risk because this could lead to an underestimation of the CRC risk. Third, by excluding studies that based patient inclusion on hospital admission records only, we made sure there was no underrepresentation of patients with less severe disease. While some of these studies are published as “population-based”, in fact they are not because not all IBD patients are admitted to the hospital. Some patients are treated only in the outpatient clinic. Finally, in case of duplicate publications or reports with overlapping data, the most recent publication with the most relevant data was selected to ensure that every incident CRC was only counted once. In addition to these measures, heterogeneity was explored for all grouped analyses by the I-squared (I^2) statistic as described by Higgins et al[10]. Publication bias was assessed with a funnel plot.

Data extraction

We derived the following variables for the meta-analyses: personyears at risk for developing CRC corrected for colectomy; observed CRC in the cohort; expected number of patients developing CRC (calculated from background populations with personyears at risk corrected for colectomy from the study cohorts); stratified personyears at risk and observed/expected cancers for disease duration, extent of disease, age of onset of IBD and sex.

Disease duration was stratified in 10-year intervals. Stratified data for extent of disease in ulcerative colitis and Crohn’s disease were extracted as follows: a) For ulcerative colitis; categories used included proctitis, left-sided disease defined as disease activity up to the splenic flexure, and extensive disease defined as disease activity extending beyond the splenic flexure, b) For Crohn’s disease; categories used included small bowel involvement only, small bowel plus colonic involvement, colonic involvement only, and any colonic involvement.

Statistical Analysis

We calculated the overall CRC risk, censored for colectomy and small bowel Crohn’s disease. By censoring personyears after a (sub)total colectomy, the risk calculation is only based on personyears of patients who actually had a colorectum. Personyears of patients who had their colorectum surgically removed were not analyzed. The same principle was applied to patients with only ileal Crohn’s disease. Since these patients had no colorectal disease, we did not include their personyears. In addition we performed sub-analyses by stratifying risks for population- and referral center studies and putative predictors of CRC such as disease duration, extent of disease, age at IBD diagnosis, and sex.

For all analyses, retrieved data on observed and expected cancers in the background population were used. Each included study presented calculated expected cancer numbers by multiplying the incidence rate of CRC in their respective background population by the personyears at risk of the study cohort. Incidence rates for the background population were always adjusted for age and sex. We calculated the standardized incidence ratio (SIR) for each study by dividing the number of observed cancers by the number of expected cancers. This ratio represents the risk of CRC in IBD patients compared to the risk of CRC in the background population adjusted for age, gender and disease duration. A Poisson distribution was assumed to calculate 95% confidence intervals for obtained standardized incidence ratios and these were subsequently pooled to obtain a weighted standardized incidence ratio for

each analysis by using standard errors. The random effects model was used to compensate for among-study variance of different geographical areas and possible different treatment options that might have influenced cancer risk.

The CRC incidence (per personyears at risk) was calculated for each study that reported observed cancers and personyears at risk for 10-year intervals. Using a random effect model, a pooled incidence rate (per 1000 personyears at risk) was calculated. Cumulative risks were calculated from these 10 year interval incidence rates by employing the following formula: Probability of CRC = $1-e^{-x*t}$, in which x is the incidence rate and t the interval in years. Cumulative risks were calculated accordingly, using the method described by Kewenter et al[1].

The influence of time periods of patients cohorts on CRC risk were investigated using meta-regression techniques. Instead of publication year we used the end of follow-up year for each study to investigate time trends.
Calculations and graphs were done with MIX 2.0 Pro software[11], STATA 12™ and Graphpad PRISM 5™.

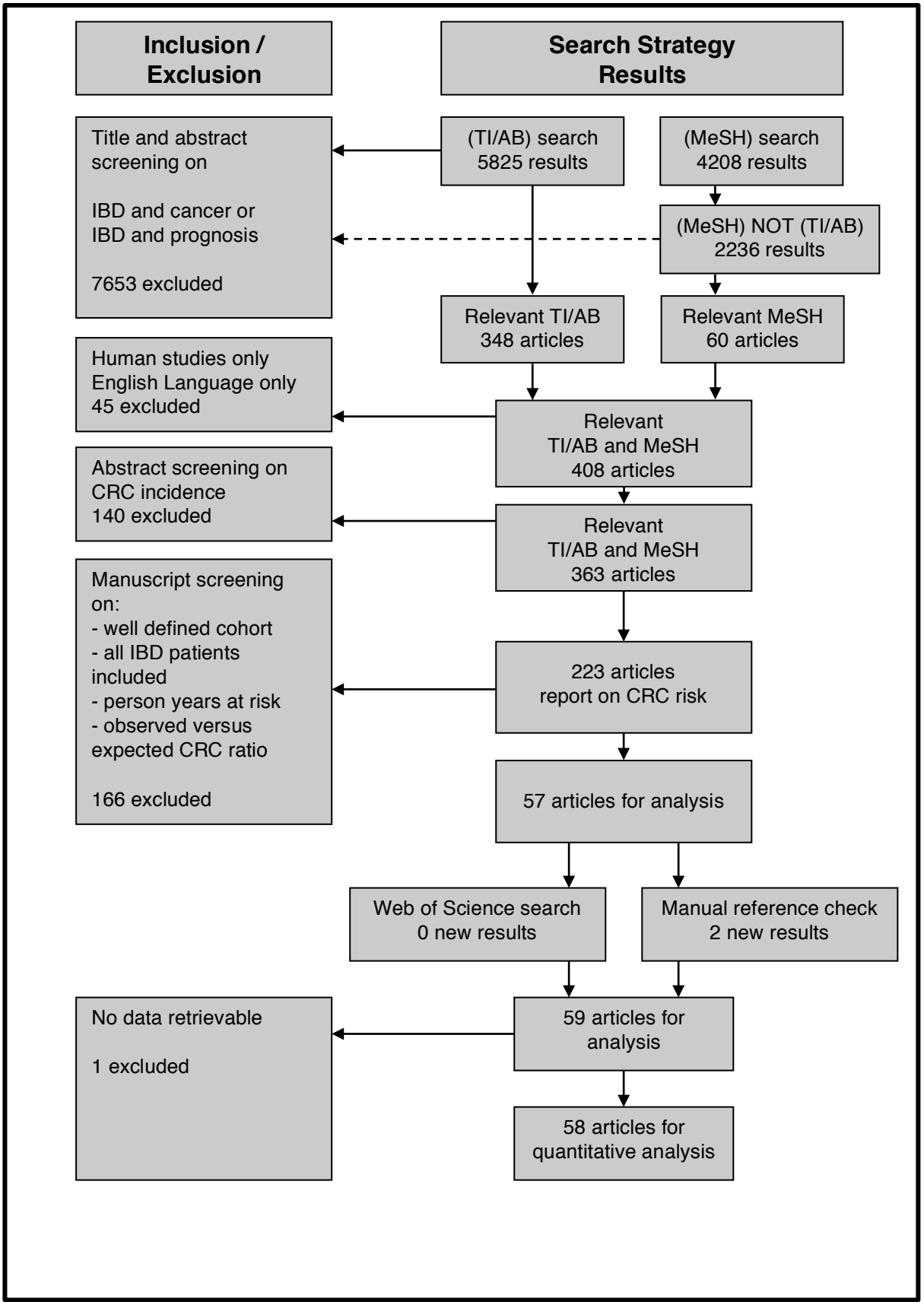
RESULTS

Search results

After applying our exclusion criteria on the search results, 223 publications were eligible. Cross-reference searches in Web of Science of these 223 articles did not yield additional studies. Subsequent screening for reports on a well defined cohort that included all IBD patients, personyears at CRC risk, mean or median disease duration, and observed and expected cancers with standardized incidence ratios resulted in 57 remaining papers[1,2,7,8,12-64]. A manual reference check of all 57 papers resulted in an additional 2 studies[65.66] that were not included in the PubMed search. In total, these 59 publications were selected for quantitative analysis. A detailed flowchart of the search procedure is shown in table 2.

One study did not report sufficient data for our intended meta-analyses[49]. From the remaining 58 articles, 10 publications[19,44,45,50,51,55-58,63] were excluded because patient selection was done by hospital discharge records only. The cohorts of 21 publications[1,13,14,17,20-22,24-26,30,32-34,36,38,39,41-43,52] were updated in 7 later publications[2,7,8,18,28,29,60]. The main risk analyses corrected for colectomy and ileal Crohn's disease was done with 9 population-based studies[2,7,8,16,22,34,35,37,65] and 4 referral center studies[20,21,30,31]. Each table with sub-analyses contains references to the studies that were used for that specific analysis.

Table 2 Flowchart of procedure and results of retrieval and selection

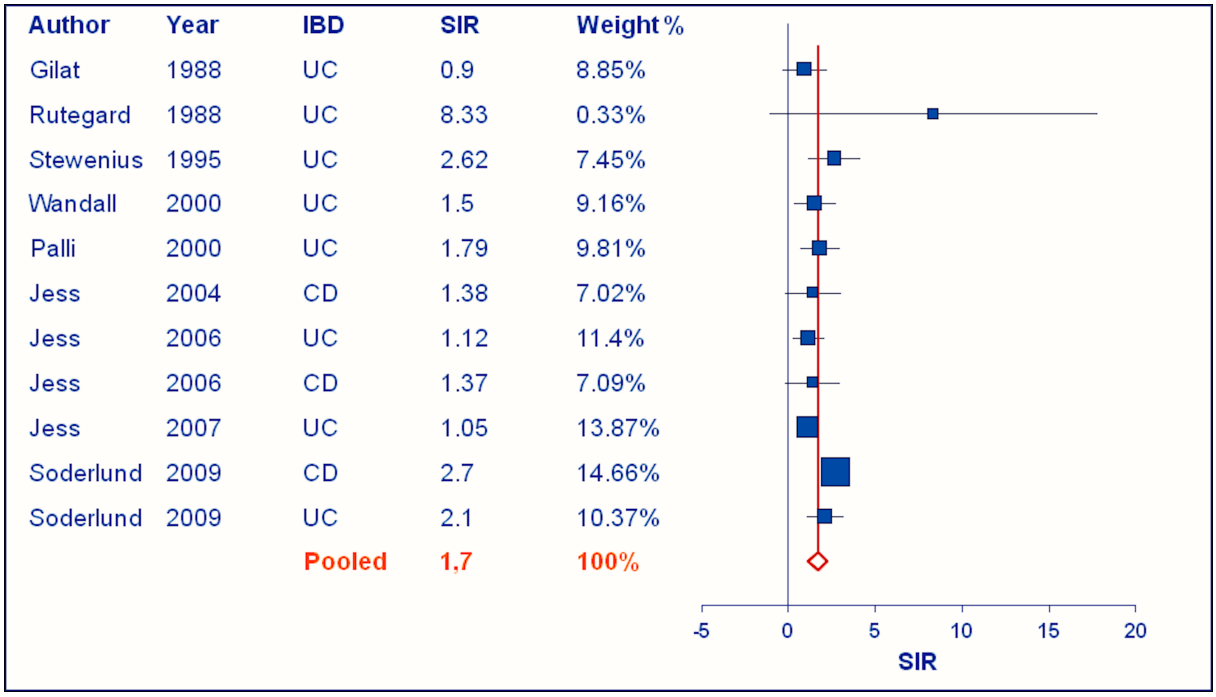


TIAB = Title/ Abstract; MeSH = Medical Subject Headings

Risk of CRC: standardized incidence ratios

The pooled CRC standardized incidence ratio in all colitic IBD patients was calculated from the most recent nine population-based studies[2,7,8,16,22,34,35,37,65]. Based on 259,266 personyears at risk, the SIR for CRC was 1.7 [1.2-2.2]. This was 6.9 [4.1-9.7] in four referral center studies[20,21,30,31] based on 29,799 personyears at risk. Specified results for ulcerative colitis and Crohn's disease are represented in Table 3, which shows equal risks for both diseases. A forest plot is shown in figure 1. We also calculated SIRs including studies that could not or did not correct for colectomy and ileal disease. These results were not different from those that excluded these studies for overall IBD, nor for UC and CD separately. Based on 323,536 personyears at risk, the SIR of CRC for IBD patients from population-based studies was also 1.7 [1.3-2.1]. Details are shown in Table 4.

Figure 1 Forest plot of population based studies



IBD = Inflammatory bowel disease; SIR = Standardized incidence ratio; UC = Ulcerative colitis; CD = Crohn's disease

Table 3 Reported colorectal cancer risk in IBD patients

IBD type (study references) Subgroup analysis	Number of patients	PYAR*	Observed CRC	Pooled SIR	95% CI	I^2
IBD [2,7,8,16,22,34,35,37,65] POPULATION-BASED	13,010	259,266	210	1.7	1.2-2.2	64%
IBD [20,21,30,31] REFERRAL CENTER	2,098	29,799	57	6.9	4.1-9.7	43%
UC [2,7,8,16,34,35,37,65] POPULATION-BASED	8,964	161,154	188	1.7	1.03-2.4	73%
UC [21,30,31] REFERRAL CENTER	1,585	22,375	48	8.3	5.9-10.7	0%
CD [7,8,22] POPULATION-BASED	4,046	98,112	22	1.7	1.01-2.5	0%
CD [20] REFERRAL CENTER	513	7,424	9	4.4	1.5-7.2	NA

IBD=Inflammatory Bowel Disease; UC=Ulcerative Colitis; CD=Crohn's Disease; PYAR=PersonYears at Risk; CRC=colorectal carcinoma SIR=Standardized Incidence Ratio; CI=Confidence Interval; NA=Not applicable; I^2 is heterogeneity statistic: higher percentages depict higher heterogeneity between pooled studies.

* Reported PYAR in this table serve as an indication of the magnitude of data on which calculations are based. PYAR from Gilat and colleagues and Persson and colleagues were not retrievable from respective papers, and PYAR from Rutegård and colleagues only represents the extensive colitis subgroup, thus PYAR are even somewhat higher than presented. For some papers PYAR were approximated for subgroups. This did not affect pooled SIR calculations because observed and expected carcinoma data were fully retrievable from all papers.

Table 4 Colorectal cancer risk in IBD patients including studies uncensored for colectomy and ileal CD

IBD type (study references) Subgroup analysis	Number of patients	PYAR*	Observed CRC	Pooled SIR	95% CI	I^2
IBD [2,7,8,12,15,16,34,35,37,54,64,65] POPULATION-BASED	20,817	323,536	304	1.7	1.3-2.1	54%
IBD [18,21,30,31,38,59,62,66] REFERRAL CENTER	4,073	56,430	82	5.3	2.8-7.8	74%
UC [2,7,8,12,16,34,35,37,65] POPULATION-BASED	11,636	180,819	237	1.8	1.2-2.4	72%
UC [21,30,31,66] REFERRAL CENTER	2,544	33,679	54	6.4	1.6-11.2	85%
CD including small bowel disease [2,7,8,12,15,64,65] POPULATION-BASED	8,188	130,964	61	1.6	1.2-2.0	0%
CD including small bowel disease [18,38,59,62] REFERRAL CENTER	1,529	22,751	28	4.4	1.5-7.4	57%

IBD=Inflammatory Bowel Disease; UC=Ulcerative Colitis; CD=Crohn's Disease; PYAR=PersonYears at Risk; CRC=colorectal carcinoma SIR=Standardized Incidence Ratio; CI=Confidence Interval; I^2 is heterogeneity statistic: higher percentages depict higher heterogeneity between pooled studies.

* Reported PYAR in this table serve as an indication of the magnitude of data on which calculations are based. PYAR from Gilat and colleagues and Persson and colleagues were not retrievable from respective papers, and PYAR from Rutegård and colleagues only represents the extensive colitis subgroup, thus PYAR are even somewhat higher than presented. For some papers PYAR were approximated for subgroups. This did not affect pooled SIR calculations because observed and expected carcinoma data were fully retrievable from all papers.

Extent of disease

The standardized CRC incidence ratio adjusted for colectomy, calculated from four population-based studies[1,7,8,34] and two referral center studies[21;31], was increased for extensive ulcerative colitis, but not for proctitis in both the population-based and referral center setting. Left-sided disease showed an increased SIR of CRC only in the pooled result from referral center studies (Table 5).

Four population-based studies[7,8,14,22] provided SIRs of CRC for colectomy and stratified observed and expected cancers for disease localization in Crohn's disease (Table 5). No increased SIR of CRC was found in Crohn's disease patients with disease activity restricted to the small bowel. Results for Crohn's disease with only colonic involvement, concomitant small bowel and colonic involvement, and colonic involvement with or without small bowel involvement had similar increased pooled SIRs of CRC, i.e., 1.7 [0.9-2.6], 1.7 [0.2-3.2] and 2.0 [0.3-3.7] respectively (Table 5). None of these were statistically significantly increased compared to the general population with the random effects model.

Table 5 Colorectal cancer risk stratified for extent of disease

IBD type (study references) Subgroup analysis	Number of Patients	PYAR*	Observed CRC	Pooled SIR	95% CI	I^2
Extensive colitis UC [1,7,8,34] POPULATION-BASED	1,887	41,640	88	6.9	1.9-11.9	84%
Extensive colitis UC [21,31] REFERRAL CENTER	681	11,164	38	21.6	15.0-31.0	0%
Left sided UC [8,13,34] POPULATION-BASED	1,093	13,148	19	1.7	0.6-4.5	47%
Left sided UC [21,31] REFERRAL CENTER	628	8,872	7	2.0	1.01-4.1	0%
Proctitis CD [8,13,37,39] POPULATION-BASED	172	12,427	16	1.0	0.5-1.6	21%
Proctitis CD [31] REFERRAL CENTER	132	1,005	0	N/A	N/A	N/A
Small Bowel only CD [8,14,22] POPULATION-BASED	817	10,633	6	1.04	0.1-2.0	0%
Small Bowel & Colon CD [8,14,22] POPULATION-BASED	688	9,119	6	1.7	0.2-3.2	0%
Colon only CD [7,8,22] POPULATION-BASED	1,146	27,432	19	1.7	0.9-2.6	0%
Any colonic involvement CD [8,14,22] POP-BASED	1,303	15,985	15	2.0	0.3-3.7	49%
Extensive colon involvement CD[17] REFERRAL CENTER	125	2,296	8	18.2	7.8-35.8	N/A

UC=Ulcerative Colitis; CD=Crohn's Disease; PYAR=PersonYears at Risk; CRC=colorectal carcinoma SIR=Standardized Incidence Ratio; CI=Confidence Interval; NA=Not applicable; I^2 is heterogeneity statistic: higher percentages depict higher heterogeneity between pooled studies.

* Reported PYAR in this table serve as an indication of the magnitude of data on which calculations are based. PYAR from Gilat and colleagues and Persson and colleagues were not retrievable from respective papers, and PYAR from Rutegård and colleagues only represents the extensive colitis subgroup, thus PYAR are even somewhat higher than presented. For some papers PYAR were approximated for subgroups. This did
not affect pooled SIR calculations because observed and expected carcinoma data were fully retrievable from all papers.

Age at IBD diagnosis

Five population-based studies[8,13,14,22,39], in which patients were stratified into two age groups, showed that age at diagnosis of IBD has a large impact on CRC risk in IBD patients with the standardized CRC incidence ratio being more than four times higher in patients diagnosed at a young age (<30 years), compared to a non-significantly increased incidence ratio in patients with an IBD diagnosis at age of 30 years or older (Table 6). Pooled data from three referral center studies[18;21;31] confirmed this finding, with the standardized CRC incidence ratio in patients diagnosed before the age of 25 being almost 13 times higher. The CRC risk in younger patients was 70 times higher than that of the general population (Table 6).

Sex

The results for sex from three population-based studies[2;8;60] showed slightly higher SIRs of CRC in males, but not statically significant with the random effects model (Table 6). The SIR of CRC was almost equal for males and females in the referral center data. However, only the SIR of CRC for females was statically significant with the random effects model.

Table 6 Stratified analyses by age at IBD diagnosis and gender

Age at IBD diagnosis Subgroup analysis (study references)	**Number of Patients***	**PYAR****	**Observed CRC**	**Pooled SIR**	**95% CI**	**I^2**
< 30 years POP BASED [8,13,14,22,39]	3,276	46,623	44	8.2	1.8-14.6	82%
≥ 30 years POP BASED [8,13,14,22,39]	3,695	46,509	92	1.8	0.9-2.7	81%
< 25 years REF CENTER [18,21,31]	520	3,575	19	70.7	15.6-320.9	90%
≥ 25 years REF CENTER [18,21,31]	1,004	6,215	28	5.5	2.0-14.9	84%
Sex Subgroup analysis (study references)	**Number of Patients**	**PYAR**	**Observed CRC**	**Pooled SIR**	**95% CI**	
Male POP BASED [2,8,60]	5,059	102,979	135	1.9	0.8-3.0	84%
Female POP BASED [2,8,60]	4,921	111,102	84	1.4	0.8-2.1	61%
Male REF CENTER [20,31,33]	1,038	5,260**	16	6.7	0.3-13.1	64%
Female REF CENTER [20,31,33]	1,052	9,515**	26	6.9	2.7-11.7	55%

IBD=Inflammatory Bowel Disease; PYAR=PersonYears at Risk; CRC=colorectal carcinoma; SIR=Standardized Incidence Ratio; CI=Confidence Interval; POP BASED=Population-based study; REF CENTER=Referral center study; I^2 = heterogeneity statistic: higher percentages depict higher heterogeneity between pooled studies.

* The patient number distribution for sex was not retrievable from the paper by Gyde et al. A manual distribution of 1:2 of the 625 patients was used as this roughly corresponded to the studies from MacDougall et al, and Gillen et al.

** Reported PYAR in this table serve as an indication of the magnitude of data on which calculations are based. PYAR from Gyde et al. were not retrievable, thus PYAR are higher than presented. This did not affect pooled SIR calculations because observed and expected carcinoma data were fully retrievable from all papers.

Cumulative Risks

Table 7 shows pooled CRC incidence rates and corresponding estimated cumulative CRC risks, censored for colectomy and ileal Crohn's disease. These data are based on four population-based studies[8,13,14,37].

The pooled CRC incidence rates for patients with extensive colitis were calculated from two population-based studies[1,34] and one referral center study[27]. These were 1.7 per 1000 personyears at risk [0.9-3.3] for the first decade, 10.9 per 1000 personyears at risk [7.1-16.7] for the second decade, and 11.2 per 1000 personyears at risk [6.8-18.6] for the third decade of disease and beyond. The corresponding cumulative risks were 2%%, 12% and 21%, respectively.

Table 7 Colorectal cancer risk stratified for disease duration grouped by population

Disease duration (study references)	Population-based studies	PYAR	Pooled CRC/1000 PYAR	95% CI	Cumulative risk
<10 years [8,13,14,37]	4	45,744	0.8	0.4-1.4	0.8%
10-20 years [8,13,14,37]	4	19,184	1.4	0.8-2.4	2.2%
>20 years [8,13,14,37]	4	7,695	2.4	0.8-7.2	4.5%
Disease duration (study references)	**Referral center study**	**PYAR**	**CRC/1000 PYAR**	**95% CI**	**Cumulative risk**
<10 years [19]	1	1,962	0.5	0.01-2.8	0.6%
10-20 years [19]	1	693	11.5	5.0-22.7	11.4%
>20 years [19]	1	379	44.9	26.1-71.8	43.4%
Disease duration (study references)	**Population-based and referral center combined**	**PYAR**	**Pooled CRC/1000 PYAR**	**95% CI**	**Cumulative risk**
<10 years [8,13,14,19,37]	5	47,706	0.7	0.4-1.4	0.7%
10-20 years [8,13,14,19,37]	5	19,877	1.9	0.8-4.7	2.6%
>20 years [8,13,14,19,37]	5	8,074	4.2	1.3-13.8	6.6%

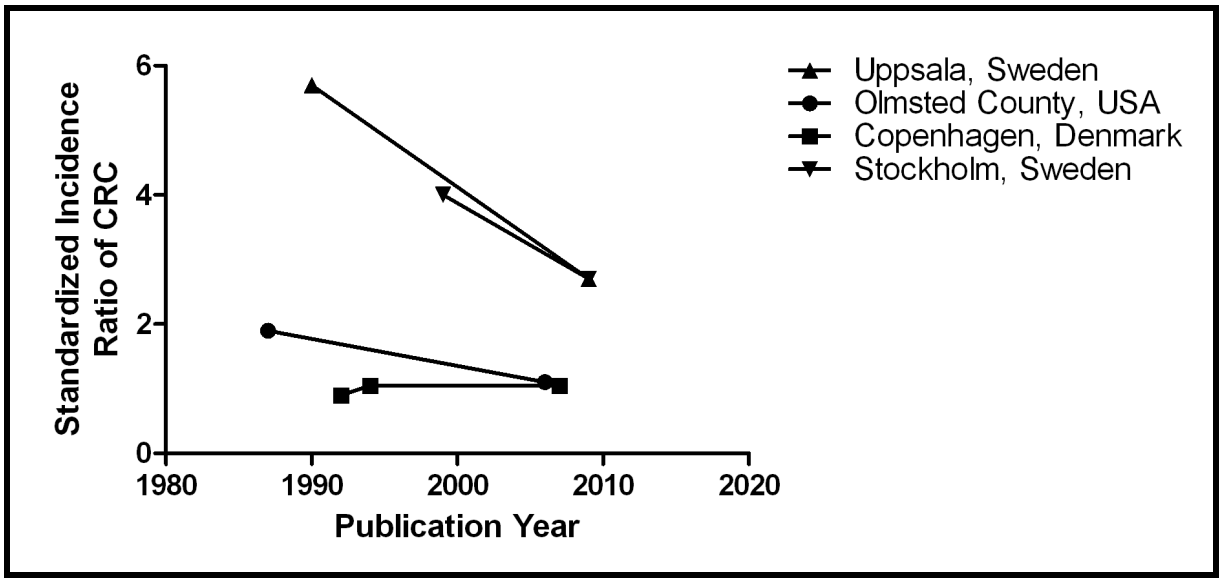
PYAR=PersonYears at Risk; CRC=colorectal carcinoma; CI=Confidence Interval

Time trends of CRC risk

Figure 2 and 3 show time trends for SIRs of CRC in 4 population-based cohorts from Uppsala[7,13,14], Stockholm[7,25,32], Copenhagen[2,22,26,39,52] and Olmsted County[8,36,41]. Soderlund et al[7] reported decreasing time trends for the Uppsala and Stockholm cohorts. The risk of CRC in Olmsted County seems to have declined as well.

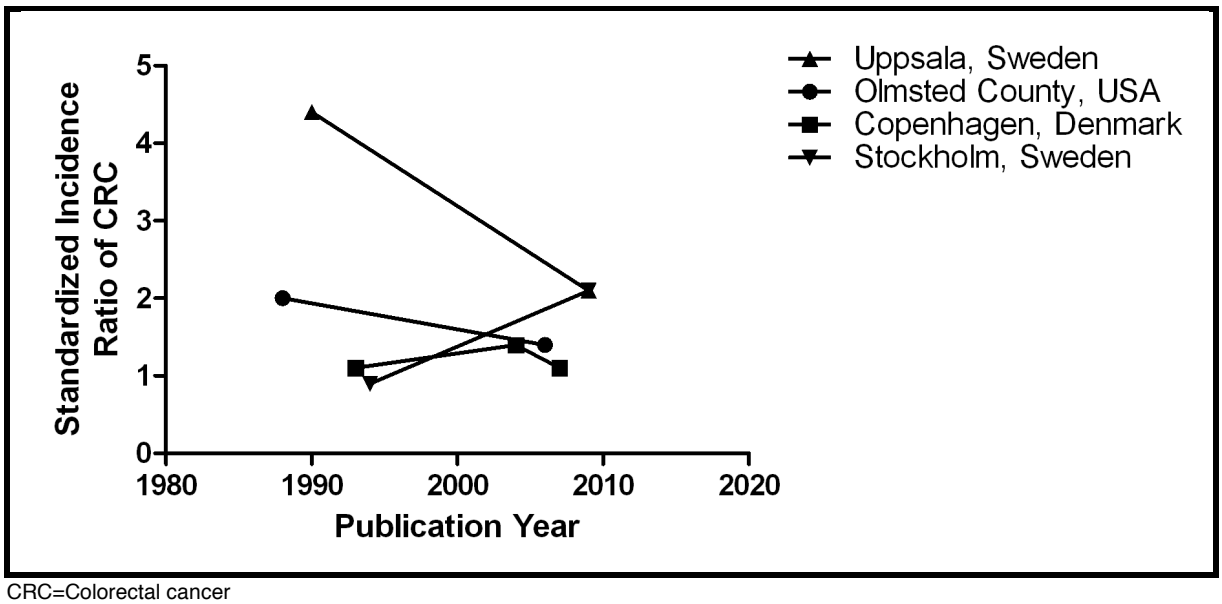
Copenhagen County never had increased risks for CRC consistently throughout several decades.
Meta-regression was performed on the population-based data and showed a decline, but this was not statistically significant, most likely due to a type II error as only 9 studies were available for analysis.

Figure 2 Decreasing standardized incidence ratios in ulcerative colitis



CRC=Colorectal cancer

Figure 3 Decreasing standardized incidence ratios in Crohn's colitis



CRC=Colorectal cancer

DISCUSSION

Based on 259,266 personyears at risk in population-based studies and 29,799 personyears at risk in referral center studies, it can be concluded that both ulcerative and Crohn's colitis are associated with an increased risk of developing CRC. This

meta-analysis shows that in ulcerative colitis and Crohn's colitis patients the risk of CRC is increased with a SIR of 1.7. Cumulative risks of CRC in the general IBD population are increased as well, but less pronounced than previously reported by Eaden et al[3] The highest CRC risks were found in patients from referral center cohorts, in patients with longer disease duration, in patients with extensive colitis and in patients diagnosed before the age of 30 years.

Especially noteworthy is the finding that population-based studies with follow-up until approximately 1990 had higher SIRs than studies with follow-up until approximately 2000. A similar decline in risk is also evident in the largest available population cohorts, i.e., those from Sweden in the Uppsala and Stockholm regions. For ulcerative colitis, Ekbom et al and Karlen et al reported a SIR of 5.7 in Uppsala and 4.0 in Stockholm in 1990 and 1999, respectively[13,25]. In an update from 2009 by Soderlund et al[7], combining both cohorts, this risk had dropped to a SIR of 2.7. Effective surveillance programs, a stringent colectomy policy and better (preventive) medication use have been hypothesized as possible mechanisms to explain this reduction in IBD-associated CRC risks over the past decades.

In our opinion, this decline could also be the result of ageing of the cohorts. The number of patients in updated studies had hardly increased between the publications[7,13,25], which could also explain the decline in risk ratio. It is not unlikely that high-risk patients had already developed CRC at the time of the first publications in 1990[13] and 1999[25], resulting in censoring of their personyears at risk. Particularly patients with no increased risk remained in the cohort and kept adding personyears at risk to the cohorts and got older. This resulted in a lower SIR (less observed CRC versus more expected CRC) of the IBD cohort due to the increased risk of sporadic CRC in the background population. This also corresponds to findings of Soderlund et al[7] who reported that the risk of CRC did not change over time within their cohorts, but had decreased as compared to the background population. This could therefore be a result of an ageing cohort in which high-risk patients were already censored early on during follow-up.

These findings stress the importance of identifying patients at a high risk of developing CRC. In this meta-analysis we were able to confirm that extensive colitis and young age at diagnosis of IBD were associated with higher SIRs. The high SIR in patients with extensive colitis has consistently been reported in the literature and is in line with the hypothesis of inflammation-induced dysplasia and CRC development in IBD. A novel finding is that ulcerative colitis patients with left-sided disease were not at an increased risk of CRC in a population-based setting. However, this finding could be due to the fact that this sub-analysis included fewer personyears at risk than other analyses. From the available data, we were not able to conclude that young age at diagnosis of IBD was a truly independent risk factor, since the associated risk can also be explained by disease duration, which is another established risk factor for colitis-related CRC. Interestingly, based on a substantial 46,509 personyears in the population-based data, the SIR for CRC was not increased in patients whose IBD was diagnosed above an age of 30 years.

The cumulative risks of CRC in patients with ulcerative colitis in our meta-analysis were lower than the risks reported by Eaden et al[3]. Apart from the abovementioned hypothesis on ageing cohorts this is most likely due to the fact that the Eaden study combined a heterogeneous set of studies, i.e., 6 population-based studies, 8 referral center studies, 3 surgical series, 2 surveillance programs and 1

private practice cohort. The inclusion of referral centers and surgical series has probably led to an overestimation of the CRC risk. We found that the addition of 1 referral center study to 4 population-based studies already resulted in higher cumulative risks of 1%, 3% and 7% at 10years, 20 years and 30 years of disease, respectively (table 7). Our analysis is based on fewer studies compared to the Eaden study[3], because we stratified between population-based and referral studies and excluded those that did not censor for personyears at risk after colectomy.

Jess et al.[4] reported a SIR of 1.9 [1.4-2.5] in patients with Crohn's disease based on 6 population-based studies. Of these studies, one was based on administrative data without information about colectomy rates, while two others included personyears at risk for CRC from Crohn's patients with disease activity restricted to the small bowel. We report a population-based standardized CRC incidence ratio of 1.7 [1.01-2.5] for Crohn's disease based on the remaining 3 papers that were also included in the Jess study[3]. Unlike Jess et al[4] who used a fixed effects meta-analytic model, we used a random effects model. Despite zero percent heterogeneity in the statistical test, we used the random effects model as we believe that, due to among-study variation (e.g. population sets from different countries with differences in therapy and approach to colectomy), random effects modeling is more appropriate for analyzing these types of data. When fixed effects analysis would have been used for the sub-analyses of extent in Crohn's disease, then all calculations would have yielded statistically significant confidence intervals, except for small bowel disease.

Canavan et al[5] and Von Roon et al[6] both reported a SIR for CRC of 2.5 in Crohn's disease. Both publications combined population-based and referral center studies, which probably explains the higher SIR in these meta-analyses. Indeed, when Von Roon et al[6] performed a sub-analysis of only population-based studies, the SIR was 1.4, which was not statistically significant increased. However, this sub-analysis was done with studies that included patients with ileal Crohn's disease and these authors did not correct for colectomies, which could have underestimated the risk.

The present study has some advantages compared to previous meta-analyses. First, studies were stratified according to whether they were population-based or referral center studies. This reduces heterogeneity of pooled data with regard to clinical characteristics of the patient population. The only other meta-analyses that took this into account reported only risk of CRC in Crohn's disease exclusively[4,6]. Second, we excluded studies in which censoring for colectomy or stratification for small bowel as disease localization of Crohn's disease was not performed. Third, we also excluded studies that based patient inclusion on hospital admission records, which are prone to selection bias by missing less severely affected patients. Finally, our study is the first updated meta-analysis on ulcerative colitis since the one by Eaden et al[3] and we included all recent population-based available data.

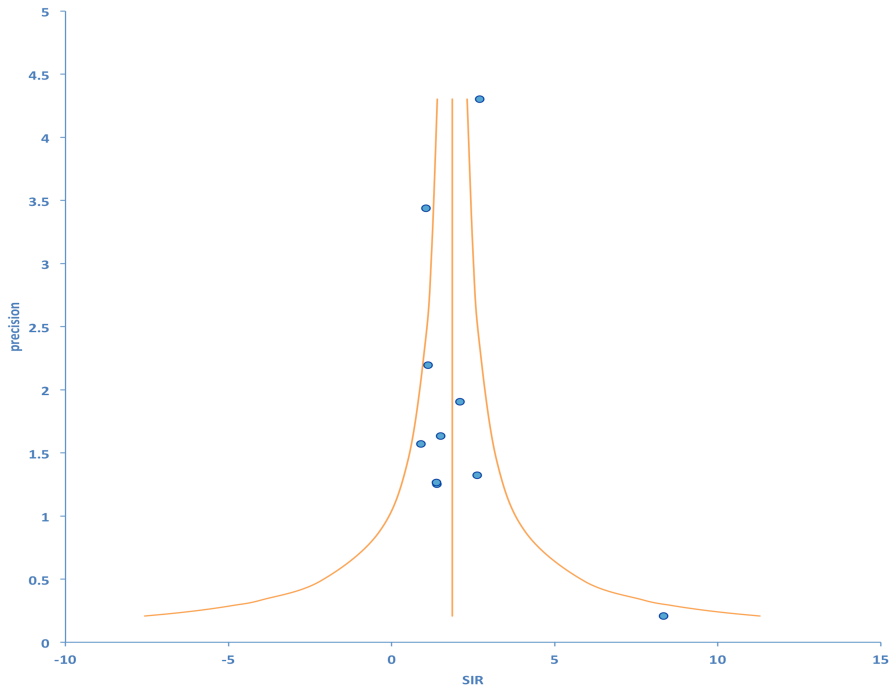
Some design issues need to be considered as well. First, due to the strict selection criteria employed, only a few publications were available for some subgroup analyses. Second, regional differences across studies and the effect of changes over time with regard to screening strategies and the approach to treatment (cohort effects) might have introduced heterogeneity between included study populations. An aggressive therapeutic approach leading to colectomy, strict adherence to

surveillance guidelines and different views regarding prescription of maintenance therapy such as aminosalicylates, thiopurines and anti-TNFα compounds might all have affected CRC risk. The employed random effects model is expected to compensate for this heterogeneity, but at the same time, results in a relative weight reduction of larger studies and wider confidence intervals. This could also explain the finding that we found no statistically significant result in our analyses for disease extent in Crohn's disease and sex. Especially the combination of fewer studies available for analysis and the random effects model may have resulted in wide confidence intervals. Finally, most population-based results were from European centers with the exception of those from Mayo clinic[8] and the Israeli data[16]. While we believe that IBD-associated colorectal cancer risks are disease specific, one might argue that this could be a limit to external validity.

We found no evidence for publication bias in a Funnel plot (Figure 4). One may argue that the funnel plot is asymmetric because some studies are missing in the lower left corner. However, studies in the lower left corner would imply a protective effect of IBD on developing CRC with a SIR ranging from 0.1 to 0.2. This is highly unlikely as this would defy all current paradigms about inflammation-induced carcinogenesis in IBD[67-69].

In conclusion, the risk of CRC in IBD is lower than previously reported and is not increased in all patients. However, part of the decline in risk as observed in the past years could be explained by ageing cohorts in which high-risk patients were already diagnosed early in the follow-up period. In this meta-analysis, we confirmed that patients treated in referral centers, especially those who have extensive disease, longer disease duration and IBD at a young age, have substantially increased risks. Future decisions on screening policy and intervals should take these diverging risk profiles into account.

Figure 4 Funnel Plot



SIR=Standardized Incidence Ratio

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CHAPTER 5

Risk Factors for Rectal Stump Cancer in Inflammatory Bowel Disease

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ABSTRACT

Background: Patients with longstanding colitis carry an increased risk of colorectal cancer and are therefore enrolled in colonoscopic surveillance programs. It is presently not known if endoscopic surveillance of colitis patients with a closed rectal stump after subtotal colectomy is justified. Neither is it clear which of these patients might be at increased risk for rectal stump cancer.

Objective: To identify risk factors for rectal stump cancer.

Design: Retrospective descriptive case-control.

Settings: Tertiary referral centers in The Netherlands.

Patients: Inflammatory bowel disease associated colorectal cancer cases diagnosed between 1990 and 2006 were selected in a nationwide pathology archive. Patients with rectal stump cancer were selected from this group. The pathology archive was also used to identify inflammatory bowel disease controls matched for referral center with a closed rectal stump after subtotal colectomy, but without neoplasia. Follow-up started at the date of subtotal colectomy with formation of a rectal stump. Demographic and disease characteristics were collected at baseline.

Main outcome measurements: Hazard ratios with 95% confidence intervals were calculated for factors associated with the development of rectal stump cancer using univariate Cox regression analysis. End points were rectal stump cancer, end of follow-up, or death.

Results: A total of 12 patients with rectal stump cancer and 18 matching controls without neoplasia were identified. Univariate analysis showed an association between rectal stump cancer and primary sclerosing cholangitis, and disease duration until subtotal colectomy.

Limitations: Retrospective design of the study and despite being the largest series to date, it still has a limited number of cases.

Conclusions: Risk factors for rectal stump cancer in a closed rectal stump after subtotal colectomy were primary sclerosing cholangitis, and disease duration until subtotal colectomy.

INTRODUCTION

Approximately 30-40% of patients with ulcerative colitis (UC) and 70-80% of patients with Crohn's disease (CD) require surgery at some point during the course of their disease[1,2]. In case of UC, this usually results in a one or two stage subtotal colectomy or proctocolectomy with generally acceptable or good postoperative functional results[1,3-5]. For several reasons, however, patients or their treating physicians may decline restorative surgery after the first stage of a subtotal colectomy, resulting in a permanent ileostomy and a closed rectal stump. In case of CD, end ileostomy with a closed rectal stump is often deemed preferable over proctectomy, as perianal complications, perforating disease or impaired healing of a perianal wound may occur[6].

Colorectal cancer (CRC) is a recognized and serious complication of both UC and CD[7,8]. Epidemiological studies have identified inflammatory disease (IBD) duration and extent, concomitant primary sclerosing cholangitis (PSC), post-inflammatory polyps, colonic strictures in UC, family history of CRC, and severity of endoscopic and histologic inflammation to be the key risk factors for IBD-associated CRC[9]. Little is known, however, about the risk of rectal cancer in IBD patients with a closed rectal stump and it is not clear whether the aforementioned risk factors or inflammation secondary to deviation influence the risk of malignant transformation in a rectal stump. We previously reported on all IBD-associated CRC in referral centers in the Netherlands. We focussed on duration interval between IBD and cancer, and survival benefit from surveillance[10,11]. Some of these cancers developed in a closed rectal stump, which piqued our interest for this subset of patients. The aim of this study was to identify determinants for increased risk of rectal stump cancer (RSC) in IBD.

MATERIALS & METHODS

Search strategy and patient population

We performed a retrospective case-control study. Cases were selected through the nationwide pathology archive (PALGA) in the Netherlands[12]. For this, we previously performed a search for all IBD-associated CRC cases in the Netherlands from January 1990 until June 2006 in tertiary referral centers. Details of this search have been described previously[10,11]. We collected clinical information from anonymized patient charts and identified patients with histological confirmed RSC. Thus, inclusion criteria were IBD patients who underwent a subtotal colectomy with the development of cancer in the closed rectal stump. These patients served as cases. Controls were selected through a second PALGA search using the same search criteria for IBD, time period and hospitals. Inclusion criteria for these results were IBD patients with a closed rectal stump. Patients were explicitly excluded from this control cohort if they had been diagnosed with colonic dysplasia or carcinoma previously.

Data collection

Two authors (ML and MB) extracted data from patient charts, which included: type of IBD, gender, date of IBD diagnosis, date of CRC diagnosis, date of colectomy with construction of a rectal stump, age at IBD diagnosis, age at CRC diagnosis, and tumor stage. The following variables were collected for the period between IBD

diagnosis and date of surgery on which the closed rectal stump was created: disease duration until rectal stump in days, maximum endoscopic extent of IBD before surgery, severity of IBD before surgery, endoscopic presence of post inflammatory polyps or stenosis before surgery, history of 5-ASA medication before surgery, concomitant primary sclerosing cholangitis.

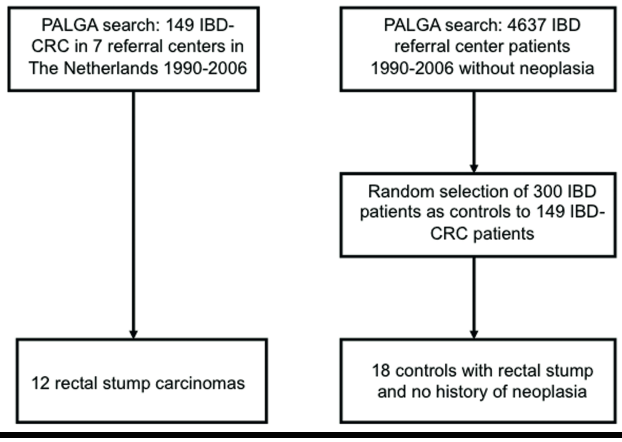
Statistics

Fisher's exact test and the independent samples T-test were used where appropriate to compare baseline characteristics. We used univariate Cox regression techniques to calculate hazard ratios for RSC. Follow-up time of cases and controls for the analysis was calculated from the date of surgery with creation of a rectal stump until the development of RSC (cases) or end of follow-up (controls). End of follow-up for controls was defined as the end of the study period (June 1, 2006), the date a patient was lost to follow-up or the date of a patient's death. SPSS version 18.0 was used for all statistical analyses. A $p<0.05$ was considered to be statistically significant.

RESULTS

Our search identified 149 patients of IBD associated CRC[10]. A total of 12 cases with RSC were enrolled in the present study, with 11 having definite cancer of the rectal stump and 1 patient having high grade dysplasia which was focally suspected for invasion of the submucosa. Our search for controls identified 4637 IBD patients in 7 university medical centers in the Netherlands who never developed neoplasia between the date of IBD diagnosis until the end of the study period (June 1, 2006). From this group 300 patients were randomly selected as controls for the initial group of IBD-associated colorectal carcinomas. Eighteen of these patients had a closed rectal stump and served as controls for this study. A flow chart of the patient selection procedure is shown in figure 1.

Figure 1 Selection Procedure Flowchart



As shown in Table 1, patient characteristics of cases and controls were similar for IBD type, gender and follow-up duration. In both groups two-thirds of patients had Crohn's disease and slightly more patients were male. Disease duration until subtotal colectomy was substantially longer in the patients with RSC. Two patients who developed RSC had a diagnosis of PSC compared to none in the control group. Patients with RSC more frequently had extensive disease and post inflammatory polyps before colectomy, but this did not reach significance. This was also true for low grade dysplasia in the rectal stump. Significantly more cases than controls had post inflammatory polyps in the rectal stump. Before subtotal colectomy, 5-ASA was used more frequently in cases, while after subtotal colectomy topical 5-ASA use was higher in controls.

Table 1 Characteristics of patients with rectal stump cancer and controls

Characteristic	Cases N=12	Controls N=18	p-value
Ulcerative colitis	4 (33%)	5 (28%)	1,00
Male	7 (58%)	11 (61%)	1,00
Extent before colectomy			
<50% of colonic mucosa	1 (8%)	4 (22%)	0.62
>50% of colonic mucosa	11 (92%)	14 (78%)	
Mean follow-up time after subtotal colectomy	10.8 years [0.6-27.9]	9.2 years [1.1-17.1]	0.57
Mean disease duration until rectal stump	14.3 years [0.1-32.1]	8.8 years [0.01-34.3]	0.17
Post inflammatory polyps before colectomy	8 (67%)	7 (39%)	0.25
Post inflammatory polyps of rectal stump	6 (50%)	1 (6%)	0.005
PSC	2 (17%)	0 (0%)	0.15
History of smoking	4 (36%)	9 (50%)	0.7
Rectal sparing before colectomy	1 (8%)	3 (17%)	1.00
LGD of rectal stump	2 (17%)	1 (6%)	0.54
5-ASA before colectomy	10 (83%)	12 (67%)	0.42
5-ASA topical in stump	2 (17%)	9 (50%)	0.12

Fisher's exact test 2-sided used for all comparisons
IBD=Inflammatory bowel disease; PSC=Primary sclerosing cholangitis; LGD=Low grade dysplasia

Table 2 shows univariate Cox regression analysis for factors associated with the development of RSC. It was found that only disease duration and PSC were significantly associated with RSC. The difference between cases and controls for post inflammatory polyps in the rectal stump was no longer statistically significant.

Table 2 Univariate Cox regression of potential risk factors for RSC in IBD

	HR	**95% CI**	**p-value**
IBD: Ulcerative colitis	1.9	0.5-6.7	0.33
Gender: male	0.8	0.3-2.9	0.78
1 year disease duration[1]	1.1	1.02-1.2	0.007
PSC	34.5	3.0-390.1	0.004
History of smoking	0.7	0.2-2.7	0.63
Extent >50% of colonic mucosa	1.5	0.2-11.8	0.71
Rectal sparing before colectomy	0.9	0.1-7.3	0.93
LGD rectal stump	1.4	0.3-6.5	0.70
Post inflammatory polyps before colectomy	2.0	0.5-7.6	0.33
Post inflammatory polyps in rectal stump	2.8	0.7-10.7	0.13
5-ASA before colectomy	1.1	0.2-5.1	0.94
5-ASA topical in stump	0.7	0.1-3.2	0.60

RSC=rectal stump cancer; IBD=Inflammatory bowel disease; HR=Hazard Ratio; CI=confidence interval; PSC=Primary sclerosing cholangitis; LGD=Low grade dysplasia
[1]Hazard ratio per year disease duration from IBD diagnosis until excluded rectal stump

DISCUSSION

We found that IBD duration until subtotal colectomy and PSC are associated with rectal stump carcinoma in IBD patients with a closed rectal stump after subtotal colectomy. There is growing evidence that IBD associated neoplasia can be attributed to a field cancerization process[13] as a consequence of chronic colonic inflammation in the intestinal mucosa. Thus, factors such as PSC and IBD duration might contribute to CRC risk of the retained rectum after subtotal colectomy as well. For post inflammatory polyps of the rectal stump, we found a difference between patients with RSC and controls, but this was no longer present after correction for follow-up time. In addition, more controls (50%), compared to cases (17%) used topical 5-ASA treatment during follow-up after subtotal colectomy with a duration of at least 3 months. After correction for follow-up time, the hazard ratio showed a protective effect, but this was not statistically significant.

As stated above, the inflammation-dysplasia-carcinoma sequence may well be involved in the pathogenesis of IBD associated RSC[14,15]. However, in an excluded rectal stump other factors may play a role as well. Diversion of the fecal stream has been shown to protect against an inflammatory recurrence in the rectal stump[16]. On the other hand, it is also known that the diverted fecal stream reduces the availability of luminal short-chain fatty acids, which have been thought be responsible for the generation of diversion colitis. Whether this protects or in fact is an additional risk for inflammation-induced carcinogenesis is unknown. In addition, the effect of discontinuation of potential chemopreventive medication, such as oral 5-ASA[17] or thiopurines[18], on cancer risk of the rectum is also unknown. Our study design did not allow us to answer the effects of these factors.

Table 3 Literature overview of the period 1978-2011 of rectal stump cancer in IBD

Author	Year of publication	# RSC	IBD CD/UC
Greenstein[24]	1978	3	3/0
Traube[25]	1980	1	1/0
Lavery[26]	1982	5	3/2
Victor Jr.[27]	1982	1	1/0
Johnson[28]	1983	1	0/1
Hamilton[29]	1983	2	2/0
Oakley[30]	1985	5	0/5
Kvist[31]	1989	2	0/2
Harling[19]	1991	1	1/0
Langholz[32]	1992	1	0/1
Nikias[33]	1995	2	2/0
Rieger[34]	1999	1	1/0
Yamamoto[6]	1999	1	1/0
Cirincione[35]	2000	2	2/0
Freeman[36]	2001	3	3/0
Petersen[21]	2008	2	1/1
Lutgens	2011	12	8/4

IBD = Inflammatory bowel disease; RSC = Rectal stump cancer; CD = Crohn's disease; UC = Ulcerative colitis

Total proctocolectomy will remove any remaining RSC risk, but this surgical procedure is liable to significant complications such as damage to the pelvic nerves with dysfunction of the urinary tract and sexuality. Thus, a significant number of patients choose to avoid these complications and accept the remaining neoplastic potential of the retained rectal stump. Patients who do not undergo restorative surgery will keep a closed rectal stump for the rest of their life. This has been reported to be the case in 16% of CD patients and 14% of UC patients following subtotal colectomy[4,19]. It is worrisome that in a recent nationwide survey we found that only 6% of Dutch gastroenterologists systematically performed surveillance proctoscopies[20]. Petersen et al.[21] recommend surveillance endoscopy on 2-year intervals for all patients with an closed rectal stump. No studies have

however been published that definitely show that surveillance proctoscopies indeed improve survival. Moreover, the evidence for a survival benefit from colonoscopic surveillance in colitis patients with their colon still in situ, as recommended by the official guidelines, is only indirect[11,22]. It is important to emphasize that in patients with a rectal stump, episodes of rectal blood loss and discharge secondary to a deviation proctitis are common, and this may well mask an underlying tumor. Failure to recognize this at an early stage might lead to a poorer prognosis in these patients. Therefore we recommend surveillance proctoscopies for IBD patients with a closed rectal stump that have more than 8 years of disease and concomitant PSC.
Kurtz et al.[22] reported 9 studies describing a total of 23 excluded RSCs in UC from 1956 to 1978. In addition, Table 3 shows an overview of the literature on this topic between 1978 and 2011 for both UC and CD with a total of 33 RSCs[6,19,21,23-36]. To our knowledge, our series is the largest to date and the first to use controls and look for potential risk factors.

There are several limitations to our study. First, there may well be a limited validity for daily clinical practice, which is due to the tertiary referral setting of our data. IBD patients in tertiary referral settings do not represent the type of IBD patients that is seen in non-referral hospitals[37]. There is a difference in cancer risks that could be related to a difference in disease severity between the two populations, i.e. referral center populations having more severe disease and higher cancer risks[38]. Second, the retrospective way of collecting data very much relies on the accuracy of documentation in the past. Finally, the major limitation of this study, despite being the largest to date, is the relatively small number of cases, preventing a meaningful multivariate analysis to be performed. Nonetheless, our results give insight into the fact that a subgroup of patients with a rectal stump is at increased risk of RSC.

In conclusion, IBD patients that underwent subtotal colectomy with a closed rectal stump may develop cancer in this excluded part. Although the pathogenetic mechanism is largely unknown, it seems that patients with longstanding IBD until subtotal colectomy and PSC are at an increased risk of RSC. Thus, patients with a closed rectal stump, PSC and disease duration of more than 8 years should be scheduled for surveillance proctoscopies every 1-2 years.

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CHAPTER 6

Predicting Colorectal Cancer Risk in Inflammatory Bowel Disease: An Internally and Externally Validated Model

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ABSTRACT

Introduction: Surveillance guidelines for IBD-associated colorectal carcinoma (CRC) are based on expert opinion derived from retrospective studies on CRC risk factors.

Aim: To create a robust CRC risk prediction score for ulcerative and Crohn's colitis based on confirmed risk factors.

Methods: This is a retrospective case-control study of two separate international cohorts, one from the University Hospital of Leuven, Belgium, and one from 7 university medical centers in the Netherlands. Multivariate Cox-regression was used to select independent risk factors in the Leuven cohort. These were used to create a risk prediction score based on regression coefficients. The predictive strength was tested by a C-statistics and was externally validated in the Dutch cohort.

Results: In total 50 CRC cases and 136 unmatched controls in Leuven, and 138 CRC cases and 206 unmatched controls in the Dutch cohort were identified. From the Leuven cohort we created a CRC risk prediction score based on 4 risk factors: IBD-type, primary sclerosing cholangitis (PSC), colonic disease extent ≥ 50%, and post-inflammatory polyps. A total score for each individual patient was calculated based on the presence or absence of these 4 risk factors. The total score per patient had a C-statistic of 0.75.

Conclusion: In both cohorts, ulcerative colitis was found to be associated with a higher risk of developing CRC than Crohn's disease. PSC was strongly associated with CRC in both Crohn's and ulcerative colitis. In addition, patients with extensive disease and post-inflammatory polyps had CRC more often than patients without these characteristics. A surveillance guideline, incorporating the relative weights of these diverging risk profiles, can be expected to perform better than the presently used guidelines.

INTRODUCTION

The risk of colorectal cancer (CRC) in inflammatory bowel disease (IBD) colitis patients is known to be increased[1] (*Lutgens et al., 2013; IBD in press*), although not as much as previously reported[2]. It is clear that the majority of most IBD patients will never develop this complication. The challenge is to identify patients at a particular high risk using established and reliable risk factors. Generally accepted factors are previously established colonic dysplasia[3], disease duration[2,4], disease extent (*Lutgens et al., 2013; IBD in press*) and primary sclerosing cholangitis (PSC)[5,6]. Endoscopic features can also assist in identifying high-risk patients. Both the presence of post-inflammatory polyps[7,8] and colonic strictures[7] have been shown to be associated with an increased cancer risk in ulcerative colitis. Conversely, a normal endoscopic appearance reduces the risk to the same level as the background non-IBD population[7]. The recently updated British Society of Gastroenterology (BSG) guideline[9] also includes family history of CRC as a risk factor based on the study by Askling et al.[10] Despite the confirmed association of these predictive and protective factors with regard to CRC development in IBD, their combined value in predicting which patients are at a low, intermediate or high risk of developing CRC has never been established. Moreover, current recommendations on risk groups and intervals in the BSG and American Gastroenterology Association (AGA) guidelines[9,11] are solely based on expert opinion. The aim of this study was to establish an internally and externally validated, easy-to-use prediction model for IBD-associated CRC.

MATERIALS & METHODS

Study Design

We performed a retrospective case-control study to identify predictive and protective factors for IBD-associated CRC. In order to validate findings in an external cohort we collected data from two separate cohorts, one from the University Hospital Leuven in Belgium and one from university hospitals in The Netherlands[12]. The Leuven cohort was used to build the prediction model while the Dutch cohort served as external validation.

Patient Selection Leuven Cohort

We used an ICD-9 coding search for the diagnoses IBD and CRC at the University Hospital Gasthuisberg, Leuven, which is a tertiary referral center in Flanders, North Belgium. Search results were available for the period September 1999 - August 2009. The search yielded 99 results. After an initial check, we identified and excluded 3 patients with isolated ileal Crohn's disease, 21 patients with unconfirmed IBD, 7 patients with concurrent IBD and CRC diagnoses, 10 patients with low-grade dysplasia but no CRC, 1 patient with high-grade dysplasia but no CRC, and 7 patients with other cancers than colorectal adenocarcinoma. In order to expand our cohort we cross-referenced the local electronic patient database with all local pathology reports from September 1990 through June 2011. This yielded 5 additional CRC cases between 1990 and 1999. Controls in Leuven were selected from the local IBD database by generating a randomly ordered patient list. Controls were then selected consecutively from the top of the list. Crohn's patients with only ileal involvement were excluded (n=12). In total, we collected data of 50 cases and 136

unmatched controls. We used unmatched controls to include as many modifiers of CRC risk as possible.

Patient Selection Dutch Cohort

The cohort from the Netherlands included all IBD-associated CRC cases from 1990-2006 in tertiary referral centers. The cohort of Dutch patients with IBD associated CRC has been reported previously[12,13]. These patients were selected using the nationwide pathology automated archive (PALGA)[14]. Search terms for colitis and carcinoma with multiple synonyms were used to identify patients with IBD and CRC. Results were manually screened for confirmed IBD and CRC. Using this method we identified 149 IBD-associated CRCs in 7 Dutch university medical hospitals. Eleven patients were excluded because of synchronous diagnoses of IBD and CRC. We selected controls by using identical search terms, but this time excluding neoplasia. A random number generator was used to select controls in a 1:2 ratio to cases. After manual screening, 94 selected controls were excluded because of isolated ileal Crohn's disease or an unconfirmed diagnosis of IBD. In total we collected data of 138 cases and 206 unmatched controls.

Data collection

Starting point of data collection and follow-up was the date of onset of symptoms that could be attributed to IBD. This was defined by a persistent change of bowel habits and/or bloody diarrhea and/or continuous abdominal pain followed by a diagnosis of IBD. If no clear onset of symptoms was recorded, the date of IBD diagnosis was used. End of follow-up for cases was the date of diagnosis of CRC. End of follow-up for controls could be any of the following: a) end of study date which was October 15th, 2011 for the Leuven data and July 1st, 2006 for the Dutch data; b) date of death by any cause; c) loss to follow-up defined by the date of last known visit to the out patient clinic; d) date of total colectomy. The following variables were collected for both cohorts: sex, IBD type defined as ulcerative colitis or Crohn's colitis (indeterminate colitis cases were analyzed with the ulcerative colitis group), smoking, defined as positive for active smoking at end of follow-up or a smoking history, family history of CRC defined as any first degree relative having a diagnosis of CRC, limited disease defined as microscopic disease extent of less than 50% and extensive disease defined as microscopic disease extent equal or more than 50% of colonic surface, concurrent primary sclerosing cholangitis (PSC), post-inflammatory polyps, dysplasia-associated lesion or mass (DALM), adenoma-like lesion, flat low-grade dysplasia, flat high-grade dysplasia, colonic stenosis, any 5-ASA use, any thiopurine use, any anti-TNF-α use, any methotrexate use, colonoscopic surveillance, pre-tumor colonic resection, age at IBD-diagnosis divided as <19 years, 19-36 years or >36years old. These age cut-offs were based on age distribution within the Leuven cohort.

Statistical Analysis

Overall risk factor analysis Leuven cohort

Before establishing the prediction model, we first identified risk and protective factors independently associated with CRC. A multivariate Cox-regression analysis was used to address different follow-up times between individual patients. This was followed by stepwise conditional elimination using the following categorical variables:

sex, IBD type, smoking behavior, microscopic extent more or less than 50% of the colonic surface, primary sclerosing cholangitis (PSC), post-inflammatory polyps, DALM, adenoma-like mass, flat low-grade dysplasia, flat high-grade dysplasia, colonic stenosis, any 5-ASA use, any thiopurine use, any anti-TNF-α use, any methotrexate use, colonoscopic surveillance, pre-tumor colonic resection, age younger than 19, and age older than 37. Entering only these two age categories and not the middle category of 19-36 enabled a comparison between the hazard ratio of the younger and older group to the middle group. The results of this analysis gave an overview from which we could select factors to use in the prediction model.

Prediction model

The main goal was to create a prediction model with a minimal number of risk factors that would be easy-to-use in clinical practice and could reliably identify patients potentially benefiting from surveillance. Hence, we only selected all independent factors associated with CRC in the Leuven cohort that could be easily used in clinical practice. For this reason we also excluded possible protective factors such as colonic resection, colonoscopic surveillance itself and medication use. We additionally excluded flat low-grade dysplasia, flat high-grade dysplasia and DALM, because we assumed that these variables were not able to determine whether patients should undergo surveillance, but rather are outcomes of surveillance, regardless of their association with CRC.

We used multivariate Cox-regression analysis with stepwise elimination to identify the remaining factors that had the strongest association with CRC in the Leuven cohort. Only factors with a final $p<0.05$ were included in the model. The selected risk factors were assigned weights that were derived from their regression coefficients (β). After division by the smallest β, all β's were converted to integer scores, e.g. a β of 2.2 corresponded to 2 points and a β of 14.3 corresponded to 14 points. A higher total score per patient indicates a higher risk of developing CRC. To test discriminative power of our model, we calculated a C-statistic for the total score of each individual patient[15,16]. To this end, we used a Survival Analysis SAS Macro publicly available from the Mayo Clinic:
(http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm).
We report C-statistic values based on calculations with ties. Calibration is the degree of correspondence between the estimated probability produced by the score and the actual observed outcomes. We assessed the calibration performance by comparing the predicted risk for CRC with the observed number of CRC in the Leuven cohort (internal validation) and the Dutch cohort (external validation). SPSS version 20 and SAS version 9 software were used for all analyses.

RESULTS

Patient characteristics

Table 1 shows the overall distribution of variables in the Leuven and the Dutch cohort. In both cohorts there were more ulcerative colitis and male patients with CRC. Disease duration was longer in the CRC groups. Active smoking or a smoking history was more prevalent in the control groups. A family history of CRC was slightly more prevalent in the Leuven control group and Dutch CRC group. Disease extent, PSC, and post-inflammatory polyp ratios were similar in the Leuven en Dutch cohort with

more extensive disease, PSC and post-inflammatory polyps in the CRC groups. DALMs were only seen in the CRC group. The Dutch control group had no dysplasia because those patients were specifically excluded when the data for this cohort were collected. More CRC cases than controls had a colonic stenosis, while a colectomy was more common in controls. Especially in the Leuven cohort more controls were on thiopurines and methotrexate medication and were treated with anti-TNF-α. Only the Dutch cohort showed a difference in 5-ASA use in favor of the control group.

Table 1 Patient characteristics and distributions between CRC cases and control in the Leuven and Dutch cohorts

Variable	Leuven CRC n=50	Leuven controls n=136	Dutch CRC n=138	Dutch Controls n=206
Ulcerative colitis	60%	50%	65%	51%
Male sex	60%	40%	60%	53%
Age at IBD Dx*	28 years	25 years	27 years	26 years
Disease duration*	21 years	17 years	21 years	22 years
Smoking yes	22%	27%	19%	31%
Family history CRC	5%	7%	9%	4%
Disease extent ≥50%	88%	52%	85%	57%
PSC	14%	5%	9%	2%
PIP	56%	33%	71%	43%
DALM	8%	0%	21%	0%
ALM	2%	6%	24%	N/A
Flat LGD	10%	2%	28%	N/A
Flat HGD	6%	2%	13%	N/A
Colonic stenosis	26%	18%	31%	14%
Surveillance***	26%	20%	27%	29%
Colectomy****	18%	27%	22%	44%
5-ASA use	85%	90%	77%	88%
Thiopurine use	36%	64%	29%	32%
Methotrexate use	6%	27%	3%	1%
TNF-α antagonist use	17%	57%	8%	5%

IBD=inflammatory bowel disease; Dx=diagnosis; CRC=colorectal cancer; PSC=primary sclerosing cholangitis; PIP=post-inflammatory polyps; DALM= dysplasia associated lesion or mass; ALM=adenoma-like lesion or mass; LGD=low grade dysplasia; HGD=high grade dysplasia; TNF=tumor necrosis factor; N/A= not available
*Age and disease duration presented as median
**Smoking behavior scored positive for active smoking at end of follow-up or positive smoking history
*** Surveillance defined as colonoscopy with random biopsies every 10 cm of the colon
****colectomy defined as any type of surgery in which (a part of) the colon was removed (ranging from ileocecal resection to subtotal colectomy).

Leuven cohort risk factors

Table 2 shows the variables that remained statistically significant after stepwise backward elimination in the multivariate Cox-regression analysis in the Leuven cohort. Disease extent, PSC, post-inflammatory polyps, age at diagnosis, DALM and flat HGD showed an independent positive association with CRC. The use of anti-TNFα medication showed a strong negative association.

Table 2 Hazard ratios for risk factors that are independently associated with developing CRC after multivariate Cox-Regression analysis in the Leuven cohort

Patient Variable	HR	95% CI
Microscopic extent ≥50%	2.9	0.98 - 8.4
PSC	3.8	1.4 - 10.4
PIP	3.0	1.6 - 5.8
DALM	7.0	1.8 - 27.0
fHGD	6.2	1.5 - 26.1
TNF-α antagonist use	0.2	0.1 - 0.5
Age at IBD Dx> 37	2.3	1.1 – 5.0

HR=hazard ratio; PSC=primary sclerosing cholangitis; PIP= Post-inflammatory polyps; fHGD= flat high-grade dysplasia

Prediction model

After exclusion of protective factors, medication use, and all types of dysplasia, the following variables remained statistically significant after stepwise elimination and subsequent entering together in a multivariate Cox-regression analysis: IBD type, PSC, microscopic disease extent and presence of post-inflammatory polyps. The results were identical for backward and forward selection elimination processes. In this process, age at diagnosis was no longer statistically significantly associated with CRC while IBD-type and disease extent were. Table 3 shows corresponding β's and resultant integer points for the prediction model.

Table 3 Prediction scores in integer points derived from corresponding regression coefficients for each patient characteristic.

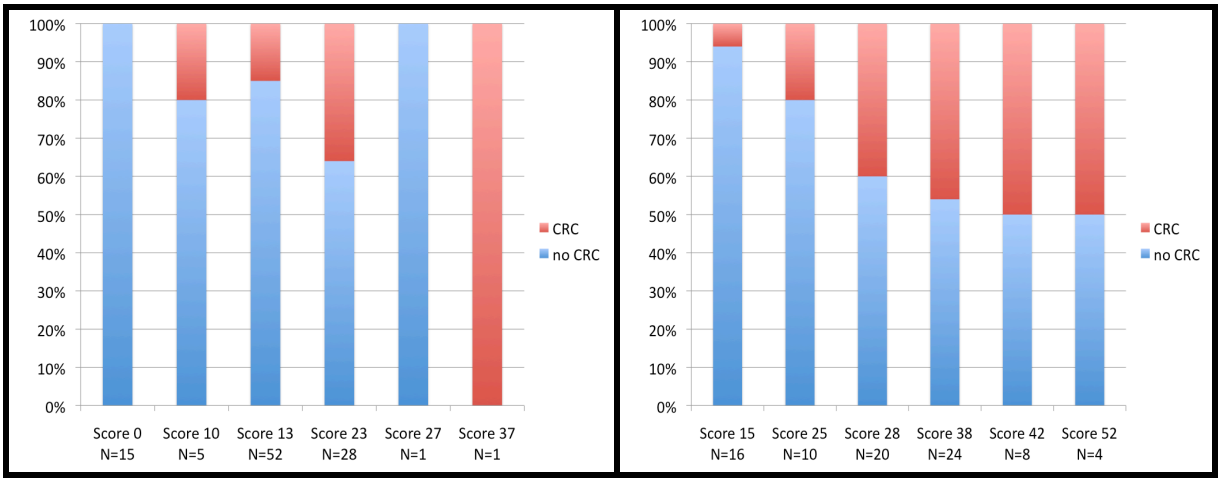
Patient Characteristic	β	HR	95% CI	P	β / 0.813	Integer
PIP	0.813	2.3	1.2 - 4.1	0.008	1	10
Microscopic disease extent ≥50%	1.070	2.9	1.0 - 8.3	0.045	1.316	13
PSC	1.127	3.1	1.3 - 7.3	0.010	1.386	14
IBD-type	1.232	3.4	1.8 - 6.4	0.000	1.515	15

PIP=post-inflammatory polyps; PSC=primary sclerosing cholangitis; IBD=inflammatory bowel disease; β=regression coefficient; HR=hazard ratio

We calculated a total score for each individual patient by adding up the integer points of the characteristics that were present in each patient. This total score per patient had a C-statistic of 0.75 (0.67-0.84; 95% confidence interval). Figure 1A and 1B show the distribution of CRC within the Leuven cohort for each score for Crohn's disease and ulcerative colitis respectively. Scores 0, 13, 23, 27, and 37 represent patients with Crohn's disease and scores 15, 25, 28, 38, 42, and 52 represent patients with ulcerative colitis. Patients with ulcerative colitis were found to have a higher risk of developing CRC. As shown in Figure 1A, Crohn's disease patients without PSC, without post-inflammatory polyps and with limited disease extent developed no CRC in the Leuven cohort. The highest risk of CRC was found in patients with ulcerative colitis, with PSC, and with post-inflammatory polyps and extensive disease (Figure 1B).

Figure 1A and 1B Leuven CRC distribution within each score

Crohn's disease **Ulcerative Colitis**

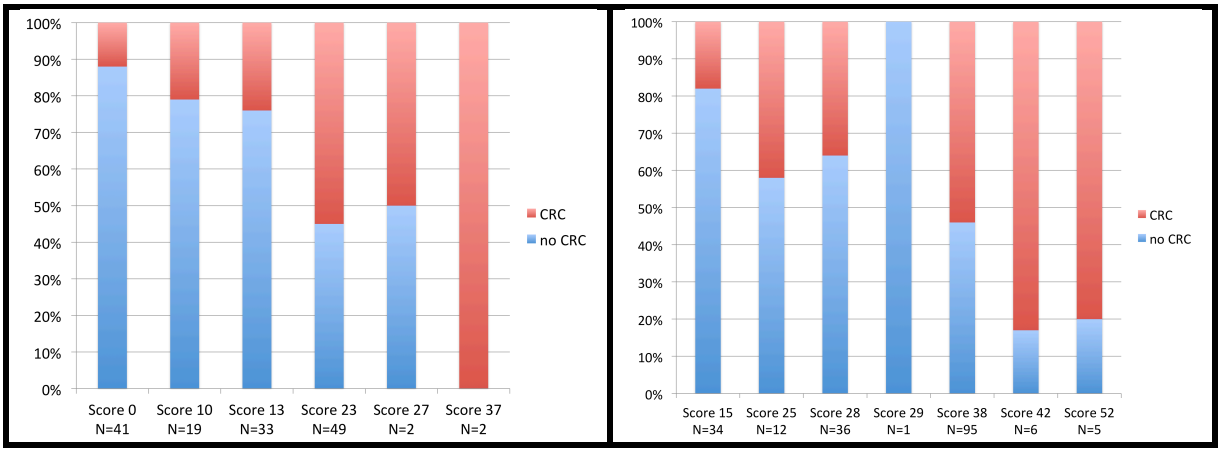


CRC = Colorectal cancer

Figure 2A and 2B shows the same distribution in the Dutch cohort based on the prediction model derived from the Leuven cohort. Again, the lowest proportion (12%) of CRC cases was found in patients with Crohn's disease with limited disease extent, without PSC or post-inflammatory polyps. Patients from the Dutch cohort with ulcerative colitis in whom all risk factors were present, had the highest CRC risk, which was as high as 80%. We found a c-statistic of 0.67 for the Dutch cohort. The Leuven and Dutch cohorts both show an increasing percentage of CRC cases with higher scores. A detailed description of the each score with corresponding CRC distributions is shown in Table 4.

Figure 2A and 2B Dutch CRC distribution within each score

Crohn's disease **Ulcerative Colitis**



CRC = Colorectal cancer

Table 4 Prediction scores and their make up of possible risk factor combinations. Higher scores show more CRC in both the Leuven and Dutch cohort.

Crohn's Colitis	**PSC**	**Extent ≥50%**	**PIP**	**% CRC Leuven**	**%CRC Dutch**
Score 0	No	No	No	0%	12%
Score 10	No	No	Yes	20%	21%
Score 13	No	Yes	No	15%	24%
Score 14	Yes	No	No	N/A	N/A
Score 23	No	Yes	Yes	36%	55%
Score 24	Yes	No	Yes	N/A	N/A
Score 27	Yes	Yes	No	0%	50%
Score 37	Yes	Yes	Yes	100%	100%
Ulcerative Colitis	**PSC**	**Extent ≥50%**	**PIP**	**% CRC Leuven**	**%CRC Dutch**
Score 15	No	No	No	6%	18%
Score 25	No	No	Yes	20%	42%
Score 28	No	Yes	No	40%	36%
Score 29	Yes	No	No	N/A	0%
Score 38	No	Yes	Yes	46%	54%
Score 39	Yes	No	Yes	N/A	N/A
Score 42	Yes	Yes	No	50%	83%
Score 52	Yes	Yes	Yes	50%	80%

PSC=primary sclerosing cholangitis; PIP=post-inflammatory polyps; N/A=Not available in cohort, i.e. no patient with that total score; CRC=colorectal carcinoma

DISCUSSION

In this study, we report an externally validated and easy-to-use prediction model for IBD-associated CRC based on two international cohorts. These results expand the findings from well-known individual risk factor studies[4,5,7,8,10,17] and for the first time support expert opinion of current surveillance guidelines to stratify patients in different risk groups.

Our model is based on 4 well-established risk factors, i.e. IBD-type, PSC, post-inflammatory polyps and disease extent. Our data demonstrate that in the presence of all these risk factors the risk of developing CRC increases significantly. Conversely, this means that in the absence of these risk factors, i.e. less than 50% of colonic involvement, no post inflammatory polyps and no PSC, the risk of CRC is low. These findings support the risk stratification strategy as proposed in the BSG surveillance guideline[9]. We could have increased the predictive power of our prediction score by adding more factors, but this would have been done at the cost of practicality and usability. For example, we could have achieved a C-statistic of 0.85 if we had included all independently associated risk factors from the Leuven cohort (Table 2). We opted for less discerning power with a C-statistic of 0.75, using 4 instead of 7 risk factors. It needs to be stressed that in a prediction model it is not essential to correct for confounding by including all possible modifiers of the CRC risk. What matters is the predictive strength of the final model.

In that respect we chose to have an unequivocal outcome variable, CRC, which is not affected by inter-observer variability. This is the reason that we did not include

dysplasia as an outcome variable because it was logistically impossible to review all pathology specimens from decades of follow-up for 2 countries, including various university medical centers[18].

We excluded medication-use from the prediction model because we did not want the protective effects of medication to overrule the decision to start colonoscopic surveillance in an otherwise extensive and severely diseased colon. However, it was interesting to observe the strong protective effect of TNF-α antagonist use on the occurrence of CRC ($p<0.001$) in the Leuven data. From our data it was not possible to determine whether this was a direct chemopreventive effect or an indirect effect through effective inflammation reduction. In order to further investigate this association we found no difference in disease severity between users and non-users of TNFα antagonists ($p=0.16$). However, due to the retrospective data collection, we scored disease severity as a maximum severity during follow-up and we did not measure disease severity before and after anti-TNFα administration. Pre-tumor colonic resections were more frequently encountered in the TNF-α antagonist user group ($p=0.008$) and patients in this group were also more often endoscoped (on average 6 endoscopies in anti-TNF-α users versus 4 endoscopies in the non anti-TNFα group; $p=<0.001$). Data on the total number of endoscopies were only available in 85% of the total group, which might have introduced a bias. One could argue that the protective effects of anti-TNF-α use could be biased because of more resections and enhanced endoscopic surveillance in this group. However, we found the protective effect to be independent in multivariate analysis (Table 2). Moreover, we found a trend towards the occurrence of less dysplasia in anti-TNFα users ($p=0.08$). We therefore believe that the increased number of resections were not the result of increased dysplasia detection through more frequent endoscopies and did not confound the protective association of anti-TNFα use. It can be concluded from these data that there seems a protective effect of anti-TNFα on CRC development, but it is not possible to be entirely sure due to the retrospective data collection. Similarly to our results, another study also reported a protective effect from anti-TNFα on CRC development[19].

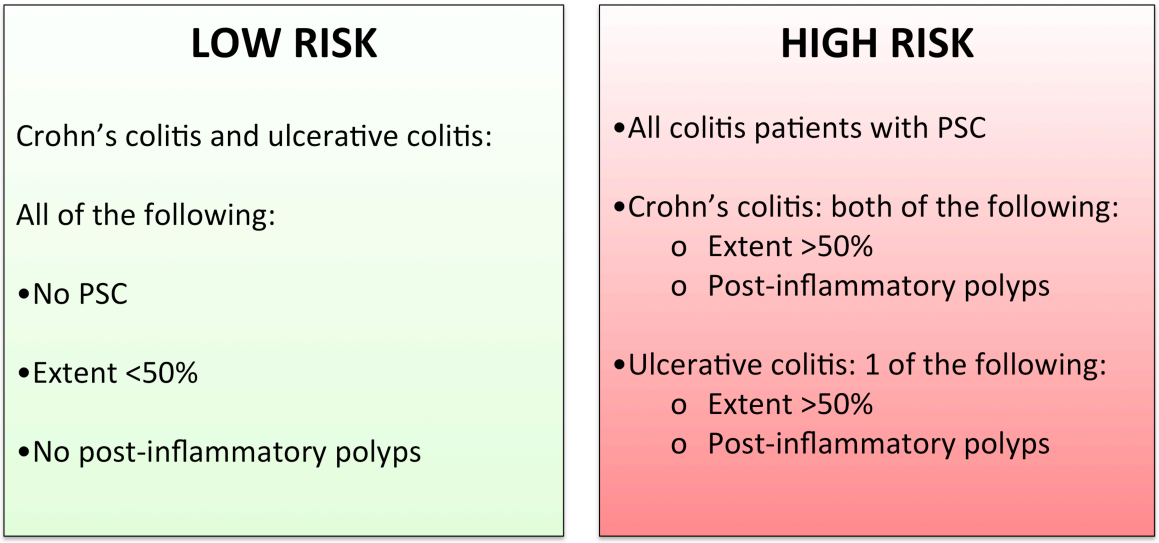
Obviously, the major limitation of our study is the abovementioned retrospective design. Study variables such as family history of CRC have a relative high number of missing data because these variables rely on accurate history taking and subsequently reporting in the patient chart by the treating physician. Some details also get lost in referral letters from regional hospitals to the referral center, such as the number of previous endoscopies and patient visits to the outpatient clinic. Another issue is inter-observer variability. For instance, the correct classification of disease activity and mucosal scarring can vary significantly per endoscopist, thereby introducing additional bias. For this reason we excluded these variables from our analyses. We assumed that post-inflammatory polyps have this problem to a far lesser extent. Moreover, when we included family history of CRC, disease severity and mucosal scarring as variables, we found them to be not statistically significant in the multivariate analysis and the statistical power decreased due too more patients being excluded from the analysis because of missing values (data not shown).

Despite our large case series and the relative low percentage of missing values (a maximum of 7.5% when a total of 19 variables were entered in the stepwise elimination regression analysis), some scores included only 1 or 2 patients, e.g. scores 27 and 37. This resulted in extreme percentages of either 0% or 100%. When

these were left out of the figures, the increase of CRC risk with higher scores was even more gradual. Notably, the scores of 27 and 37 contained only patients with extensive Crohn's disease plus PSC or post-inflammatory polyps. Based on our clinical experience, these are rare combinations. Similarly, this might also explain why not a single patient had scores of 24 or 39. These scores meant that a patient had to have post-inflammatory polyps and PSC, but a limited disease extent of <50% of the colon. Apparently this combination of characteristics is extremely rare. When PSC is left out of the prediction model, the C-statistic of a model based on the remaining 3 risk factors dropped slightly to 0.73, which is still fair. One could argue that PSC patients should always undergo colonoscopic surveillance and therefore this model should be restricted to non-PSC patients.

In summary, we established an easy-to-use prediction score based on IBD-type, PSC, presence of post-inflammatory polyps and colonic disease extent. Based on our results we present a risk stratification proposal (Figure 3). We recommend stricter surveillance in patients with ulcerative colitis with PSC, extensive disease and post-inflammatory polyps compared to Crohn's disease patients without these features. The next step should be to validate this recommendation in a prospective cohort and determine surveillance intervals for different risk groups.

Figure 3 Risk stratification proposal. The low-risk group has patients with limited disease extent and absence of PSC and inflammatory polyps. The high-risk group has all PSC patients; Crohn's colitis with extensive disease and post-inflammatory polyps; ulcerative colitis patients with either extensive disease or post-inflammatory polyps



PSC=Primary sclerosing cholangitis

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CHAPTER 7

Which Guideline to Follow for CRC Surveillance in IBD Patients? A Cost-Effectiveness Analysis Comparing AGA with BSG Guidelines

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ABSTRACT

Background: Surveillance for colonoscopic neoplasia is recommended in patients with inflammatory bowel disease (IBD)-related colitis. Data on cost-effectiveness predate current international guidelines on surveillance.

Aim: To compare cost-effectiveness of two recently updated international guidelines from the American Gastroenterological Association (AGA) and British Society of Gastroenterology (BSG) based on contemporary cost data and incidence rates of colorectal neoplasia.

Design: We performed a decision analysis by using a state-transition Markov model. We compared two surveillance strategies for a base-case colitis patient of 40 years. The AGA surveillance guideline distinguishes two groups: a high-risk group with annual surveillance and an average-risk group with bi-annual surveillance, while the BSG surveillance guideline distinguishes 3 risk groups with yearly, 3-yearly or 5-yearly surveillance. All patients started in the no-dysplasia state with colonoscopic surveillance. Then patients could stay in that stage, or move to one of 3 states for which proctocolectomy is indicated: 1) dysplasia / local cancer 2) regional / metastasized cancer 3) refractory disease. After proctocolectomy a patient was transferred to a no-colon state without surveillance. Patients were followed for 40 years. Transition probabilities, costs and health utilities were derived from the literature. Neoplasia incidence rates were calculated for risk groups based on relative risks of risk factors for the relevant group based on pilot data.

Outcome measurements: Direct medical costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs).

Results: For the base-case patient, BSG surveillance dominated AGA surveillance with $9846 per QALY. Both strategies were equally effective with 24.16 QALYs, but BSG surveillance was associated with fewer costs because of fewer colonoscopies performed. Costs related to IBD, surgery or cancer did not affect cost-effectiveness.

Conclusion: The updated risk profiling approach for surveillance of IBD-CRC by the BSG is more cost-effective than that of the AGA.

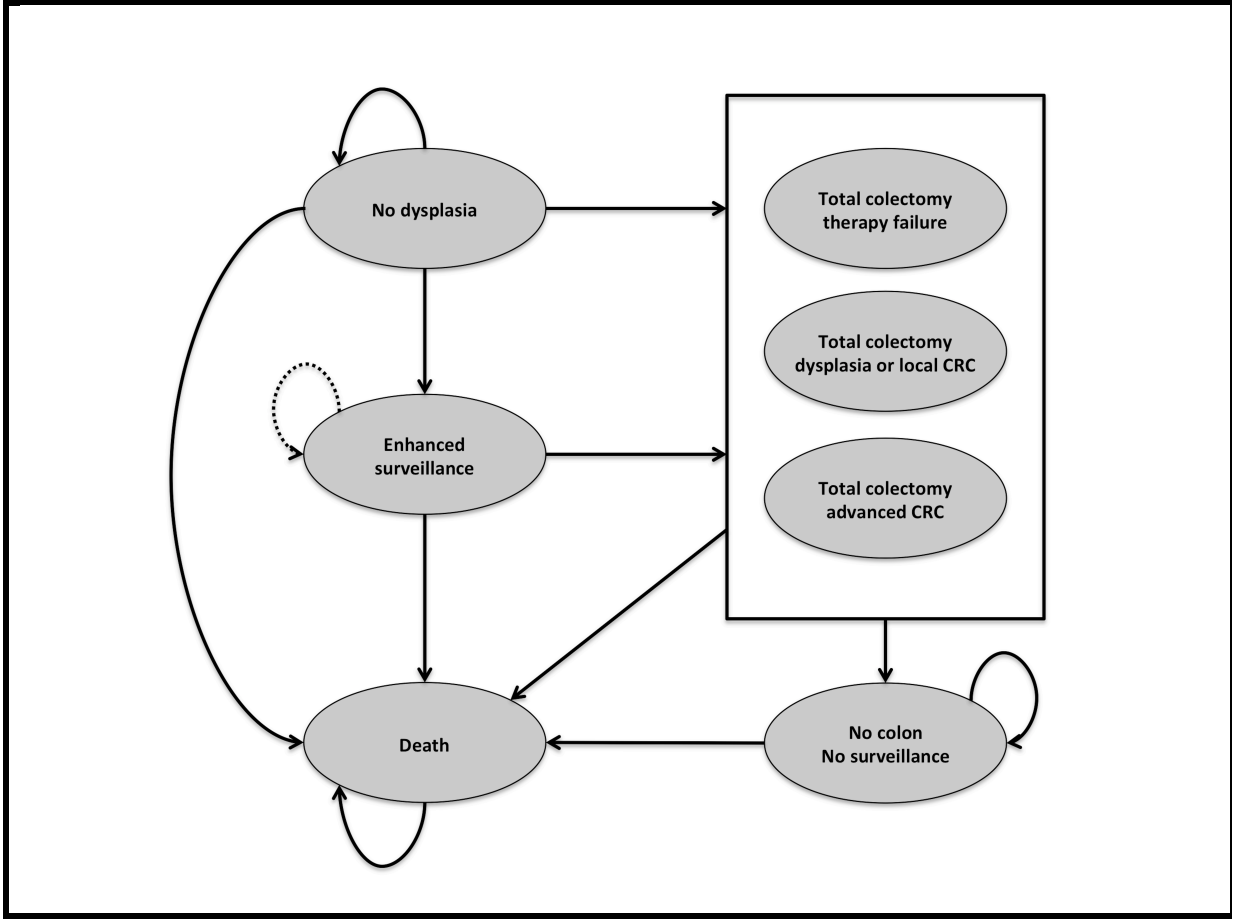
INTRODUCTION

Patients with ulcerative and Crohn's colitis are recommended to undergo colonoscopic surveillance for neoplasia after 8-10 years of disease duration. Several guidelines are currently available, with the most important being the AGA[1] and BSG[2] guidelines. Data on the cost-effectiveness of these guidelines predate the publication of these guidelines[3,4] or focus on specific subsets of patients[5,6].
Both the British Society of Gastroenterology (BSG) and American Gastroenterological Association (AGA) updated their guidelines in 2009[2] and 2010[1], respectively. With this update the BSG included a risk profiling approach by appointing IBD patients to risk groups that determined the interval between surveillance colonoscopies. The AGA did not make a clear recommendation with regard to risk profiling besides that these guidelines recommend yearly surveillance for patients with primary sclerosing cholangitis (PSC). This strategy for PSC has not changed and already was advocated by both AGA and BSG guidelines since the previous iterations of the guidelines in 2002[7] and 2003[8].
Apart from the decision analysis by Nguyen et al.[5], distinguishing between continued surveillance and total colectomy when low-grade dysplasia is found, no overall analysis describing the cost-effectiveness of these guidelines has been published. We hypothesized that risk profiling as proposed by the BSG would be more cost-effective than bi-annual surveillance as recommended by the AGA for the majority of patients. Our aim was to therefore to compare the cost-effectiveness between the BSG and AGA guidelines.

MATERIALS & METHODS

We performed a decision analysis by developing a state-transition Markov model to simulate the clinical course of IBD patients at the start of surveillance for the remainder of lifetime (Figure 1). We compared the colonoscopic surveillance guidelines of the AGA and BSG. AGA surveillance consists of annual or bi-annual colonoscopic surveillance depending on the presence or absence of PSC respectively. The BSG recommends surveillance colonoscopy annually, every 3 years, or every 5 years depending on the risk profile of each individual patient. The outcomes of this study were cost, quality of life adjusted life years (QALYs), and the incremental cost per QALY gained.

Figure 1 One-year Markov cycle health states and possible transitions for a 40-year-old patient with ulcerative or Crohn's colitis with a life expectancy of 80 years.



All patients start in the no-dysplasia health state, in which they stay until they die, develop neoplasia, or undergo proctocolectomy due to therapy-refractory disease. After proctocolectomy they are transferred to the no-colon no surveillance health state in which they stay until they die. The enhanced surveillance is an optional health state to which patients are transferred after they are diagnosed with low-grade dysplasia and have declined surgery. They stay here until they die or develop high-grade dysplasia or colorectal carcinoma, which transfers them to one of the appropriate proctocolectomy health states. The corresponding transitions to enhanced surveillance are represented with dotted lines.

Patient population

Our study was designed for a base case IBD patient with either ulcerative colitis or Crohn's colitis that was diagnosed at the age of 30 and started colonoscopic surveillance after 10 years of disease at the age of 40 with an intact colon[9]. Life expectancy at the age of 40 was another 40.0 years[10].

Model Structure

Patients were assigned to either AGA or BSG surveillance and followed through one-year Markov cycles over a lifetime horizon. All patients started in a health state of no neoplasia. At the end of a cycle patients could remain neoplasia free, transfer to one of three total colectomy health states or die. The three proctocolectomy health states were: 1) proctocolectomy for therapy-refractory disease; 2) proctocolectomy for low-grade dysplasia, high-grade dysplasia, or local cancer; 3) proctocolectomy for regional or distant cancer including chemotherapy. After proctocolectomy, patients transferred to a no-colon health state where they remained until death. Although guidelines recommend proctocolectomy for confirmed non-adenoma-like low-grade

dysplasia, many physicians perform enhanced surveillance when low-grade dysplasia is found. We incorporated this optional health state, which indicated two colonoscopies per year until high-grade dysplasia or cancer was found. These patients would then undergo proctocolectomy or die.

Clinical representation

To determine annual incidence rates of neoplasia for each risk group of annual, bi-annual, 3-yearly or 5-yearly surveillance, we derived yearly incidence rates from the literature (Table 1). Subsequently, these incidence rates were proportionally multiplied by applicable risk multipliers (Table2). To determine the distributions between risk groups and proportions of risk multipliers within risk groups, we used data from our cohort as recently reported by Mooiweer et al.[11], in which 1018 consecutive patients undergoing colonoscopic surveillance in our tertiary referral center and 1 large general hospital were studied. This allowed allocation of patients to AGA and BSG risk groups.

Table 1 Incidence rates for neoplasia in different surveillance interval groups, colectomy, and mortality

Variable	Incidence / pyr	95% CI	Reference
From no dysplasia			
LGD	0.021 / pyr	0.015 - 0.03	12
HGD / CRC	0.004 / pyr	0.001 - 0.018	13
From LGD			
HGD / CRC	0.03 / pyr	0.012 - 0.076	12
High-risk AGA annual surveillance			
LGD	0.107 / pyr	0.048 - 0.249	This paper
HGD	0.020 /pyr	0.003 - 0.149	This paper
Average-risk AGA bi-annual surveillance			
LGD	0.091 / pyr	0.022 - 0.237	This paper
HGD	0.017 / pyr	0.002 - 0.142	This paper
High-risk BSG annual surveillance			
LGD	0.134 / pyr	0.036 - 0.334	This paper
HGD	0.026 / pyr	0.002 - 0.200	This paper
Intermediate-risk 3-yearly surveillance			
LGD	0.094 / pyr	0.027 - 0.222	This paper
HGD	0.018 / pyr	0.002 - 0.133	This paper
Low-risk 5-yearly surveillance			
LGD	0.071 / pyr	0.015 - 0.206	This paper
HGD	0.014 / pyr	0.001 - 0.124	This paper
Total colectomy therapy failure	0.036 / pyr	0.03 - 0.042	14
Death by any cause	0.007 / pyr	Not available	15
Death after colectomy therapy failure	0.018 / pyr	0.006 – 0.041	16
Death by localized cancer	0.020 / pyr	0.013 – 0.06	5
Death by regional cancer	0.083 / pyr	0.064 – 0.131	5
Death by metastasized cancer	0.482 / pyr	0.373 – 0.869	5

LGD=low-grade dysplasia; HGD=high-grade dysplasia; CRC= colorectal carcinoma; pyr=personyear; AGA=American Gastroenterological Association; CI=Confidence interval

Following the AGA guidelines, 6% of patients should have to undergo annual surveillance and the remaining 94% bi-annual surveillance. When employing the BSG guidelines, 20% of patients should have to undergo annual surveillance and 39% 3-yearly and 41% 5-yearly surveillance. All distributions, proportions and risk multipliers are shown in Table 2.

Table 2 Patient distributions in risk profile groups and risk multipliers derived from the literature

Variable	Distribution		Reference
BSG low-risk group	**41%**		11
Left-sided colitis or <50% of colon	68%		11
Extensive colitis without activity	32%		11
BSG intermediate-risk group	**39%**		11
Extensive colitis with mild activity	46%		11
Post inflammatory polyps	48%		11
Family history of CRC in FDR >50yr	6%		11
BSG high-risk group	**20%**		11
PSC	32%		11
Family history of CRC in FDR <50yr	4%		11
Extensive colitis with severe activity	64%		11
AGA average-risk group	**94%**		11
Left-sided colitis or <50% of colon	30%		11
Extensive colitis without activity	47%		11
Post inflammatory polyps	20%		11
Family history of CRC in FDR <50yr	1%		11
Family history of CRC in FDR >50yr	2%		11
AGA high-risk group	**6%**		11
PSC	100%		11
Variable	**RR**	**95% CI**	**Reference**
PSC	5.1	3.2 – 8.3	17
Extensive disease	6.9	1.9 – 11.9	Lutgens et al. IBD. 2013
Left sided disease	1.7	0.6 – 4.5	Lutgens et al. IBD. 2013
Family history CRC in FDR <50yr	9.2	3.7 – 23	18
Family history CRC in FDR >50yr	1.7	0.8 -3.4	18
Post inflammatory polyps*	2.5	1.4 – 4.6	19,20, Lutgens et al. IBD 2013

BSG=British Society of Gastroenterology; CRC= colorectal carcinoma; FDR=first degree relative; AGA=American Gastroenterological Association; PSC=primary sclerosing cholangitis; RR=relative risk N/A=Not applicable
*pooled RR from 3 studies with random effects; individual studies weighted by sample size.

Mortality

Annual incidence of death of the general US population[10] was multiplied by standardized mortality ratios for ulcerative colitis and Crohn's disease after 10 years of disease (1.1 and 1.49 respectively)[21]. This was done in a ratio of 1.7 : 1 for ulcerative colitis versus Crohn's disease based on prevalence data of Olmsted County in the US[9,22,23]. Annual mortality rates for colectomy and cancer were derived from literature (Table 1).

Utilities

In order to calculate QALYs, we derived utility values from the literature (Table 3). Utilities represent the preference of a patient to be in a particular health state and ranges from 0 (worst possible health) to 1 (perfect health). A weighted utility value was calculated for regional and distant colorectal cancer together based on a distribution of 78% local cancer, 20% regional cancer and 2% distant metastasized cancer[5]. An annual discount rate of 3% was used for all utilities.

Table 3 Health utility states associated with colonoscopic surveillance for colorectal cancer in inflammatory bowel disease-related colitis

Variable	Base-case analysis	Sensitivity analysis	Reference
No dysplasia	0.94	0.94 - 1.00	5
Enhanced surveillance	0.74	0.69 - 0.78	5
Colectomy therapy failure	0.80	0.32 - 0.94	5
Colectomy dysplasia / local CRC	0.74	0.69 - 0.78	5
Colectomy regional / distant CRC*	0.56	0.51 - 0.66	5
No colon, no surveillance	0.92	0.85 - 0.94	5

*composite weighted

Cost calculations

We adopted the third-party payer perspective and therefore only used direct medical costs. These were estimated from literature (Table 4). The no-dysplasia health state consisted of annual IBD-colitis costs before proctocolectomy plus costs for surveillance colonoscopy[5,24]. The no-colon-no-surveillance health state was based on IBD-costs after proctocolectomy[24]. The costs for the colectomy-for-refractory-disease health state were calculated by using direct medical costs associated with performing a proctocolectomy as published by Loftus et al[25]. Costs for colectomy health states including cancer were calculated with the following formula: (costs_colitis_pre_colectomy*0.5)+(costs_colitis_post_colectomy*0.5)+(costs_colectomy)+((1-annual_incidence_death)*initial_costs_cancer stage)+(annual_incidence_death*terminal_costs_cancer stage). Initial and terminal costs for cancer stage were derived from the paper by Nguyen et al[5]. We calculated costs in dollars because the literature from the US provided the most accurate cost estimates for our health states. Costs were discounted at a rate of 3%.

Table 4 costs for variables that were used to calculate total costs per health state

Variable	Annual costs	95%CI	Reference
Colonoscopy with 32 random biopsies	$ 1752	$ 1215 - 3056	5
Colitis before proctocolectomy	$ 8966	$ 4483 - 17932*	24
Colitis after proctocolectomy	$ 3510	$ 1755 - 7020*	24
AGA annual surveillance	$ 10718	$ 5359 - 21436*	5,24
AGA bi-annual surveillance	$ 9842	$ 4921 - 19684*	5,24
BSG annual surveillance	$ 10718	$ 5359 - 21436*	5,24
BSG 3-yearly surveillance	$ 9550	$ 4775 - 19100*	5,24
BSG 5-yearly surveillance	$ 9316	$ 4658 - 18633*	5,24
Enhanced surveillance	$ 12470	$ 6235 - 24940*	5,24
Colectomy therapy failure	$ 90445	$ 45223 - 180890*	25
Colectomy dysplasia / local CRC	$ 123327	$ 61663 - 246653*	5,24,25
Colectomy regional / distant CRC	$ 162909	$ 81445 - 325820*	5,24,25

*50% and 200% 95% confidence interval chosen when they weren't reported in referenced publication or a composite cost was calculated.
AGA=American Gastroenterlogical Association; BSG=British Society of Gastroenterology; CRC=colorectal carcinoma

Sensitivity analyses

One-way sensitivity analysis was performed to get an overview of the most influential modifiers on cost-efficiency results. We used variations based on estimated ranges available from literature. If these variations were not available or comparable for costs, 50% and 200% of the base-case value were used for low and high values, respectively. We applied a willingness-to-pay threshold of $50,000 per QALY to obtain parameter threshold values at which BSG or AGA switched cost-efficiency. To address the issue of potentially more interval carcinomas with longer surveillance intervals, we performed a separate analysis by adding risk multipliers to the surveillance interval groups that were longer than 1 year. No data exist that report neoplasia incidence rates between varying lengths of surveillance intervals. Therefore we chose to multiply the incidence rate of interval carcinomas with the corresponding length of surveillance in years. As a surrogate for the incidence rate of interval carcinomas we chose the incidence rate that was reported by Lim et al. [47] for high-grade dysplasia or colorectal cancer without previous established low-grade dysplasia. After applying the risk factor multipliers as described above, this incidence rate was additionally multiplied by 2, 3, and 5 for bi-annual AGA surveillance, 3-yearly BSG surveillance and 5-yearly BSG surveillance respectively.

RESULTS

For our base-case colitis patient of 40 years old, we found equal effectiveness for both BSG and AGA surveillance with QALYs of 24.16. As the costs for BSG surveillance was $9,846 per QALY compared to $9944 per QALY for AGA surveillance, BSG surveillance dominated AGA surveillance. If we consider the enhanced surveillance option, then BSG surveillance was still found to be more cost-effective with $10,834 per QALY compared to $10,982 for the AGA.

A sensitivity analysis of colonoscopy costs, colitis costs before and after colectomy, and cancer related costs did not change our results. Higher neoplasia incidence rates in the population at risk did however change our results, resulting in the BSG surveillance schemes to become less effective. High incidence rates for high-grade dysplasia and CRC or low-grade dysplasia in BSG surveillance resulted in slightly lower QALYs for these groups (Table 5).

Table 5 Sensitivity analyses: high values of BSG neoplasia incidence rates

Variable	Incidence rate	BSG QALY	AGA QALY	ICER
BSG yearly HGD/CRC	0.20 / personyear	24.15	24.16	$ 296,209
BSG 3-yearly HGD/CRC	0.13 / personyear	24.14	24.16	$ 92,319
BSG 5-yearly HGD/CRC	0.12 / personyear	24.13	24.16	$ 59,085
Variable	**Incidence rate**	**BSG QALY**	**AGA QALY**	**ICER**
BSG yearly LGD	0.33 / personyear	24.15	24.16	$ 392,169
BSG 3-yearly LGD	0.22 / personyear	24.14	24.16	$ 128,993
BSG 5-yearly LGD	0.21 / personyear	24.13	24.16	$ 80,662

ICER=incremental cost-effectiveness ratio; BSG=British Society of Gastroenterology; HGD=high-grade dysplasia; CRC=colorectal carcinoma

The corresponding ICERs, however, were very high and above our chosen willingness-to-pay threshold of $50,000. To a similar extent, higher incidence rates of neoplasia for AGA surveillance resulted in lower QALYs for AGA surveillance,

consequently rendering the BSG guideline even more cost-effective compared to the base-case analysis.
If risk multipliers were added to the longer surveillance interval groups to address the issue of interval carcinomas when longer surveillance intervals are employed, then AGA surveillance was more effective but with an incremental cost effectiveness ratio of $131,869.

DISCUSSION

The results of our cost-effectiveness study suggest that BSG surveillance is equally effective as AGA surveillance but can be performed at lower costs. The fact that BSG surveillance and AGA surveillance had the same QALY indicates that colorectal cancer incidences for both strategies were similar. This is expected, as the inherent overall neoplasia risk does not differ between patients irrespective of which surveillance strategy they follow. This also indirectly validates our model, because overall cancer incidence was almost the same in the AGA and BSG group despite different distributions of risk factors in the risk groups. As a consequence a similar number of patients were transferred to the proctocolectomy health-states resulting in equal QALYs for both surveillance strategies. Therefore, costs remained the main factor driving the cost-effectiveness. Because following the BSG guideline results in fewer surveillance colonoscopies to be performed, and therefore in lower costs, this was the strategy that came out superior in our decision analysis.

One important issue that we tried to address is that of interval carcinomas. Obviously, longer surveillance intervals like the BSG 5-yearly surveillance interval, might lead to more interval cancers. We tried to evaluate this by incorporating an incidence rate for high-grade dysplasia/colorectal cancer without a previous state of low-grade dysplasia of 0.004 per personyear to all risk groups multiplied by their respective risk factors. This strategy was adopted because currently no population-based prospective data are available on differences of interval carcinoma rates between different surveillance intervals. Intuitively, longer intervals between colonoscopies might result in higher interval carcinoma rates. On the other hand, the longest intervals are employed in patients with the lowest risk profile. Due to our design, our model was based on the latter approach and, as a result, higher rates of interval carcinomas were calculated in the short-interval groups. In order to explore the opposite scenario we did an analysis in which we applied higher risk multipliers for interval cancers in the long-interval groups as described in the methods. In this scenario, BSG surveillance did not dominate AGA surveillance anymore. AGA surveillance was then likely to be more effective, but at an incremental cost effectiveness ratio of $131.869 per QALY gained. This is above the predefined willingness-to-pay threshold of $50.000 and indirectly suggests that shortening surveillance intervals to prevent interval carcinomas is not cost-effective. The same effect was observed in the sensitivity analysis for neoplasia incidence rates (Table 5). This sensitivity analysis is of course a hypothetical situation in which we only increased the BSG neoplasia incidence rates to the highest values of their variations. For a correct reflection of a real life situation when one uses the high value for BSG incidence rates, one should also use these high values for the AGA incidence rates. However, we did it to illustrate the difference in the model when only one surveillance strategy has higher neoplasia incidence rates. When the highest values of the

variation for incidence rates are only used in the BSG group, then QALY's are slightly lower compared to the AGA surveillance. However, none of the ICERs were below the willingness-to-pay threshold. In other words, if BSG surveillance would lead to more interval cancers, then it would still not be cost-effective to follow the AGA guideline as an alternative.

A drawback of our model is that only neoplasia and colectomy resulted in a lower quality of life. In the real life situation, the length of surveillance intervals might also influence quality of life. One might expect patients with longer surveillance intervals to experience a better quality of life because this could reduce the number of these invasive and unpleasant procedures. This is only an assumption and no data are available to compare quality of life between patients with annual, bi-annual, 3-yearly or 5-yearly colonoscopic surveillance. Our model did not allow us to compare fictional utilities for different surveillance intervals. However, we can speculate that this would favor the BSG surveillance because of a lower surveillance burden. Moreover, our study, like all medical decision analyses, depended on the assumptions that are made to reflect clinical practice as closely as possible. This is somewhat limited when empirical data are missing for a particular transition probability or if costs are unknown for a particular health state. For instance, we were not able to identify solid data on the incidence of proctocolectomy for treating refractory Crohn's colitis. Studies that report incidence rates for therapy refractory colitis are mainly based on ulcerative colitis patients. We therefore assumed that incidence rates for proctocolectomy for Crohn's colitis are the same, while in clinical practice these numbers may be different for Crohn's patients. Another difficult issue is estimating costs accurately. We tried to compensate for this limitation by using a wide range of values for our sensitivity analyses. Neither the high nor the low values caused AGA surveillance to dominate over BSG surveillance, or resulted in a significant change of ICERs to drop below or rise above the willingness-to-pay threshold. Finally, costs in our study were derived from American literature because this provided us with the most accurate data for the health states of our model. This is difficult to extrapolate to the European practice due to different health care reimbursement systems per country and different philosophies about the willingness-to-pay threshold. For example, the Netherlands maintains threshold of €20,000-80,000 depending on the disease. In the US this number is usually higher.

In summary, we demonstrate that the risk profiling approach of the BSG with 3 risk groups with different surveillance intervals is more cost-effective than AGA surveillance.

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CHAPTER 8

Summary and Conclusions

Summary and Conclusions

In the period 2008-2013, we published or submitted for publication 6 studies that all focused on colonoscopic surveillance in patients with inflammatory bowel disease (IBD). In **Chapter 2** we showed that a large proportion of patients (10-20%) do not benefit from surveillance because they already had developed colorectal cancer before the recommended starting date of surveillance. Our data did not allow us to investigate whether these patients had already longstanding but subclinical colonic inflammation or an accelerated inflammation-dysplasia-cancer sequence. However, starting surveillance immediately after the diagnosis of IBD in all patients at risk to prevent early colitis-associated cancer would not be cost-effective. We therefore suggested that more studies are needed to identify this subgroup of patients. These results were published in 2008 in Gut[1]. In December 2009, the British Society of Gastroenterology (BSG) updated their guideline and proposed to define low, intermediate and high-risk patient groups with corresponding surveillance intervals of 5 years, 3 years, and 1 year, respectively[2]. The start of surveillance was changed from 10 years after a diagnosis to 10 years after the first symptoms that could be attributed to IBD. This is more in line with our conclusions and might permit identification of at least a number of early colitis-associated carcinoma cases.

Subsequently, we analyzed our dataset to retrospectively assess the efficacy of colonoscopic surveillance for neoplasia in IBD (**Chapter 3**). We concluded that surveillance reduced both colorectal cancer-related and overall mortality, due to detection of lesions at an earlier stage. Our study adds to the evidence that was summarized in a review on this topic by the Cochrane Collaboration in 2006[3]. The main conclusion of this review was that the beneficial effect of colonoscopic surveillance reported in literature was prone to lead-time bias. Our study had a similar setup as the study by Choi et al.[4], one of the three studies on which the Cochrane review was based, and would therefore have the same design flaw. We respectfully disagree with this opinion, because lead-time bias can only play a role when the intervention has no effect on the outcome. It is generally accepted that the detection of early stage cancer improves survival. Moreover, a recent publication has suggested that screening for sporadic colorectal cancer is most optimal for patients with a life expectancy longer than 10 years[5]. In case of IBD, life expectancy usually exceeds this limit by far, because of the young age at diagnosis of IBD[6]. This suggests that surveillance is beneficial in most IBD patients.

Prior to making a proposal for a modified surveillance guideline, we decided to perform a new meta-analysis to re-evaluate the risk of colorectal cancer in ulcerative and Crohn's colitis patients. In fact, the results of this new review were also required for the Markov analysis that we performed in **Chapter 7**. In our opinion, we could not use data from previously published meta-analyses because these were all based on results from heterogeneous study populations and had included data from patients after total colectomy or patients with isolated ileal Crohn's disease that are not at an increased risk for developing colorectal cancer. Using strict inclusion criteria to avoid selection bias, we showed that the risk of colorectal cancer was lower than previously reported (**Chapter 4)**. Our estimate of the cumulative risk of colorectal cancer after 30 years of IBD is 5% in population-based studies. This is substantially lower compared to the 18%, reported by Eaden et al. in 2001[7]. Thus, the risk of colorectal

cancer in ulcerative and Crohn's colitis after 30 years of disease is comparable to the lifetime risk of sporadic colorectal cancer. Of particular interest was the decline in risk in some cohorts as already pointed out in the introduction of this thesis. A number of reasons have been suggested for this decline in risk, specifically the increased use of chemopreventive drugs such as mesalazine[8] or thiopurines[9], a better disease control, and the increasing practice of surveillance programs in these patients. While there is much to say on the roles of chemoprevention and enhanced surveillance, we believe that other factors may play a role as well. For example, it is likely that ageing of IBD patients in these cohorts is an important factor. For example, the Swedish Uppsala cohort, as reported in the publications of Ekbom[10,11] and Soderlund[12], did not enroll new patients. Therefore it is conceivable that most high-risk patients dropped out of this cohort, thereby reducing the overall risk in the remaining cohort if it would be followed-up indefinitely. Moreover, because the risk of sporadic cancer in the background population will increase with age, the incidence ratios will fall further (a lower rate of observed and a higher rate of expected colorectal cancer). This is in line with Soderlund's conclusion in 2009 that the risk had declined compared to the background population, but had not much changed within the cohort itself[12]. This hypothesis is also in line with the results of a recent publication by Herrinton et al. [13] They report a contemporary and new cohort of IBD patients from California from 1998 to 2010. In this new cohort an increased incidence of colorectal cancer in IBD patients was observed that had remained stable over time.

Despite lower overall standardized incidence ratios and cumulative risks, it is generally accepted that there are still patients with much higher risks, such as patients with extensive colitis and primary sclerosing cholangitis. We reported that patients with extensive ulcerative and Crohn's colitis had a nearly 7 times higher risk of developing colorectal cancer than the background population. Therefore we believe it is not efficient to develop guidelines that do not take these diverging risk profiles in account. We support an approach in which patients are stratified into low, intermediate and high-risk groups as proposed in the updated BSG guidelines[2]. These recommendations were based on individual studies reporting predictive factors of colorectal cancer risk in IBD patients, but these recommendations were not prospectively evaluated. This prompted us to develop a risk prediction model that incorporated all these factors. For this, we collaborated with the University Hospital Leuven in order to perform an external validation of our model, which is an essential step to establish a risk prediction model (**Chapter 6**). Based on only four factors we developed a prediction model with a fairly good predictive power with a C-statistic of 0.75. The factors included were ulcerative colitis or Crohn's colitis, concomitant primary sclerosing cholangitis, presence or absence of post-inflammatory polyps and disease extent of more or less than 50% of colonic mucosa. This was verified in our Dutch cohort and resulted in a proposal of a modified surveillance guideline that is depicted in Figure 3 of Chapter 6. This is the first study that combines risk factors to predict colorectal cancer development and also performs an external validation. It provides specific evidence for the risk profiling approach by the updated BSG guidelines.

Our final study from **Chapter 7** shows that the risk profiling approach of the BSG guideline is more cost-effective than that of the AGA guideline. This can largely be explained by lower costs due to fewer colonoscopies because 41% of IBD patients are in the low risk group, with recommended surveillance intervals of 5 years.

Because the AGA guideline recommends surveillance intervals of 1 to 3 years for all IBD patients that do not have primary sclerosing cholangitis, we decided to use bi-annual surveillance for this group. This means that 94% of patients have a surveillance colonoscopy every 2 years when following the AGA guideline. Despite being more cost-effective, one can argue that longer intervals can lead to more interval cancers. When we applied higher risk multipliers to the groups with longer intervals, the BSG surveillance no longer dominated the AGA guideline, but it was not cost-effective with an incremental cost-effective ratio of more than $130.000, which is much higher than any willingness-to-pay threshold.

In summary, we started with the observation that surveillance guidelines from 2002 and 2003[14,15] resulted in 10-20% of patients developing colorectal cancer before the first surveillance colonoscopy. Furthermore, we found that the overall risk of colorectal cancer in the average IBD patient was 5% after 30 years of disease, which is significantly less than previously thought. This decreasing cumulative risk is probably due to implementation of surveillance regimens, the increased use of more effective and chemopreventive drugs and the inclusion of older age cohorts in studies on which recent meta-analyses, including our own, were based. The next step was to find ways to improve the present guidelines by identifying patients with the highest risk of developing colorectal cancer. We confirmed that the risk of IBD related colorectal cancer was much higher in subsets of patients with primary sclerosing cholangitis, extensive disease and post-inflammatory polyps. In combination with the type of IBD (either Crohn's disease or ulcerative colitis) it is possible to identify patients at high risk for colorectal cancer. Finally we showed that a risk profiling approach is likely to be cost-effective.

In this thesis we only focused on clinical parameters to predict cancer risk. In the near future it might be possible to combine clinical parameters with biomarkers for neoplastic progression, e.g. abnormal DNA-ploidy and p53 immunopositivity[16]. These two biomarkers have been shown to be associated with hazard ratios of 4.7 and 3.0 of developing colorectal cancer in patients with colitis in a study by Gerrits et al[17]. These parameters could be valuable additions to the risk prediction model presented here. Biopsy material from the Dutch IBD Biobanking Project "Parelsnoer" will enable us to investigate this in more detail.

In order to further improve surveillance guidelines, we propose that future studies need to focus on the following items:

1) Validation of the risk profiling approach in prospectively followed cohorts of IBD patients;
2) Validation of the proposed surveillance intervals of 1, 3 and 5 years for the corresponding low, intermediate and high risk groups;
3) Addition of molecular biomarkers for neoplastic progression to the current risk profiling

This will undoubtedly aid in further tailoring surveillance guidelines to the individual patient and in achieving the most cost-effective way of preventing colorectal cancer in IBD.

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CHAPTER 9

Dutch Summary – Nederlandse Samenvatting

Nederlandse Samenvatting

In de periode van 2008-2013 werden in totaal 6 studies verricht die gericht waren op het ophelderen van verschillende aspecten van colorectaal carcinoom bij patiënten met de inflammatoire darmziekten (IBD) colitis ulcerosa of morbus Crohn van het colon.

In **Hoofdstuk 2** lieten we zien dat een groot deel (10-20%) van de IBD patiënten geen baat heeft bij surveillance, omdat er al sprake is van een colorectaal carcinoom op het moment dat de eerste surveillance coloscopie uitgevoerd zou moeten worden volgens de toen geldende richtlijnen. Met onze gegevens was het niet mogelijk om te onderzoeken of deze patiënten reeds lang bestaande, maar subklinische, ontsteking van het colon hadden, danwel versneld de inflammatie-dysplasie-carcinoom sequentie doorliepen. Direct na de IBD diagnose starten met coloscopische surveillance heeft mogelijk een nadelig effect op de kwaliteit van leven en is waarschijnlijk ook niet kosten effectief. Daarom concludeerden wij dat er meer studies nodig zijn om de subgroep van patiënten te identificeren die een verhoogd risico hebben op colorectaal carcinoom of dit snel ontwikkelen. In december 2009 heeft de British Society of Gastroenterology (BSG) een vernieuwde surveillance richtlijn uitgebracht [1]. Zij stellen voor om subgroepen van laag, gemiddeld en hoog risico patiënten te identificeren met bijbehorende surveillance intervallen van respectievelijk 5, 3 en 1 jaar. De start van surveillance is ten opzichte van 2002 veranderd van 10 jaar na de diagnose van IBD naar 10 jaar na de eerste symptomen van IBD [1,2]. Dit is meer in overeenstemming met onze bevindingen (zie Hoofdstuk 2 en 6) en zou mogelijk een aantal vroege carcinomen eerder kunnen identificeren.

In Hoofdstuk 3 werd binnen ons retrospectief cohort van IBD patiënten met CRC de 5-jaars overleving van de patiënten die wel surveillance hadden ondergaan, vergeleken met de 5-jaars overleving van patiënten die geen surveillance hadden ondergaan. Wij concludeerden dat surveillance de colorectaal carcinoom-gerelateerde alsmede de totale sterfte verminderde als gevolg van detectie van laesies in een vroeger stadium. Onze studie vult de resultaten aan van een Cochrane review uit 2006 [3]. De belangrijkste conclusie van dit review was dat het gunstige effect van coloscopische surveillance, zoals dat gemeld werd in de literatuur, gevoelig was voor lead-time bias. Onze studie heeft een soortgelijke studie-opzet als de studie van Choi et al. [4], één van de drie studies waarop het Cochrane review is gebaseerd. In het verlengde hiervan kan men redeneren dat ook onze resultaten beïnvloed zijn door lead-time bias. Wij zijn echter van mening dat lead-time bias geen rol speelt bij surveillance van colorectaal carcinoom omdat deze vorm van bias alleen een rol kan spelen als de interventie geen effect heeft op de uitkomst. Het is algemeen aanvaard dat de detectie van kanker in een vroeg stadium de overleving verbetert.

Hoofdstuk 4 laat de resultaten zien van een nieuwe meta-analyse over het risico op colorectaal carcinoom bij patiënten met colitis ulcerosa en morbus Crohn van het colon. Wij hebben hierbij geen gebruik gemaakt van gegevens uit eerdere meta-analyses [5-8], omdat deze deels gebaseerd zijn op resultaten van heterogene onderzoekspopulaties. Verder werden in deze eerdere meta-analyses gegevens uit studies gebruikt, waarin patiënten geïncludeerd zijn na totale colectomie of met een geïsoleerde morbus Crohn van het ileum. Deze patiënten hebben geen verhoogd risico op een colorectaal carcinoom omdat er geen colon meer aanwezig is of omdat

het colon nooit ontstoken is geweest. Wij probeerden deze tekortkomingen te vermijden door met strikte inclusiecriteria selectiebias tot een minimum te beperken. Onze schatting van het cumulatieve risico op colorectaal carcinoom na 30 jaar IBD is 5% in de doorsnee IBD populatie. Dit is aanzienlijk lager dan de 18% die werd gerapporteerd door Eaden et al. in 2001 [5]. Het risico op colorectaal carcinoom in ulceratieve colitis en morbus Crohn van het colon na 30 jaar ziekte is dus vergelijkbaar met het levenslange risico op het sporadisch colorectaal carcinoom in de algemene bevolking. De daling van de risico's op colorectaal carcinoom in sommige IBD cohorten zoals reeds aangegeven in de inleiding van dit proefschrift is opvallend. Een aantal oorzaken is hiervoor in de literatuur aangedragen. Met name het toegenomen gebruik van chemopreventieve medicatie zoals mesalazine preparaten [9] en thiopurines [10], een betere controle van inflammatie, en het toenemend volgen van de richtlijn voor coloscopische surveillance kan deze afname wellicht verklaren. Hoewel er veel te zeggen valt over de rol van chemopreventie en surveillance in dit verband, zijn wij van mening dat ook epidemiologische factoren een rol kunnen spelen. Het is bijvoorbeeld mogelijk dat de veroudering van IBD patiënten in studie cohorten een belangrijke factor gespeeld kan hebben. In het Zweedse Uppsala cohort [11-13] bijvoorbeeld, werden gedurende follow-up van de studie geen nieuwe patiënten geïncludeerd. Het is denkbaar dat het merendeel van de hoog risico patiënten vroeg uit dit cohort wegviel, waardoor het totale risico in het resterende cohort afnam. Bovendien zal de cumulatieve toename van het risico op het sporadisch colorectaal carcinoom in de achtergrond populatie bij een verouderend cohort de ratio tussen waargenomen en verwachte aantallen gevallen van colorectaal carcinoom verder doen dalen. Dit is in overeenstemming met de conclusie van Soderlund in 2009 dat het risico op colorectaal carcinoom is afgenomen ten opzichte van de algemene bevolking, maar niet of nauwelijks is veranderd binnen het cohort zelf [13]. Deze hypothese correspondeert ook met de resultaten van een recente publicatie van Herrinton et al. [14] Hierin wordt gerapporteerd over een eigentijds en nieuw cohort van IBD patiënten uit Californië in de periode 1998 tot 2010. In dit cohort werd een verhoogde incidentie van colorectaal carcinoom bij IBD patiënten waargenomen dat in de tijd stabiel bleek te zijn.
Ondanks de lagere gestandaardiseerde incidentie ratio's en cumulatieve risico's uit recente publicaties, inclusief onze eigen meta-analyse, blijft het algemeen aanvaard dat er IBD patiënten zijn met een veel hoger risico, zoals bijvoorbeeld patiënten met een uitgebreide colitis of een primaire scleroserende cholangitis. Dit bevestigden wij in onze meta-analyse, nl. dat patiënten met uitgebreide colitis een bijna 7 maal hoger risico op ontwikkeling van colorectaal carcinoom hebben dan de algemene bevolking.
In Hoofdstuk 5 beschrijven wij risicofactoren voor het ontstaan van colorectaal carcinoom in een subgroep IBD patiënten met een blind gesloten rectumstomp. Na correctie voor de duur van follow-up, bleek uit de univariate analyse dat een langere ziekteduur en het hebben van primair scleroserende cholangitis met een carcinoom in de rectumstomp zijn geassocieerd.

Wij zijn van mening dat het niet efficiënt is om richtlijnen voor surveillance te gebruiken als hierin geen rekening wordt gehouden met risico-stratificatie. Een voorbeeld hiervan is de vernieuwde BSG richtlijn. Overigens zijn de aanbevelingen van de BSG gebaseerd op individuele studies die voorspellende factoren voor het risico op colorectaal carcinoom bij IBD patiënten beschrijven. Dit was voor ons

aanleiding om een predictie model te ontwikkelen dat al deze factoren samen brengt. Hiervoor hebben we samengewerkt met het Universitair Ziekenhuis in Leuven om een externe validatie van ons model uit te kunnen voeren. **In Hoofdstuk 6** wordt ons predictiemodel beschreven dat gebaseerd is op 4 patiënt karakteristieken met een redelijk tot goede voorspellende waarde. Deze karakteristien zijn het type IBD, namelijk colitis ulcerosa of de ziekte van Crohn, gelijktijdige aanwezigheid van primaire scleroserende cholangitis, aan- of afwezigheid van post-inflammatoire poliepen en ten slotte de betrokkenheid van de IBD van meer of minder dan 50% van de colon mucosa. Dit werd geverifieerd in ons Nederlandse cohort en resulteerde in een voorstel tot wijziging van de risico stratificatie die wordt weergegeven in Figuur 3 van Hoofdstuk 6. Dit is de eerste studie die een combinatie van risicofactoren gebruikt om de kans op colorectaal carcinoom bij IBD patiënten te voorspellen en tevens een externe validatie heeft uitgevoerd om dit te bevestigen.

In hoofdstuk 7 beschrijven wij dat de risico stratificatie benadering van de BSG richtlijn kosteneffectiever is dan die van de AGA richtlijn. Dit kon grotendeels worden verklaard door de lagere kosten als gevolg van minder coloscopieën, omdat binnen de BSG richtlijn 41% van de IBD-patiënten in de laag risico groep viel met aanbevolen surveillance intervallen van 5 jaar. Aangezien de AGA-richtlijn surveillance intervallen van 1 tot 3 jaar adviseert voor alle IBD-patiënten zonder primaire scleroserende cholangitis, werd besloten om het gemiddelde van tweejaarlijkse surveillance intervallen te gebruiken voor onze analyses. Dit betekende dat in onze studie 94% van de patiënten een surveillance colonoscopie om de 2 jaar onderging bij het volgen van de AGA richtlijn. Ondanks het feit dat de BSG-richtlijn kosteneffectiever lijkt, is het denkbaar dat het gebruik van langere surveillance intervallen leidt tot meer interval carcinomen. Als wij hiervoor probeerden te corrigeren met een sensitiviteits analyse, dan was de BSG richtlijn niet langer dominant over de AGA richtlijn. Echter, dit was niet kosteneffectief met een “incrementele kosteneffectiviteits ratio” van meer dan $130.000. Dit is veel hoger is dan de *willingness-to-pay* drempel welke in Nederland op $60.000 ligt.

Samengevat werd in dit proefschrift geconcludeerd dat het strikt volgen van de surveillance richtlijnen uit 2002 en 2003 [2,15] er toe kan leiden dat 10-20% van de IBD patiënten een colorectaal carcinoom ontwikkelt voordat surveillance geïndiceerd wordt geacht. Verder vonden wij dat het risico op colorectaal carcinoom in de gemiddelde IBD patiënt 5% was na 30 jaar ziekte, wat aanzienlijk lager is dan eerder werd gerapporteerd. Deze afname van het risico is mogelijk het gevolg van het beter volgen van surveillance richtlijnen, het toegenomen gebruik van effectievere en chemopreventieve medicatie en het opnemen van oudere leeftijdsgroepen in studies waarop recente meta-analyses, zoals ook de onze, zijn gebaseerd.
Wij bevestigden dat het risico op IBD-gerelateerd colorectaal carcinoom veel hoger is in subgroepen van patiënten met primaire scleroserende cholangitis, uitgebreide ziekte en post-inflammatoire poliepen. In combinatie met het type IBD (colitis ulcerosa of morbus Crohn van het colon) was het mogelijk om patiënten te identificeren met een hoog risico op het ontwikkelen van colorectaal carcinoom. Tot slot lijkt een risico-stratificatie benadering kosteneffectiever te zijn.
In dit proefschrift hebben we ons alleen gericht op klinische karakteristieken om het risico op colorectaal carcinoom te voorspellen. In de nabije toekomst is het wellicht mogelijk om klinische parameters te combineren met biomarkers voor neoplastische

progressie, bijvoorbeeld abnormale DNA-ploïdie en p53 immunopositiviteit [16]. Deze twee biomarkers blijken geassocieerd te zijn met hazard ratio's van 4,7 en 3,0 op het ontwikkelen van colorectaal carcinoom bij patiënten met colitis in een studie van Gerrits et al. [17] Deze parameters kunnen waardevolle toevoegingen zijn op ons predictie model. Materiaal uit het Nederlandse IBD Biobank Project "Parelsnoer" zal ons in staat stellen om dit in meer detail te onderzoeken.
Met het oog op het verbeteren van surveillance richtlijnen, stellen wij voor dat toekomstige studies zich moeten richten op de volgende zaken:

1) Validatie van de risico stratificatie benadering in prospectief gevolgde cohorten van IBD-patiënten.

2) Validatie van de voorgestelde surveillance intervallen van 1, 3 en 5 jaar voor de overeenkomstige laag, gemiddeld en hoog risico groepen.

3) De toevoeging van moleculaire biomarkers voor neoplastische progressie aan de huidige risicostratificatie.

Dit zal ongetwijfeld helpen bij het afstemmen van surveillance richtlijnen op de individuele patiënt en om de meest kosteneffectieve manier te verwezenlijken om colorectaal carcinoom bij patiënten met IBD te voorkomen.

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Dr. M. Van Oijen, beste Martijn. Mijn 6 weken in Los Angeles waren in zekere zin de meest productieve van de afgelopen 7 jaar. Jouw kritische blik heeft mijn publicaties ontzettend veel goed gedaan. Bedankt voor al je tijd en energie!

Alle leden van de Initiative on Crohn and Colitis bedankt. Met name diegenen die hun deuren openstelden in de eerste jaren van mijn onderzoek: Ad van Bodegraven, Pieter Stokkers, Gerard Dijkstra, Dirk de Jong, Daan Hommes, en Janneke van der Woude. Jullie hebben een uniek samenwerkingsverband wat beginnende onderzoekers een perfect voorbeeld geeft over hoe onderzoek verricht moet worden in academisch Nederland.

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To everyone with a connection to 111: Thank you for making my academic career so much easier by teaching me the ways around Americans and the English language in particular.

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Lieve Claran, de orde in mijn chaos. Jouw grenzeloze energie en vrolijkheid hielden mij de afgelopen jaren overeind. De afgelopen maanden was ik mijn vrije tijd bijna volledig kwijt aan dit proefschrift. Dat is nu gelukkig voorbij. Ik denk dat mijn vrijgekomen tijd besteed gaat worden aan de voorbereidingen voor 21 juni 2014. Ik hou van je.

Maurice Lutgens werd geboren op 4 april 1982 te Maastricht. Hij haalde zijn gymnasium diploma aan het Jeanne d'Arc College in Maastricht. In 2000-2001 studeerde hij 1 jaar aan het University College Utrecht. In 2002 begon hij aan de studie geneeskunde in het UMC Utrecht. Vanaf zijn 5e studiejaar verrichte hij onderzoek bij Dr. B. Oldenburg en Dr. F.P. Vleggaar naar colorectaal carcinoom bij patienten met colitis ulcerosa en de ziekte van Crohn. Dit resulteerde in December 2007, na het behalen van zijn bul, in een promotie plek onder Prof. Dr. P.D. Siersema. Na 1 maand full-time onderzoek startte hij op 1 januari 2008 met de opleiding tot Maag-, Darm- Leverarts. Dankzij een ZonMw AGIKO beurs kon hij 10 maanden full time aan onderzoek besteden in 2011-2012. Op dit moment doorloopt hij het 5e jaar van de opleiding in het UMC Utrecht. Opleider Prof. Dr. P.D. Siersema.