SOLID INTRA- AND EXTRA-INTESTINAL MALIGNANCIES IN INFLAMMATORY BOWEL DISEASE

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TABLE OF CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

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INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis, is a group of chronic inflammatory disorders of the gastrointestinal tract with prevalences that vary between 37.5-248.6 per 100,000 in North America and 4.9-505 per 100,000 in Europe.[1] It is estimated that in The Netherlands currently between 57,000 and 90,000 inhabitants suffer from IBD.[2] The disease follows a relapsing course, characterized by a variety of symptoms such as abdominal pain, (hemorrhagic) diarrhea, weight loss and/or fatigue. In order to reduce symptoms and inflammation, but also to prevent long term complications, most patients are treated with medical therapy. First-line medical treatments for induction of remission are anti-inflammatory drugs such as topical and systemic steroids and 5-aminosalicylic acid. More severe IBD warrants maintenance treatment with immunosuppressive therapy, such as thiopurines, methotrexate or anti-TNFα therapy.

Despite the wide therapeutic arsenal, both intra- and extra-intestinal complications of IBD still occur. For example, IBD patients may develop gastro-intestinal bleeding, toxic megacolon and/or colorectal cancer (CRC) often requiring surgery. Indeed, approximately 70-80% of CD patients and 20-30% of UC patients eventually require gastrointestinal surgery.[3, 4] Furthermore, extra-intestinal complications may occur, such as arthropathies, mucocutaneous (erythema nodosum and pyoderma gangrenosum) and ophthalmological (episcleritis and uveitis) manifestations as well as extra-intestinal malignancies.

Both intestinal malignancies and several extra-intestinal malignancies occur more frequently in patients with IBD.[5, 6] This can be mainly attributed to two causes including (1) chronic inflammation and (2) immunosuppressive medical therapy.[7] Chronic inflammation is considered one of the key players in the development of intestinal malignancies and control of mucosal inflammation with anti-inflammatory and/or immunosuppressive maintenance therapy is therefore warranted. On the other hand, these medical therapies may promote or inhibit the development of (extra-)intestinal malignancies by impairing immunosurveillance of tumor cells or inducing DNA damage.[8-11] Further evidence is required to optimize management strategies that can achieve reduction of chronic inflammation with an acceptable safety profile while reducing cancer risk.

INTESTINAL MALIGNANCIES - COLORECTAL CANCER

Incidence and prevalence

CRC is one of the most detrimental complications of IBD with significant morbidity and mortality.[12] It occurs 1.5 to 2 times more frequently in IBD patients compared to the general population.[13-15] Initially, high cumulative CRC incidences were found in a meta-analysis in 2001 of 2% by 10 years, 8% by 20 years, and 18% by 30 years.[5] However, lower CRC risks have been described in more recent years.[15, 16] This might be attributed to inclusion bias since mainly single center studies rather than population-based cohorts were included in the previous meta-analysis.[5] Furthermore, better anti-inflammatory treatment and improved management and surveillance strategies may contribute to a lower CRC risk.

Risk factors

Several genetic, phenotypic and additional risk factors have been elucidated for CRC development in IBD. For example, those with longstanding, extensive colitis, post-inflammatory pseudopolyps or strictures have an increased CRC risk. A genetic predisposition, such as a positive CRC family history, also increases the risk to develop CRC. In addition, patients with primary sclerosing cholangitis are at increased risk.[13, 14] Anti-inflammatory and immunosuppressive therapies may also impact cancer risk. On one hand the reduction of chronic inflammation curtails cancer risk. Moreover, a specific anti-carcinogenic effect of 5-ASA has been advocated on the basis of molecular data.[16] By contrast, immunosuppressive therapy may stimulate carcinogenesis by impairing immunosurveillance of tumor cells or inducing DNA damage.[8-11] Contradictory results have been reported in the literature regarding the protective or risk-enhancing effect of various therapeutic options.[15, 17-20]

Pathogenesis

The key genetic event that drives the onset and progression of CRC in general is the clonal outgrowth of mutated cells. As such, a sequential accrual of somatic mutations in for example p53 and KRAS contribute to cancer development. Similar molecular genetic events occur in sporadic and colitis-associated CRC, although the timing and sequence of events often differs.[15] Furthermore, CRC develops in less than 10% of CRC patients in the context of an inherited genetic disorder such as familial adenomatous polyposis or Lynch Syndrome (LS) with germline mutations in respectively the adenomatous polyposis coli gene or mismatch repair (MMR) genes.

Environmental factors, such as inflammation and altered microbiota, could trigger and impact carcinogenesis. Colitis-associated cancers for example, develop in chronically inflamed mucosa and are believed to develop via an inflammation-dysplasia-carcinoma sequence.[21] Oxidative stress induces DNA damage resulting in the activation of pro-carcinogenic genes and silencing of tumor-suppressor pathways, which could both induce and progress carcinogenesis. Moreover, a "field change" of cancer-associated molecular alterations may have been developed before there is any histological evidence of dysplasia due to chronic inflammation.[15] For example, p53 mutations occur before the onset of dysplasia as a field change and normal cell populations are widely replaced according to this concept of "field cancerization".[22, 23]

Outcome and management

Colitis-associated cancers behave more aggressively with a faster growth pattern and worse stage-specific survival compared to sporadic CRC.[20] As such, IBD patients with CRC are younger and have more frequently multiple cancerous lesions. Given the increased CRC risk and worse outcome, endoscopic colonic surveillance is widely recommended to detect and potentially remove precancerous lesions and CRC. This is further supported by a reduced CRC incidence and CRC-related mortality among IBD patients undergoing surveillance, although these results may also be the consequence of optimized treatment strategies.[24, 25] In case of multifocal low-grade dysplasia, high-grade dysplasia, or CRC, there is a generally well-

accepted indication for colectomy with subsequently several surgical scenarios available as shown in Figure 1. The choice between different procedures depends on indication, comorbidity and patient's wish.

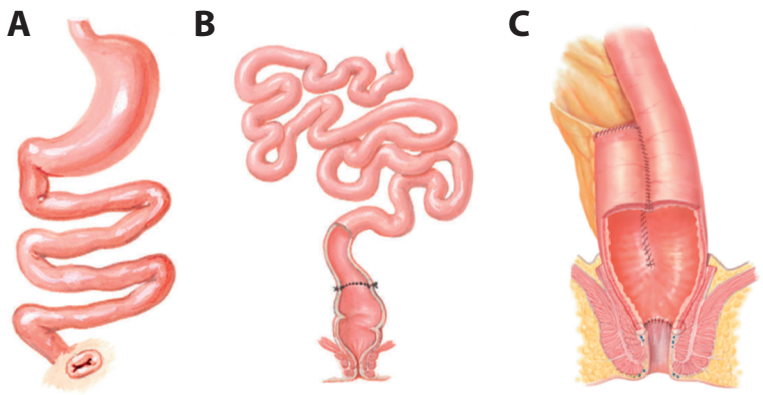

Figure 1. Post-surgical scenarios after colectomy (Adapted from Netter's Gastroenterology 2nd Ed.). (A) Ileostomy with rectal stump: after removal of the colon, the end of the small intestine is pulled through the abdominal wall of the belly and creates a stoma. A rectal stump is often left in situ. (B) Ileorectal anastomosis: after removal of the colon, the end of the small intestine is anastomosed to the rectum. (C) Ileal pouch-anal anastomosis: after removal of the colon and rectum, a new reservoir (the "pouch") is constructed by folding the last part of the small intestine and anastomosing it with the anus.

Post-colectomy CRC risk

Although colectomy, with or without reconstructive surgery, substantially reduces CRC risk, IBD-associated CRC can still develop in the remaining bowel. Given this risk, endoscopic surveillance may also be necessary in the post-colectomy setting. However, current evidence is insufficient to make firm recommendations on this topic. A risk profile for cancer development in the remaining bowel parts, in combination with more knowledge on pathogenesis, prognosis and outcome would be helpful to guide these recommendations. More data on these separate items, including an appropriate interpretation, are needed to develop a post-surgical surveillance strategy.

INTESTINAL MALIGNANCIES – NEUROENDOCRINE TUMORS

Epidemiology and pathogenesis

In addition to increased CRC risk, IBD patients may have an increased risk to develop neuroendocrine tumors (NET) since inflammation may cause hyperstimulation of entero-endocrine cells leading to hyperplasia and neoplasia.[26-28] As such, the association between NET and IBD is described in 58 patients.[29] Nevertheless, contradicting results regarding NET risk in IBD have been reported. Risks vary from a comparable risk until a relative risk

between 9 and 15 compared to the general population.[26, 28, 30] In general, NET have a very low incidence (2-5 per 100,000 patients per year).[31]

Clinical characteristics

NET can arise from various anatomic locations, but most commonly originate from the lungs, gastrointestinal tract, and pancreas. As a consequence, heterogeneous site-specific symptoms exist in addition to symptoms caused by peptide release, such as flushing or carcinoid syndrome.[31] NET in the gastrointestinal tract are frequently located submucosally, sometimes extending to the muscular layer. Symptoms include hematochezia, pain, and change in bowel habits.[32] Main anatomic sites include the small intestine (44.7% of all gastrointestinal NET), followed in descending frequency by the rectum (19.6% of all gastrointestinal NET), appendix (16.7% of gastrointestinal NET) and colon (10.6% of all gastrointestinal NET; mainly in the descending colon followed by the cecal region; Figure 2).[33]

Diagnostics and outcome

NET are generally asymptomatic and most are detected during surveillance colonoscopy or after IBD-related surgery.[34] This frequent incidental detection may result in an increased NET prevalence in IBD compared to the general population. Moreover, the real incidence in the general population may be underestimated.[29] In general, NET follow an indolent clinical disease course with an excellent prognosis.[35] Rectal NET are small and associated with a very low malignant potential, while colonic NET proximal to the rectum behave more aggressively.[32] Coexistence of IBD and NET may result in a worse prognosis compared to non-IBD patients.[29]

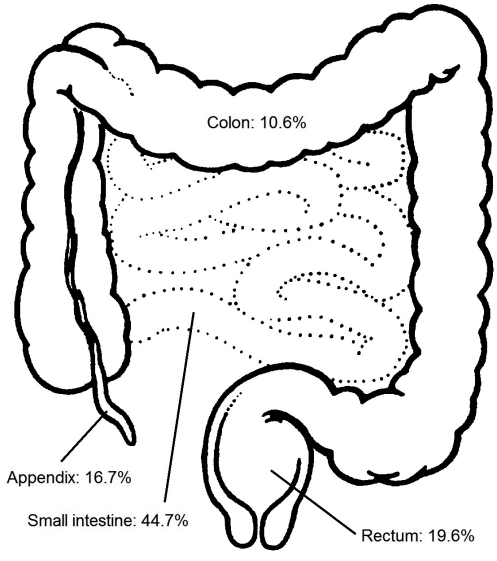

Figure 2. Distribution of gastrointestinal NET.

EXTRA-INTESTINAL MALIGNANCIES

Epidemiology and pathophysiology

As IBD primarily affects the intestinal tract, intestinal cancers in IBD are studied thoroughly. By contrast, the risk of extra-intestinal cancer in IBD has obtained less attention, although extra-intestinal manifestations are seen in 35% of patients, such as primary sclerosing cholangitis, nefrolithiasis, and rheumatologic, dermatologic and ophthalmologic disorders.[6] Furthermore, immunosuppressive treatment regimens in IBD may contribute to the development of extra-intestinal malignancies, which is also shown in immunosuppressed post-transplant patients.[36] Prescription of immunosuppressive and anti-TNFα therapies for IBD increased in recent decades with earlier introduction of these agents in the disease course.[37] Together with the aging IBD population, this has resulted in a growing concern about extra-intestinal malignancies in IBD.

The overall risk to develop extra-intestinal malignancies in IBD is not increased in a meta-analysis consisting of 8 population-based cohort studies (17,052 patients).[6] However, assessing individual cancer types, some cancers occurred more commonly in IBD compared to the background population. As such, CD patients had an increased risk of cancer of the upper gastrointestinal tract, lungs, urinary bladder, and skin. UC was associated with an increased risk of liver-biliary cancer and leukemia, but with a decreased risk of pulmonary cancer. Findings might be explained by smoking habits, extra-intestinal manifestations of IBD, and involvement of the upper gastrointestinal tract in CD.

Renal cell carcinoma

IBD patients may bear an increased risk to develop renal cell carcinoma (RCC). Indeed, urinary tract cancers seems to be more prevalent in IBD patients on thiopurines in a nationwide prospectively followed cohort.[7] Moreover, RCC risk is increased in other autoimmune conditions, such as rheumatoid arthritis.[38] In addition, RCC occurs more frequently in post-transplantation patients exposed to immunosuppressive medication.[36]

In general, RCC accounts for 2% of all cancers. Due to improved imaging techniques, they are increasingly discovered as incidentalomas (up to 40%).[39-41] Similar to CRC and NET, there is evidence for a genetic etiology for RCC development, such as in Von Hippel-Lindau Syndrome. Furthermore, environmental and demographic factors, such as male gender, smoking and obesity, increase RCC risk. The classic triad of symptoms in RCC involves hematuria, abdominal pain, and a palpable mass in the flank or abdomen. However, small, localized tumors rarely produce symptoms and consequently escape clinical detection, similar to NET, resulting in often incidentally discovered RCC.[42] Surgical kidney resection is the cornerstone of treatment for RCC. Depending on the stage of the disease, several systemic treatment options are available, such as immunotherapies and targeted therapies.

Clinical questions regarding extra-intestinal malignancies

Several important clinical questions with respect to IBD, IBD therapy and extra-intestinal cancer deserve further attention and research.[10] First, it could be questioned which factors

contribute to the risk to develop extra-intestinal malignancies. For example, is medical therapy for IBD a risk factor for development of extra-intestinal cancer? Second, it remains unknown whether and how IBD (and IBD therapy) impacts risk of cancer recurrence, outcome and survival. Both questions have been extensively studied for CRC and some studies evaluated these issues for extra-intestinal malignancies in general. However, cancer site specific data, for example for RCC, are scarce or lacking while case-by-case management is encouraged based on the characteristics and expected evolution of the cancer, the probable impact of IBD therapy on cancer evolution, and IBD severity.[8, 10]

AIM

The long-term vision of my thesis is to optimize management and surveillance strategies in IBD patients at risk for/with solid intra- and extra-intestinal malignancies, both before and after cancer development. For this purpose, we formulated two main aims, including:

1. Epidemiological risk assessment of intra- and extra intestinal solid malignancies in IBD patients, including incidence, prevalence, and risk profile.

2. Translation of risk profiles into recommendations for daily clinical practice, including consequences for surveillance and IBD management.

As there are several types of malignancies, I limited this thesis to rare solid malignancies. Therefore, my thesis incorporates the following cancers in combination with IBD: LS related CRC, CRC in the rectal stump, CRC in the ileorectal anastomosis (IRA), CRC in the IPAA, colonic NET and RCC. Although these malignancies in IBD are rare, more knowledge in this field is of importance since these malignancies can occur in all IBD patients and thus data are relevant for the IBD population at large. Furthermore, these patients usually undergo oncologic treatment, requiring data regarding optimal cancer management in IBD. To improve outcome of both IBD and cancer, more data are needed that support (1) decision management for IBD in patients with cancer and (2) cancer management and surveillance in patients with IBD.

APPROACH

In order to address the abovementioned issues we used different study designs.

Retrospective case control and cohort studies based on PALGA searches

For epidemiological risk assessment we performed several PALGA searches. PALGA is the Dutch nationwide network and registry of histo- and cytopathology.[43] This registry contains pathology reports generated in the Netherlands since 1971 and has complete national coverage since 1991 encompassing all pathology laboratories from all academic and non-academic hospitals in the Netherlands. Search terms such as "*ulcerative colitis*" and "*Crohn's disease*" in combination with search terms for specific malignancies enabled

us to identify (nationwide) all IBD patients with that diagnosis. Subsequently, we identified IBD controls without that specific malignancy or without IBD (with or without PALGA), and performed several case control and cohort studies. As such, we assessed the risk and associated risk factors to develop NET, pouch neoplasia, and RCC in IBD patients and the risk to develop CRC in patients with both IBD and LS.

Systematic review and meta-analysis

We performed a systematic review of observational studies for further epidemiological risk assessment, determining prevalence, incidence and risk factors to develop post-colectomy neoplasia in IBD. In addition, a meta-analysis was conducted if sufficient data were available for pooling purposes. As such, we determined a pooled CRC incidence and prevalence, and compared these among subgroups (rectal stump, IRA, IPAA). Furthermore, we analyzed risk factors for developing post-colectomy neoplasia in a pooled model. A systematic review and meta-analysis compares and collects all available evidence and is considered one of the highest grades of evidence. By using this approach for epidemiological risk assessment of post-colectomy neoplasia development, we assessed, summarized and interpreted all available data. In turn, these calculated CRC risk percentages aid in guiding endoscopic surveillance intervals. Thus, this approach provided us with an ideal starting point for translation of the available epidemiological evidence into daily clinical practice.

Interpretation and discussion

Study results require interpretation and implementation in order to translate findings into clinical practice. To interpret our data and the available data in literature, we shaped and discussed our opinion in several articles. In some, we integrated risk assessment, interpretation and consequences in one manuscript. In other situations, we expressed our opinion in separate articles, for example in a letter to the editor or in a viewpoint. As such, we gave our opinion on surveillance pouchoscopy in reply to a systematic review of IPAA cases with pouch neoplasia. Furthermore, we formulated our vision on pouch surveillance in a viewpoint.

OUTLINE

The background and framework for the thesis is described in **Chapter 1**. It provides background information about intra- and extra intestinal cancers in IBD and shows the gaps of knowledge.

Part I describes cancer risk for several types of cancer. In **Chapter 2** we assessed the risk to develop CRC in patients with both IBD and LS as genetic predisposition with concurrent inflammation might increase CRC risk. **Chapter 3** evaluates the risk to develop NET in IBD. Since prevalences of NET could be increased due to frequent gastrointestinal surgery with incidental NET detection, we compared NET prevalences between IBD and others with gastrointestinal surgery (diverticulitis and ischemia). In **Chapter 4** we determined the risk of RCC development in IBD. By adopting a case control study design we established a risk

profile to develop RCC and investigated the impact of IBD and IBD therapy on outcome and survival.

Part II evaluates CRC risk in IBD patients who underwent a colectomy. In the different post-surgical scenarios after colectomy, including the permanent end ileostomy and rectal stump, IRA and IPAA, risk profiles for CRC development are established. **Chapter 5** describes the cumulative incidence of pouch dysplasia and carcinoma in IBD. Furthermore, risk factors for pouch cancer development are identified. In **Chapter 6** we performed a systematic review and meta-analysis assessing prevalence, incidence and risk factors for CRC development in the rectal stump, IRA and IPAA. **Chapter 7** translates the results of the two preceding chapters into surveillance recommendations for daily clinical practice.

Part III contains de general discussion including future perspectives (**Chapter 8**). Subsequently, we summarized our main findings.

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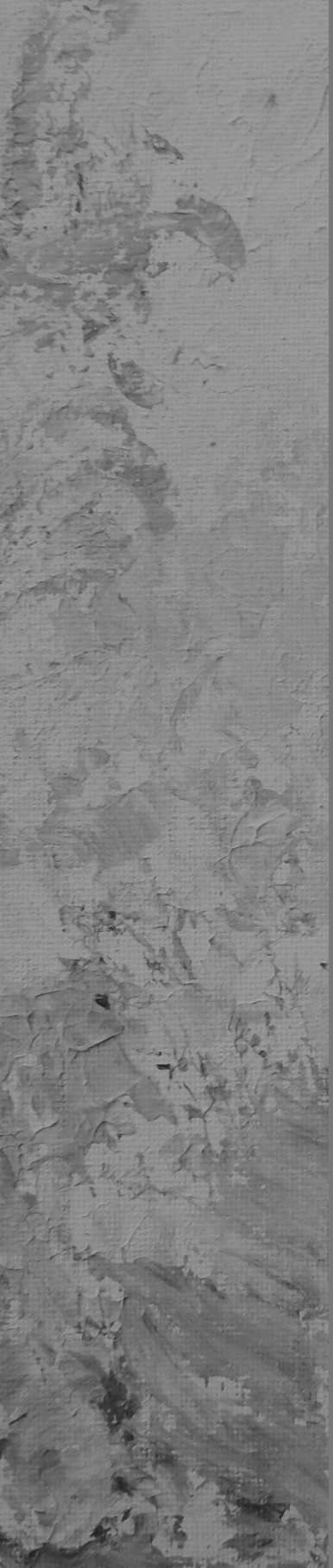

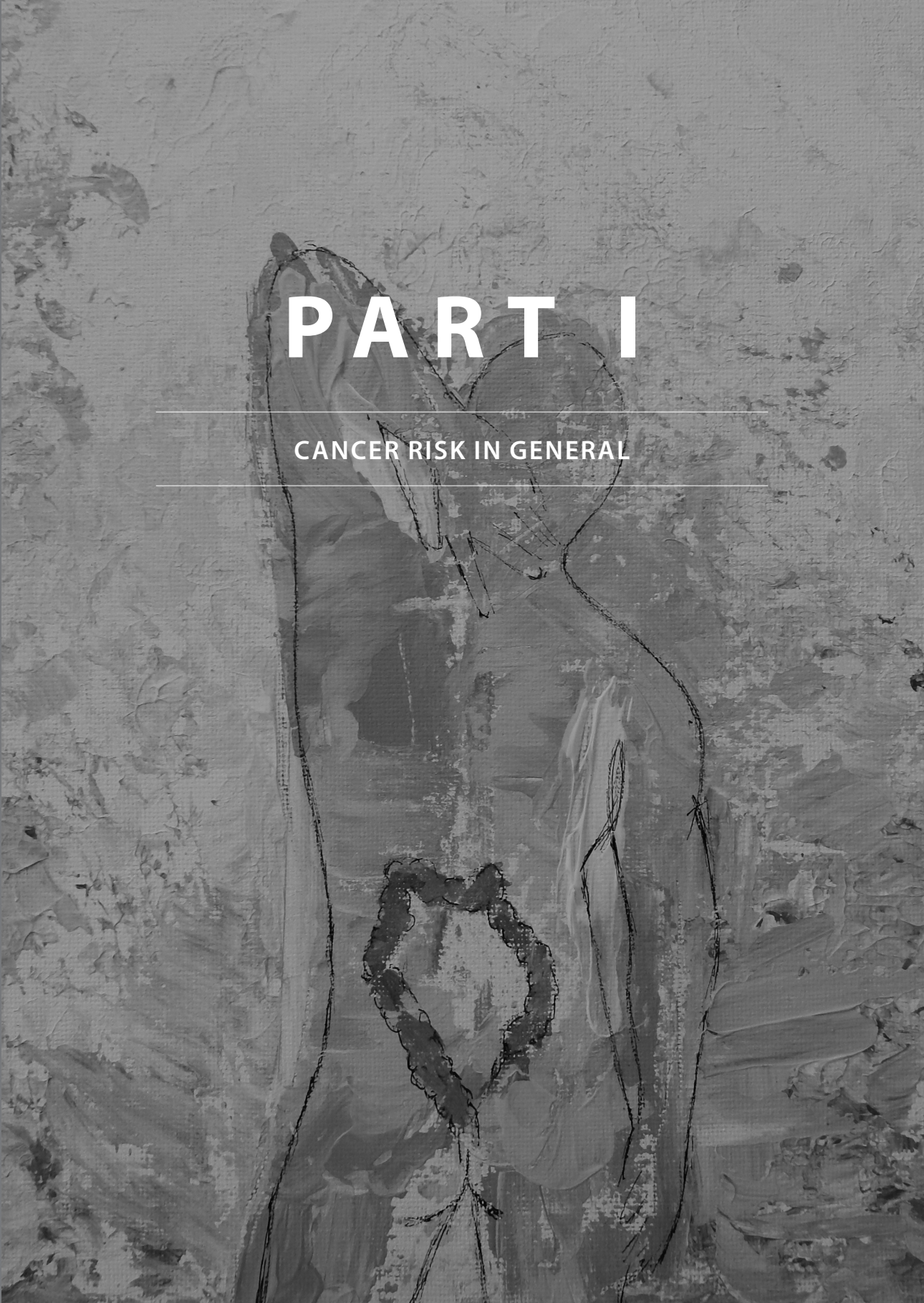

PART I

CANCER RISK IN GENERAL

CHAPTER 2

COLORECTAL CANCER RISK IN PATIENTS WITH BOTH LYNCH SYNDROME AND INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Lynch Syndrome and inflammatory bowel disease (IBD) are associated with an increased colorectal cancer (CRC) risk due to genetic and inflammatory factors. It is unknown whether CRC risk is further increased in patients who suffer from both Lynch Syndrome and IBD. We therefore aimed to establish CRC risk in patients with both Lynch Syndrome and IBD.

We established a cohort of Lynch Syndrome patients based on two Lynch Syndrome referral centers in The Netherlands. This cohort was linked to PALGA (Dutch nationwide Pathology Registry) to identify those having IBD. Subsequently, we compared phenotypes of patients suffering from both Lynch Syndrome and IBD (cases) to Lynch Syndrome patients without IBD (controls) by adopting a retrospective cohort study approach.

15/1046 (1.4%) Lynch Syndrome patients also carried a diagnosis of IBD. Despite a younger age in the case group (median 38.0 y versus 52.0 y, $p = 0.001$), the rate of CRC development was not significantly different between cases (4/15, 26.7%) and controls (311/1031, 30.2%). Cases developed CRC at a younger age compared to controls (median 36.0 y versus 46.0 y, $p = 0.045$). However, cumulative CRC incidence was similar in both groups ($p = 0.121$). All CRC patients in the case group had ulcerative colitis, resulting in a higher cumulative CRC incidence for this IBD subgroup compared to controls ($p < 0.001$).

Concurrence of Lynch Syndrome and IBD raises the risk for CRC at a younger age, especially in those with ulcerative colitis.

INTRODUCTION

Lynch Syndrome (LS) and inflammatory bowel disease (IBD) are associated with an increased colorectal cancer (CRC) risk due to genetic (LS) and inflammatory (IBD) factors. Reported lifetime risk of CRC development in LS ranges from 22 to 74%, resulting in an approximately 4 to 15 times increase in CRC risk compared to the general population.[1, 2] The mean age of CRC diagnosis in LS is 44–61 years compared with 69 years in sporadic cases of CRC.[1] IBD patients bear a 1.7 times greater CRC risk in comparison with the general population, which is further exacerbated by additional risk factors such as IBD diagnosis at younger age and greater disease extent.[3] Recommendations for endoscopic surveillance have been adapted to reflect these higher CRC risks. Although relevant for surveillance and treatment strategies, it is unknown whether CRC risk is further increased in patients who suffer from both LS and IBD.

The literature contains a few cases of LS patients with IBD who developed CRC.[4, 5] In a case series of 12 patients with both LS and concomitant IBD, four patients developed CRC at the age ranging from 32 to 47 years.[5] Two other case reports described a 28- and 51-year-old LS patient with in respective ulcerative colitis (UC) and Crohn's disease (CD) who developed CRC.[4, 6] Although CRC arose at a relatively young age in these patients, no firm conclusions regarding CRC risk can be drawn based on these single cases as they comprise a high risk of selection bias and lack a control group.

The molecular mechanism that drives CRC in LS has been investigated in experimental models.[7, 8] MSH2 deficient or MLH1 deficient mice (recapitulating human LS) were treated with dextran sodium sulfate to induce an inflammatory colitis. Mismatch repair (MMR) deficient mice with colitis developed significantly more colorectal neoplastic lesions compared to those without colitis. In the same vein, combination of a MSH2 deficiency and inflammation resulted in accelerated carcinogenesis.[7]

As a corollary from described cases and mice models, we hypothesize an increased and accelerated CRC risk for LS patients with IBD compared to those with LS only. In the current study, we aimed to establish CRC risk in patients with both LS and IBD.

PATIENTS AND METHODS

Study design

We established a Dutch cohort of LS patients derived from two referral centers. Patients in the LS cohort who developed IBD were identified by linkage with PALGA, the Dutch Pathology Registry with national coverage.[9] Subsequently, we compared LS patients with IBD (cases) and LS patients without IBD (controls) by adopting a retrospective cohort study approach in order to establish CRC risk.

The study was approved by the Privacy Commission and Scientific Council of PALGA and by the Medical Ethics Review Committee region Arnhem - Nijmegen (Registration number 2013/468).

Patient identification

Patients with confirmed mutations in the MMR genes associated with LS in either the Radboud University Medical Center (Nijmegen, The Netherlands) or Academic Medical Center (Amsterdam, The Netherlands) were eligible for inclusion. LS associated mutations included heterozygous germline mutations in MLH1, MSH2 (and EPCAM deletion-mediated MSH2 methylation), MSH6 or PMS2, excluding patients with bi-allelic MMR gene mutations. All carriers who were tested and/or treated at the Gastroenterology and Human Genetics department between 1998 and 2014 in those two centers were included.

For the identification of IBD patients in the established LS cohort, we linked the identified LS patients to PALGA, the Dutch Pathology Registry. PALGA (Dutch nationwide network and registry of histo- and cytopathology) contains pathology reports generated in the Netherlands since 1971 and has complete national coverage since 1991 encompassing all pathology laboratories from all academic and non-academic hospitals in the Netherlands.[10, 11] Via a trusted third party (ZorgTTP), which replaces all identifiable data by unique pseudonyms, we extracted data from PALGA without jeopardizing privacy.[12] We obtained all pathology reports of the gastrointestinal tract from patients in the LS cohort and made an initial selection of patients with both LS and possible IBD (Figure 1).

Cases with both IBD and LS were further confirmed or excluded after careful evaluation of individual medical records. Diagnoses of UC, indeterminate colitis or CD were based on a combination of endoscopic, radiologic and histological evidence.[13] We excluded patients with infectious colitis or transient periods with atypical inflammation from the IBD group. Uncertainties regarding IBD diagnosis were resolved by discussion and consensus with two investigators (L.D. and L.S.) and a third expert gastroenterologist (F.H.).

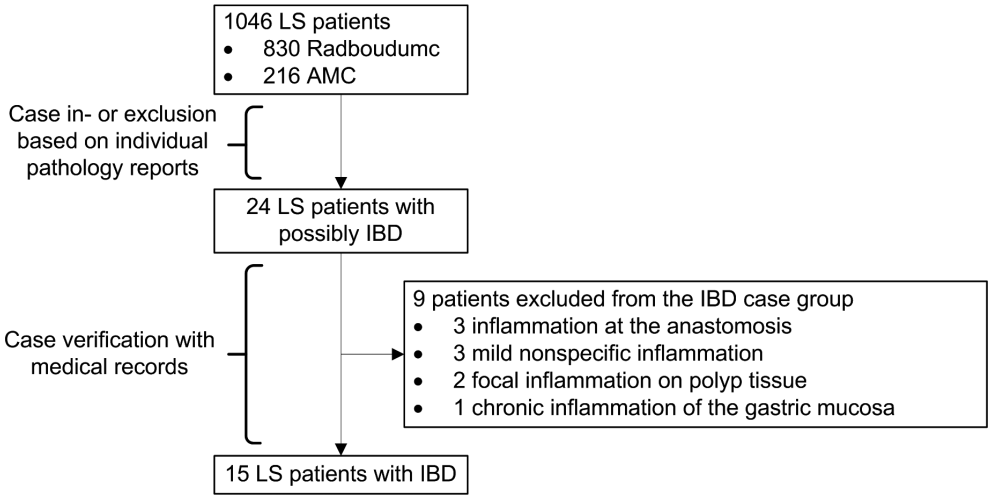

Figure 1. Patient flowchart.

Data collection

One author (L.S.) extracted data from anonymized medical records for patients with both LS and IBD. Extracted variables included age, gender, smoking behavior, primary sclerosing cholangitis, MMR gene mutation, age at LS diagnosis, IBD characteristics, and the history of (extra-)intestinal neoplasia including microsatellite instability (MSI). Age was defined as the age during the PALGA search or, if deceased, the age at death. We collected the following IBD characteristics: age at IBD diagnosis, IBD phenotype according to the Montreal classification, and medical and surgical treatment. Exposure to 5-aminosalicylic acids, thiopurines, anti-TNFα agents, cyclosporine or methotrexate was defined as "used" or "not used".

For all patients included in the LS cohort, data were extracted from local prospectively registered LS databases and the PALGA database. Extracted variables from these databases included: gender, MMR gene mutation, age at LS diagnosis and history of colorectal neoplasia. Both synchronous CRC at the time of diagnosis as well as metachronous CRC during follow-up (interval > 6 months since first CRC) were recorded.[14]

Histopathological reassessment

One expert gastrointestinal pathologist (I.N.) reassessed all gastrointestinal neoplasia specimens from patients with both LS and IBD, while blinded to clinical, endoscopic and radiographic features. This reassessment included the grade and type of neoplasia, classified according to Riddell into indefinite for dysplasia, low grade dysplasia (LGD), high grade dysplasia or adenocarcinoma.[15] Revised results were used for further analyses.

Immunohistochemistry and MSI status

The MMR mutation and, if not determined before, MSI status were (re)assessed in neoplasia specimens from patients with both LS and IBD. Immunohistochemistry was performed with antibodies against MLH1 (1:40, Clone G168-15, BD Biosciences, NJ, USA), MSH2 (1:40, Clone GB12, Merck Millipore Calbiochem®, Darmstadt, Germany), MSH6 (1:500, Clone EPR3945, Abcam, Cambridge, UK) and PMS2 (1:100, Clone A16-4, BD Biosciences, NJ, USA) on formalin-fixed paraffin-embedded tissue with colorectal neoplasia to determine the MMR mutation.

For determination of the MSI status, we performed a multiplex PCR comprising five mononucleotide repeat markers (NR-27, NR-21, NR-24, BAT-25 and BAT-26).[16] Lesions were defined as MSI when three or more of the five markers showed instability.[16, 17]

Since hypermethylation of the MLH1 promotor causes MSI as well, we evaluated the methylation status of this promotor region in all neoplasia specimens. For this purpose a methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) kit (SALSA MLPA ME011-B2, MRC Holland, Amsterdam, The Netherlands) was used according to manufacturer's protocol. Products were analyzed on a 3730 Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistics

Descriptive statistics were performed for LS patients with IBD. Categorical variables were expressed as numbers with percentages and continuous variables were expressed as means (if normally distributed) or medians (if not normally distributed) with a minimum – maximum range.

Subsequently, cases and controls were compared with univariable analysis. $\chi 2$ test or Fisher exact test (if expected cell counts were < 5) were used for categorical data and independent Student t test (if normally distributed) or Mann-Whitney U test (if not normally distributed) were used for continuous data. Cumulative CRC incidences were counted with 1 minus Kaplan-Meier curves and compared with log rank analysis.

A *P* value of < 0.05 (2 sided) was considered to be statistically significant. All missing values were considered to be at random and were excluded from analyses. All statistical analyses were performed with IBM SPSS statistics version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient identification

We established a LS cohort consisting of 1046 patients (Figure 1) with a known MMR deficiency. Linkage with PALGA and further evaluation of patient records showed that 15/1046 (1.4%) LS patients also carried a confirmed diagnosis of IBD.

LS patients with IBD

Characteristics of the 15 cases with both LS and IBD, including 8 (53.3%) with UC, 6 (40.0%) with CD and 1 (6.7%) with indeterminate colitis are shown in Table 1. Median age at IBD-diagnosis was 30 years (range 10-63) and median duration of IBD until our PALGA search (or until death if deceased) was 7 years (range 0-19). Six out of 15 cases (40%) were diagnosed with LS prior to IBD diagnosis. Disease extent in UC involved the complete colon in 62.5% (5/8) and the left-sided colon in 37.5% (3/8). CD patients had either ileal involvement (50%, 3/6) or ileocolonic involvement (50%, 3/6; 2/3 with < 50% affected colon). In the single patient with indeterminate colitis, lesions were restricted to the cecal region. Three patients without CRC underwent surgery due to disease activity, including one CD patient with an ileocecal resection, one CD patient with both an ileocecal resection and subtotal colectomy, and one UC patient with restorative proctocolectomy and ileoanal pouch construction.

LS patients with IBD versus LS patients without IBD

The comparison between LS patients with and without IBD is shown in Table 2. Despite a younger age at study inclusion in the case group (median 38.0 y versus 52.0 y, p = 0.001), the percentage of patients who developed CRC did not significantly differ between cases (4/15, 26.7%) and controls (311/1031, 30.2%; p = 1.000). The 4 cases developed CRC at a younger age compared to controls (median 36.0 y versus 46.0 y, p = 0.045). However, cumulative CRC incidence was similar between both groups (p = 0.121). All CRC patients had UC resulting in a higher cumulative CRC incidence for the UC subgroup (4/8, 46.4% at

age of 38) compared to controls (311/1031, 7.0% at age of 38, $p < 0.001$). The distribution of mutated mismatch repair genes between cases and controls was similar ($p = 0.414$).

Table 1. IBD characteristics of 15 patients with both LS and IBD.

Variable	IBD and LS cases (n = 15)
Male sex	7 (46.7)
Ever smoked	3 (20.0)
Primary sclerosing cholangitis	0 (0.0)
Age at IBD diagnosis, median (range)	30 (10-63)
IBD type	
Ulcerative colitis	8 (53.3)
Crohn's disease	6 (40.0)
Indeterminate colitis	1 (6.7)
Ulcerative colitis[a]	
Extend	
Proctitis (E1)	0 (0.0)
Left-sided colitis (E2)	3 (37.5)
Pancolitis (E3)	5 (62.5)
Crohn's disease[a]	
Extend	
Ileum (L1)	3 (50.0)
Colon (L2)	0 (0.0)
Ileocolonic (L3)	3 (50.0)
Upper digestive (L4)	0 (0.0)
Perianal disease activity	0 (0.0)
Phenotype	
Non stricturing/penetrating (B1)	2 (33.3)
Stricturing (B2)	2 (33.3)
Penetrating (B3)	1 (16.7)
Stricturing and penetrating	1 (16.7)
Medical therapy prior to CRC diagnosis	
Steroids	9 (60.0)
5-aminosalicylic acids	11 (73.3)
Thiopurines	4 (26.7)
Methotrexate	0 (0.0)
Cyclosporine	2 (13.3)
Anti-TNFα therapy	3 (20.0)
Gastrointestinal surgery	7[b] (46.7)

All values are expressed as n (%) unless otherwise noted.
[a] Classified according to the Montreal classification.
[b] 4/7 patients underwent surgery due to CRC development.

Table 2. Comparison between cases with both LS and IBD, and LS controls without IBD

Variable	IBD and LS (n = 15)	LS controls (n = 1031)	P value
Male sex	7 (46.7)	474 (45.3)	0.916
Age[a], median (range)	38 (26-69)	52 (18-100)	0.001
MMR mutation			0.414
MLH1	5 (33.3)	256 (24.8)	
MSH2	2 (13.3)	310 (30.1)	
PMS2	1 (16.7)	128 (12.4)	
MSH6	7 (46.7)	337 (32.7)	
Colorectal cancer	4 (26.7)	311 (30.2)	1.000
Multiple CRC[b]	2 (50)	66 (21.2)	0.205
Synchronous CRC	2 (50)	19 (20.7)	0.023
Metachronous CRC	1 (25)	52 (16.7)	0.523
Age at diagnosis CRC, median (range)	36 (34-42)	46 (16-86)	0.045

All values are expressed as n (%) unless otherwise noted.
[a] Age is defined as the age during the PALGA search or, if deceased, the age at death.
[b] Both patients with synchronous and/or metachronous CRC.

LS patients with IBD and colorectal neoplasia

Eight of 15 LS patients with IBD developed a LS-associated neoplasia, including 4 CRC, 3 colorectal dysplasia and 1 endometrial/urothelial cell carcinoma. Histopathological reassessment did not change these results. An overview of the patients who developed a colorectal neoplasia is displayed in Table 3. All 4 patients with CRC had UC, either pancolonic (3 patients) or left-sided (1 patient). Two patients developed CRC prior to LS and IBD diagnoses. CRC was diagnosed in 1 patient (case 1 in Table 3) after absence of surveillance colonoscopies during 5 years. Subsequently, 3 metachronous CRC developed 3 years later following an incomplete colonoscopy due to poor bowel preparation. Only one (with LGD) out of 7 patients who developed colorectal neoplasia used azathioprine for more than 12 years until end of follow-up. One out of 4 CRC patients died 11 months after CRC diagnosis, whereas 3 patients were alive after respectively 3, 4 and 12 years of follow-up.

Two patients had multiple adenocarcinomas. The first patient (case 1 in Table 3) developed after an IBD-history of 12 years 3 synchronous adenocarcinomas in his rectum resulting in a rectum and os coccygis amputation with an end colostomy. After this resection, LS diagnosis was made. Three years later, 3 new synchronous colorectal adenocarcinomas were detected in the colostomy, sigmoid colon and appendix. The patient underwent a total colectomy and chemotherapy, and was alive with metastatic disease 3 years after his last CRC. The second patient (case 2 in Table 3) had 3 synchronous CRC in her sigmoid colon before LS and IBD diagnosis. A subtotal colectomy was performed and no metastasis developed in 4 years of follow-up. The percentage of patients with multiple CRC was not significantly different between cases and controls (2/4 (50%) versus 66/311 (21.2%), p = 0.205; Table 2). However, duration of follow-up after first CRC was shorter in the case group (median 6.5 y (4-11) versus 11 y (0-38)), although not significantly different (p = 0.262). Nevertheless,

the total number of CRC was remarkable in patients with both LS and IBD (cases: 1 patient with 3 CRC, 1 patient with 6 CRC; controls: 47 patients with 2 CRC, 17 patients with 3 CRC, 2 patients with 4 CRC).

All colorectal neoplastic lesions from patients with both LS and IBD were MSI. Remarkably, one patient with UC and a MLH1 MMR deficiency who developed 3 synchronous CRC showed hypermethylation of the MLH1 promotor region in all 3 CRC. This was not observed in the other patients with both LS and IBD who developed colorectal neoplasia.

DISCUSSION

The key finding of our study is that patients with both LS and IBD developed CRC at a younger age compared to LS patients without IBD, although cumulative CRC incidence was similar. Our unique cohort highlights that CRC specifically developed in LS patients with UC rather than CD and that this subgroup has a higher cumulative CRC incidence.

Although other studies comparing LS patients with and without IBD are lacking, our findings are confirmed by previous reports. As such, one series from a single center reported 4 patients with CRC out of 12 patients (33%) with both LS and IBD at the age ranging from 32 to 47 years, which is in line with our results (4 CRC out of 15 patients with LS and IBD, 27%; age 34-42).[5] Only 1 patient in this case series who developed CRC had CD (ileitis), supporting our finding that especially LS patients with UC bear an increased CRC risk. However, almost none of the CD patients had colonic involvement both in literature and in our study, not allowing us to draw conclusions on CRC risk for colonic CD.

The higher cumulative CRC incidence and younger onset in LS patients with UC may be caused by the interaction of MMR deficiencies and inflammation. Inflammation can induce DNA damage and inactivate or repress MMR responses.[18] In LS patients with already affected MMR systems, these consequences of the inflammatory process may further facilitate carcinogenesis. This is supported by data from two MMR deficient (MLH1, MSH2) mice models (recapitulating human LS), that suggest increased and accelerated colorectal carcinogenesis in dextran sodium sulphate induced colitis.[7, 8] In our study 2 patients had multiple CRC, which might be the result of an increased and/or accelerated carcinogenesis. By contrast, both in our study and in literature, CRC sometimes developed prior to IBD diagnosis and/or mucosal inflammation did not involve CRC location.[19] Possible explanations may be a delayed diagnosis of IBD (mucosal inflammation can be present years before IBD diagnosis) or the absence of inflammatory involvement in the underlying CRC pathway in these specific cases.

Another linkage between the carcinogenesis in LS and IBD might be a defect in MMR genes. As such, a specific polymorphism in MSH2 (frequency background population: 10%) was associated with high grade dysplasia and CRC in UC patients, although not confirmed in a second study.[20, 21] In addition to MMR deficiencies, MSI can be the result of inflammation-induced promotor hypermethylation of MLH1. Contrasting sporadic CRC, low frequencies of MLH1 promotor hypermethylation are found in IBD- and LS-associated CRC.[22, 23] Moreover, various clinical features of IBD-associated CRC (for example young age and no female

Table 3. Overview of LS patients with IBD who developed a colorectal neoplasia

	Case 1		Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
MMR mutation	MLH1		MLH1	PMS2	MSH6	MSH 6	MLH1	MLH1
Age at LS diagnosis	35		35	NA	45	27	44	42
Gender	M		F	F	M	M	F	M
Smoking behaviour	NA		Never	NA	Never	Never	Never	NA
IBD								
Type	UC		UC	UC	UC	UC	UC	CD
Extend[a]	E3		E3	E2	E3	E2	E2	L3
Age at IBD diagnosis	22		39	19	48	30	34	34
Immunosuppression	No		No	No	No	No	No	Azathioprine
Neoplasia								
Age at neoplasia	34	37	34	38	42	37	48	47
Grade	3 synchronous CRC	3 synchronous CRC	3 synchronous CRC	CRC	CRC	LGD	LGD	LGD
TNM[b] (Stage)	T2N1Mx (III)	T4aN2M1 (IV)	T2N0M0 (I)	TxNxM1 (IV)	T3N2M0 (III)			
Histology								
classification / differentiation	1: Not otherwise specified carcinoma / moderately 2: Not otherwise specified carcinoma / moderately 3: Not otherwise specified carcinoma / moderately	1: Mucinous, partly signet ring cell carcinoma / poorly 2: Micropapillary, partly mucinous carcinoma / poorly 3: Mucinous carcinoma / moderately	1: Not otherwise specified carcinoma / moderately 2: Mucinous carcinoma / moderately 3: Partly medullary carcinoma / well	NA	Mucinous carcinoma / moderately	Traditional serrated adenoma	Tubulovillous adenoma	Tubular adenoma

Table 3. (continued)

	Case 1		Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Genetics								
MSI	Yes (all 3 CRC)	Yes (all 3 CRC)	Yes (all 3 CRC)	NA	Yes	Yes	Yes	NA
Hypermethylation MLH 1 promotor	No	No	Yes (all 3 CRC)	NA	No	No	No	NA
Location neoplasia	Rectum	Sigmoid, appendix	Sigmoid	Hepatic flexure	Splenic flexure	Transverse colon	Transverse colon	Ascending colon
Treatment	Rectum and os coccygis amputation, neoadjuvant chemoradiation	Total colectomy, adjuvant chemotherapy, HIPEC	subtotal colectomy	NA	Left hemicolectomy, adjuvant chemotherapy	Endoscopic resection	Endoscopic resection	Endoscopic resection
Follow-up	Alive with metastatic disease 3 years after last CRC		Alive without metastatic disease 4 years after CRC	Died 11 months after CRC	Alive without metastatic disease 12 years after CRC	Alive without dysplasia 1 year after LGD	Alive 1 month after LGD	Alive without dysplasia 3 years after LGD

[a] Classified according to the Montreal classification.
[b] According to 5th TNM staging system.
NA, not available; M, male; F, Female; HIPEC, hyperthermic intraperitoneal chemotherapy.

predominance) resemble LS-associated CRC and differ from sporadic-CRC.[22] In our series, all cases with a colorectal neoplasia had MSI.

The prevalence of concomitant IBD in our LS cohort (15/1046; 1.4%) is in line with another study that determined a prevalence of 1.5% (5/329), which is relatively high compared to the highest reported IBD prevalence in the general population in Europe (507/100,000 persons; 0.5%).[24] This may be the result of routine endoscopic surveillance in LS patients resulting in increased detection of latent IBD. However, 6/15 (40%) patients with both LS and IBD in our cohort received their IBD diagnosis prior to their LS diagnosis. An alternative hypothesis might be a shared genetic pathway, a view that is shared by others since mucosal abnormalities are found in LS patients.[25] Two studies described an association between various MLH1 haplotypes with different MLH1 polymorphisms and IBD.[9, 26] Used markers in these studies were close to a susceptibility locus for IBD as determined in a genome-wide association study.[27]

Several clinically relevant conclusions can be drawn from our study results. First, as patients with LS and IBD can develop CRC at a very young age, careful compliance to the existing LS and IBD surveillance recommendations is advised.[28, 29] This importance is underlined by the observation that inadequate bowel preparation and inadequate surveillance intervals were the most important risk factors for interval CRC in general IBD patients.[30] Our first case (case 1, Table 3), who developed multiple CRC following insufficient follow-up, underlines this. Whether or not current surveillance intervals are sufficient is difficult to assess, since the interval CRC in our cases developed while surveillance guidelines regarding preparation and intervals were not followed. Second, a diagnosis of CRC in patients with both LS and IBD requires a colectomy given the risk of recurrence as well as multiple CRC as evidenced by our described cases. Moreover, colorectal dysplasia may already warrant colectomy, although another case series described 4 LS patient with IBD and LGD who underwent prophylactic colectomy not revealing malignancy.[5] Finally, our data emphasize that IBD patients with CRC at young age could also have LS. An already existing diagnosis of IBD, prohibiting further MSI testing, may be a confounding factor for LS diagnosis in these patients as also reported in literature.[22] Therefore, careful evaluation of young IBD patients with CRC considering LS is of major importance since it has clinical implications for the genetic counseling of these patients. Importantly, hypermethylation of the MLH1 promotor region often causing MSI in non-LS patients, does not exclude a diagnosis of LS in patients with IBD (case 2, current study).[31]

This study has some limitations. Although we established the largest LS cohort with concomitant IBD thus far, the first limitation includes the relatively small number of cases. This could have resulted in sampling bias and in type II error in the comparison between LS patients with and without IBD. Second the retrospective nature of this study may have resulted in missing variables. We took great care and achieved to limit the proportion of missing variables. Third, patients came from 2 LS referral centers which contribute to an element of selection bias. Indeed, the relatively young age of our cohort (cases median 38 years; controls median 52 years), probably results from earlier and more aggressive surveillance in this population. Finally, data regarding surveillance frequency are lacking, which is relevant to CRC detection and development.

In conclusion, patients with both LS and IBD in our cohort developed CRC at a younger age, which might be the result of combined inflammation and MMR deficiencies. Especially UC patients were at increased CRC risk and strict adherence to surveillance guidelines in these patients should be encouraged.

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CHAPTER 3

INCREASED PREVALENCE OF COLONIC NEUROENDOCRINE TUMORS IN A NATIONWIDE INFLAMMATORY BOWEL DISEASE COHORT

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ABSTRACT

Inflammatory bowel disease (IBD) patients may bear an increased neuroendocrine tumor (NET) risk. These tumors are mostly reported as coincidental findings during surgery. We aimed to determine the prevalence of colonic NET in a Dutch nationwide IBD cohort and calculate the prevalence rate ratios (PRR) compared with the general Dutch population. Our second aim was to investigate whether a high bowel surgery rate in IBD could result in a high PRR for NET.

The Dutch Pathology Registry (PALGA) was searched to identify all IBD patients with colonic NET in The Netherlands between 1991 and 2011. We determined the prevalence and PRR of colonic NET in a 20-year period. For our second aim, we compared NET prevalence in colonic resection specimens between IBD cases and non-IBD controls (diverticulitis and ischemia).

We identified 51 IBD patients who developed colonic NET resulting in a prevalence of 60.4–89.3 per 100,000 patients in a 20-year period with a PRR of 2.8–4.1. However, adjusted for resection type, sex and age, a higher NET prevalence was shown in diverticulitis (OR 5.52, 95% CI 3.47–8.78) and ischemia (OR 1.97, 95% CI 1.09–3.58) compared with IBD.

Our key finding is that NET are more prevalent in IBD patients compared with the general population (PRR 2.8–4.1). This might be attributed to a high rate of incidental NET as IBD patients frequently undergo intestinal surgery. A lower adjusted NET prevalence in colonic resection specimens for IBD compared to ischemia and diverticulitis supports this hypothesis.

INTRODUCTION

Colorectal cancer (CRC) risk is increased in patients with inflammatory bowel disease (IBD).[1, 2] As IBD duration, extent and severity of disease drive CRC risk, it is assumed that chronic intestinal inflammation is an important contributing factor.[3] In addition to an increased CRC risk, IBD patients also carry a risk to develop other types of neoplasia such as neuroendocrine tumors (NET). Several authors have reported cases of both IBD and NET resulting in the hypothesis that inflammation may cause hyperstimulation of enteroendocrine cells leading to hyperplasia and neoplasia.[4–6] However, convincing epidemiological evidence of an association between IBD and NET is lacking so far.

NET risk in IBD patients has been poorly investigated and reported results are variable. Two studies including, respectively, 590 and 111 IBD patients, found an increased risk of NET development compared to the background population.[5, 7] By contrast another study among 705 IBD cases did not detect an increased prevalence.[6] However, all these data were collected from single tertiary referral centers introducing referral and selection bias and as such may not be representative for the IBD population at large. Furthermore, high surgery rates in IBD (25–30% in ulcerative colitis [UC] and 70–80% in Crohn's disease [CD]) may lead to high NET risks, as these tumors are mostly detected by coincidence during surgery.[8, 9] Therefore, the comparison of NET risks across studies is difficult given the variable rates of bowel surgery in control groups in the aforementioned studies.

To resolve the discrepancy in reported NET prevalence we designed a nationwide study to determine the prevalence of colonic NET in a Dutch IBD cohort. Research questions were restricted to the colon as both UC and CD are located to this part of the gastrointestinal tract and colonic tissue is available for most IBD patients. First, we aimed to investigate whether IBD patients have an increased colonic NET prevalence compared with the general Dutch population. Second, we hypothesized that an increased NET prevalence in IBD patients is explained by a high rate of colonic resections and thus a high rate of incidental findings. We therefore compared NET prevalence between IBD cases and non-IBD controls, both with a colonic resection.

MATERIAL AND METHODS

Study design and data sources

We established a cohort consisting of all IBD patients with concomitant colonic NET in The Netherlands assembled over 20 years using the nationwide Dutch pathology database PALGA.[10] Subsequently, the prevalence of NET was calculated by dividing these IBD patients with colonic NET by the total Dutch IBD population.[11, 12]

For our first aim, we compared the determined NET prevalence in the IBD population with the reported NET prevalence in the general Dutch population.[13] The NET prevalence in the general population was provided by the Dutch Cancer Registry of which data are also based on PALGA. Using this registry, a previous study reported NET and carcinoma prevalence in The Netherlands between 1990 and 2010 according to different sites.[13]

To investigate our second hypothesis, we compared the NET prevalence in IBD cases and non-IBD controls, both with one or more colonic resections. Control groups included

diverticulitis and ischemia patients since these patients frequently undergo a colonic resection but evidence for an increased NET risk is lacking.

Patient identification

PALGA, the nationwide network and registry of histopathology and cytopathology, was searched to identify all patients with concomitant IBD and colonic NET between 1991 and 2011 in The Netherlands. The PALGA registry contains pathology reports generated in The Netherlands since 1971 and has complete national coverage since 1991 encompassing all pathology laboratories from all academic and nonacademic hospitals in The Netherlands.[10] With approval of their Privacy Commission and Scientific Council, we performed a PALGA search with the following search terms: "*ulcerative colitis*", "*Crohn's disease*", "*indeterminate colitis*", "*chronic idiopathic inflammatory bowel disease*", or "*colonic inflammation*" combined with "*carcinoid*", "*neuroendocrine tumor*", or "*neuroendocrine carcinoma*", located in the "*colon*", "*appendix*" or "*ileocecal region*" (Figure 1).

For our second aim, we identified diverticulitis and ischemia patients with colonic NET. A second PALGA search in the same period was performed. Search terms for NET were combined with "*diverticulitis*", or "*diverticulosis*" to identify diverticulitis patients with NET, and with "*circulatory insufficiency*" and "*ischemia*" to identify ischemia patients with NET. In addition, we estimated for our second aim total IBD, diverticulitis and ischemia populations with a colonic resection. In two years within the inclusion period, we identified all IBD, diverticulitis and ischemia patients who had a colonic resection using PALGA and linearly extrapolated the results to all years of inclusion (1991–2011). Since on one hand anti-TNFα agents might decrease the need for surgery and however, increasing IBD incidences over time might elevate the number of colonic resections, we chose to evaluate the number of resections in one separate year before and after anti-TNFα approval in the late nineties. For this reason we evaluated the number of resections in 1995 (without the availability of anti-TNFα agents) and in 2005 (with the availability of anti-TNFα agents) for estimating total

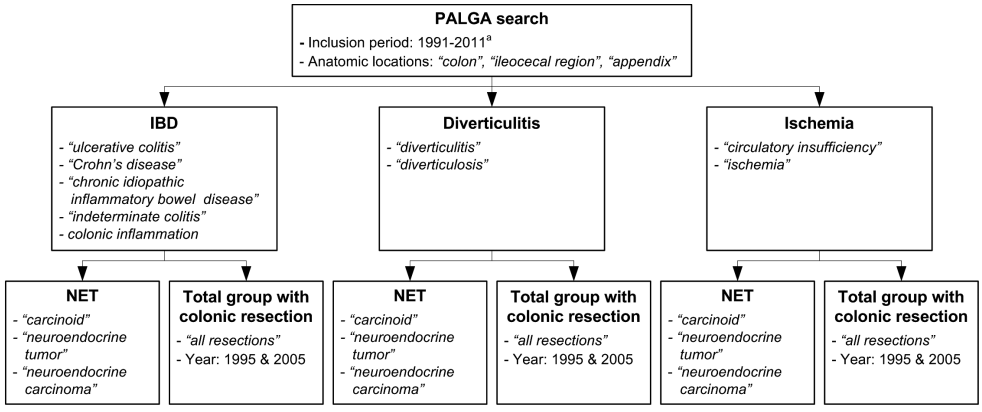

Figure 1. Schematic overview of the PALGA search strategy for patient identification. [a] This inclusion period applies to the search strategies with NET.

populations.[14, 15] Patients were allowed to be included in more than one group since each group is considered to be an independent sample of the total population.

Inclusion and exclusion criteria

Patients with UC, colonic CD, indeterminate colitis (IC), diverticulitis or colonic ischemia who developed a NET or who had a colonic resection in 1995 or 2005 were eligible for inclusion. Diagnoses of IBD, diverticulitis or ischemia were confirmed or excluded after careful evaluation of individual pathology reports. NET included both well and poorly differentiated NETs and carcinomas (NET grade 1 to 3 according the WHO 2010 criteria).[16] We included microcarcinoids (tumor size between 0.5 and 5 mm) and excluded mixed adenoneuroendocrine carcinomas.[17] Primary tumors had to be located in a colonic biopsy or resection specimen, which was defined as any partial or complete colonic resection including an appendectomy and ileocecal resection. NET cases diagnosed in a colonic biopsy or polypectomy were excluded from the comparison between IBD, diverticulitis and ischemia patients, as total populations in this comparison were based on patients who underwent a colonic resection. Furthermore, we excluded patients in whom a diagnosis of

IBD, diverticulitis or ischemia was made after NET development, or after their colonic resection. Patients who developed NET prior to 1991 or after 2010 were also excluded.

Data extraction

Two authors (L.D. and W.V.) extracted data from PALGA and from anonymized pathology reports. Extracted variables included gender, type of IBD, age at IBD onset, colonic resection type, NET location, TNM stage according to the WHO 2010 criteria[18] and age at colonic resection or NET diagnosis. The age of IBD onset was defined by the first biopsy or resection specimen suggesting IBD. Colonic resection type was divided into four categories taken the length of the resection specimen and the NET incidence at the different anatomical sites into account.[13] Categories included ileocecal resection (including appendectomy), rectosigmoid resection, partial colonic resection (including hemicolectomy) and total colonic resection.

Total Dutch IBD population

Based on different approaches, we estimated the total IBD population in The Netherlands between 1991 and 2011 for prevalence calculations. Our first approach included the use of a report by the Dutch national Institute for Public Health and Environment, which estimated a total Dutch IBD population of 57,000 in 2007 based on general practitioners registrations.[11] For our second approach, we extrapolated the highest reported IBD prevalence of northern Europe from a recent publication of the European Crohn's and Colitis Organisation Epidemiology Committee (507/100,000) to The Netherlands (n = 516,655,799), resulting in a total Dutch IBD cohort of 84,445 patients in 2011.[12,19]The range (57,100–84,445) of estimated IBD patients is a result of increasing IBD prevalence and variably reported prevalence rates of IBD due to geographical and methodological differences.

Statistics

We calculated the prevalence of NET in a 20-year period (1991–2011) in the nationwide IBD population by dividing the IBD patients with NET by the total Dutch IBD population. Subsequently, the calculated NET prevalence in the IBD population was compared to the NET prevalence in the general Dutch population resulting in a prevalence rate ratio (PRR).

Next, we compared the prevalence of NET during a 20-year period in colonic resection specimens between IBD cases and non-IBD controls. For this purpose, the total number, type and age of colonic resections determined in two years (1995 and 2005) were linearly extrapolated to a 20-year period (1991–2011). Confounders for NET development were univariately compared within the NET group and the total group with a colonic resection using $\chi 2$ test. We performed a binary logistic regression model adjusted for gender, age and resection type to compare NET prevalence in colonic resection specimens between diseases. To verify the robustness of the analyses based on linear extrapolation between 1995 and 2005, we performed two additional sensitivity analyses. In the first, we assumed yearly a similar number of patients as in 1995, to estimate the total population during a 20-year period (estimated total population = number of patients in 1995 x 20). Likewise, we estimated total populations for our second sensitivity analysis using the total number of patients in 2005. All missing values were considered to be at random and were excluded from analyses. A *P* values below 0.05 was considered statistically significant. All statistical analyses were performed with Statistical Analysis Software version 9.2 (SAS Institute, Cary, NC) or IBM SPSS statistics version 20.0 (SPSS, Chicago, IL).

RESULTS

IBD patients with NET

Our PALGA search identified 51 IBD patients who developed colonic NET, including 22 UC patients, 25 CD patients and 4 patients with IC (Figure 2). Median age of IBD and NET diagnoses were respectively 40 and 48 years. Tumors were localized in the appendix (n = 531; 72.1%), rectosigmoid colon (n = 56; 14.0%), descending colon (n = 53; 7.0%) and cecum (n = 53; 7.0%). In 8 patients NET locations were not further specified than ileocecal region (n = 53) or colon (n = 55). Detection of NET was performed with a colonic resection in 46 patients and with colonic biopsies in 5 patients. Tumor stages were distributed as follows: 36.1% (13/36; n = 515 missing) were stage I, 11.1% (4/36) were stage I or II, 25.0%

(9/36) were stage II, 19.4% (7/36) presented with lymph node metastases (stage III) and 8.3% (3/36) presented with distant metastases (stage IV).

NET prevalence and PRR

An estimated total Dutch IBD population between 57,100 and 84,445 patients resulted in a 20-year NET prevalence between 60.4 and 89.3 per 100,000 patients (Table 1). Compared with a 20-year colonic NET prevalence of 21.9 per 100,000 patients in the general population, this yields a PRR between 2.8 and 4.1.

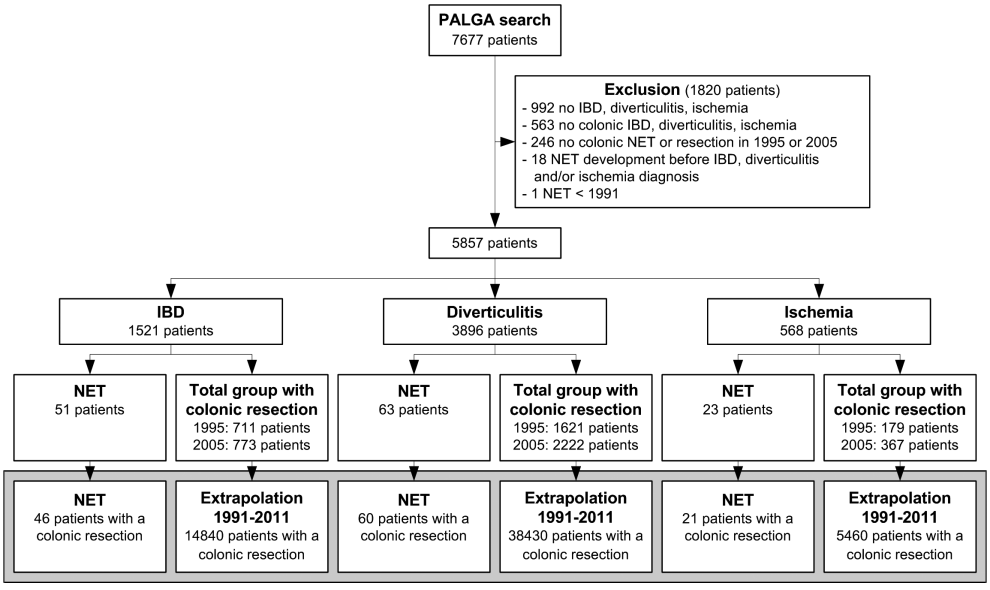

Figure 2. Patient inclusion flowchart. The light gray box represents the patients included for the comparison of NET PRR between IBD, diverticulitis and ischemia patients.

Table 1. Prevalence rate ratio of NET for IBD patients compared to the general population.

		IBD Population		Total Dutch population		
		Cases (n)	Prevalence in a 20-y period (n/100,000 patients)	Cases[a] (n)	Prevalence in a 20–y period (n/100,000 patients)	PRR
A	**IBD**	51	89.3	3440	21.9	4.1
	Ulcerative colitis[b]	26	81.7	3440	21.9	3.7
	Crohn's disease	25	99.2	3440	21.9	4.5
B	**IBD**	51	60.4	3440	21.9	2.8
	Ulcerative colitis[b]	26	55.2	3440	21.9	2.5
	Crohn's disease	25	67.0	3440	21.9	3.1

A: Estimated IBD prevalence of 57,100 patients as reported by the Dutch national Institute for Public Health and Environment.[11]
B: Estimated IBD prevalence of 84,445 patients based on literature.[12]
[a] The number of NET cases in the general Dutch population is previously determined.[13]
[b] 4 patients with indeterminate colitis are included in the UC subgroup.

IBD versus diverticulitis and ischemia

An inclusion flowchart of the patients included for the comparison of NET prevalence between different cohorts with a colonic resection is displayed in Figure 2. As patients were excluded in whom NET was detected with colonic biopsies, we included 46 out of 51 IBD

patients with NET, 60 out of 63 diverticulitis patients with NET and 21 out of 23 ischemia patients with NET. Extrapolation of the total number of patients with one or more colonic resections in 1995 and 2005 resulted in 14,840 IBD, 38,430 diverticulitis and 5460 ischemia patients (Figure 2). This resulted in a significantly lower 20-year prevalence of NET in colonic resection specimens for diverticulitis (0.16%) compared with IBD (0.31%; odds ratio [OR] 0.50, 95% confidence interval [CI] 0.34–0.74) and ischemia (0.39%; OR 0.41, 95% CI 0.25–0.67). No statistically significant different prevalence of NET was observed between IBD and ischemia (OR 1.24, 95% CI 0.74–2.08).

Patient characteristics of the included patients are depicted in Table 2. Both NET patients and all colonic resection patients were significantly younger in the IBD group ($p < 0.05$). All IBD patients with a colonic resection underwent more frequently ileocecal resections ($p < 0.05$) compared with diverticulitis and ischemia patients while in NET patients the resection types were equally distributed across groups ($p = 0.154$). This resulted in a different prevalence of NET in colonic resections across subgroups, especially in those based on resection type (Table 3). A multivariate binary logistic regression model was performed to adjust for these potential confounders. A higher adjusted 20-year NET prevalence was shown in diverticulitis patients (OR 5.52, 95% CI 3.47–8.78) and ischemia patients (OR 1.97, 95% CI 1.09–3.58) compared with IBD. Similar results were found in our sensitivity analyses based on extrapolation of data from 1995 or 2005 only (data not shown).

NET prevalence in IBD subtypes

As the comparison with the general population demonstrated a slightly increased NET prevalence for CD than for UC patients (Table 1), we subsequently compared NET prevalence in colonic resection specimens across IBD subtypes. No statistical different NET prevalence was found in CD versus UC colonic resection specimens (OR 0.59, 95% CI 0.32–1.07). However, a multivariate analysis adjusted for resection type showed a significantly lower 20-year NET prevalence for CD compared with UC patients (OR 0.30, 95% CI 0.13–0.68).

DISCUSSION

The key finding of this study is an increased colonic NET prevalence in IBD patients in comparison with the general population with a PRR between 2.8 and 4.1. However, adjusted for resection type, gender and age, a lower NET prevalence was shown in IBD patients with a colonic resection compared to diverticulitis and ischemia patients with a colonic resection. This latter finding suggests that the increased NET prevalence in IBD patients could be attributed to incidental findings as a result of frequent colonic resections.

Previous studies are in line with the increased NET risk for IBD patients in comparison with the general population. Although data were retrospectively collected from single tertiary referral centers, one study reported a relative risk of approximately 9 for rectal carcinoid development and another reported an OR of approximately 15 for carcinoid tumor development.[5,7] This increased risk accords with our study in which we calculated a population

Table 3. NET prevalence in colonic resections during a 20-year period displayed for different subgroups

	NET prevalence in colonic resections (%)			Multivariate analysis (Final binary logistic regression model; odds ratio, 95% CI)
Variable	**IBD**	**Diverticulitis**	**Ischemia**	
Disease type				
Ischemia	n/a	n/a	0.385	1.97 (1.09–3.58)
IBD	0.310	n/a	n/a	1.00
Diverticulitis	n/a	0.156	n/a	5.52 (3.47–8.78)
Gender				
Female	0.373	0.153	0.456	1.00
Male	0.230	0.160	0.323	0.86 (0.59–1.25)
IBD type				
Ulcerative colitis	0.414	n/a	n/a	n/a
Crohn's disease	0.243	n/a	n/a	n/a
Indeterminate colitis	0.769	n/a	n/a	n/a
Age at colonic resection				
≤ 50 y	0.266	0.292	0.244	1.00
50 – 70 y	0.411	0.136	0.513	1.62 (1.03–2.54)
> 70 y	0.391	0.127	0.335	1.63 (0.97–2.73)
Colonic resection type				
Ileocecal resection	0.414	5.250	1.122	1.00
Rectosigmoid resection	0.145	0.029	0.171	0.10 (0.06–0.18)
Partial colonic resection	0.567	0.172	0.176	0.01 (0.01–0.02)
Total colonic resection	0.205	0.952	0.606	0.32 (0.17–0.61)

based NET PRR between 2.8 and 4.1 for IBD patients. Comparing the determined colonic NET prevalence in IBD with the highest reported NET prevalence by the WHO results in similar PRR (2.9–4.2).[20] The calculated PRR might be an underestimation as cases only comprise CD patients with colonic disease activity while the total Dutch IBD population included all CD patients regardless of disease localization.

The increased PRR of NET in IBD may be attributed to incidental findings in resection specimens, as hypothesized by previous studies.[6, 21, 22] This is supported by the lower colonic NET prevalence in multivariate analysis for IBD patients with a resection compared to diverticulitis and ischemia patients with a resection. Similar comparisons have not been made in literature before and only case reports regarding NET in diverticulitis or ischemia patients are available.[23–33] Prevalence rates of carcinoid tumors in appendectomy specimens were similar in IBD patients compared with non-IBD controls, supporting our findings.[6] Another study reported 9 cases (5 CD and 4 UC), all discovered incidentally, in 2284 patients undergoing intestinal surgery for IBD resulting in a prevalence of 0.26% which was nearly identical to a rate of 0.27% in non-IBD patients undergoing intestinal surgery.[6, 22, 34, 35]

Table 2. Characteristics of patients with NET and all patients with a colonic resection in the IBD, diverticulitis and ischemia cohort. Total number, type and age of colonic resections determined in two years (1995 and 2005) were extrapolated to a 20-year period (1991–2011).

	NET (1991–2011)				Colonic resections (1991–2011)				
Variable	**IBD (n = 46)**	**Diverticulitis (n = 60)**	**Ischemia (n = 21)**	**Univariate analysis P value**	**IBD (n = 14,840)**	**Diverticulitis (n = 38,430)**	**Ischemia (n = 5460)**	**Univariate analysis P value**	**Missings (n; NET/ colonic resections)**
Gender				0.273				< 0.05	0
Female	31 (67.4)	34 (56.7)	11 (52.4)		8320 (56.0)	22,190 (57.7)	2410 (44.1)		
Male	15 (32.6)	26 (43.3)	10 (47.6)		6520 (44.0)	16,240 (42.3)	3050 (55.9)		
IBD type				n/a				n/a	0
Ulcerative colitis	19 (41.3)	n/a	n/a		4590 (30.8)	n/a	n/a		
Crohn's disease	24 (52.2)	n/a	n/a		9860 (66.4)	n/a	n/a		
Indeterminate colitis	3 (6.5)	n/a	n/a		390 (2.6)	n/a	n/a		
Age at colonic resection				< 0.05				< 0.05	0
≤ 50 y	27 (58.7)	17 (28.3)	2 (9.5)		10,150 (68.4)	5820 (15.1)	820 (15.0)		
50 – 70 y	14 (30.4)	23 (38.3)	10 (47.6)		3410 (23.0)	16,860 (43.9)	1950 (35.7)		
> 70 y	5 (10.9)	20 (33.3)	9 (42.9)		1280 (8.6)	15,750 (41.0)	2690 (49.3)		
Colonic resection type:				0.154				< 0.05	7/7050
Ileocecal resection	26 (59.1)	42 (47.2)	11 (61.1)		6280 (47.7)	800 (2.3)	980 (23.4)		
Rectosigmoid resection	3 (6.8)	9 (15.5)	2 (11.1)		2070 (15.7)	30,430 (88.6)	1170 (28.0)		
Partial colonic resection	8 (18.2)	5 (8.6)	3 (16.7)		1410 (10.7)	2900 (8.4)	1700 (40.7)		
Total colonic resection	7 (15.9)	2 (3.4)	2 (11.1)		3400 (25.8)	210 (0.6)	330 (7.9)		

All values are expressed as n (%) unless otherwise noted.

Prevalence rates are similar to our results (0.33%) and are further supported by another study that identified 3 carcinoids among 1000 CD patients undergoing intestinal surgery (0.33%).[21] Finally, the relatively high percentage of stage I (36.1–47.2%) and low percentage of stage IV (8.3%) NET in our IBD patients compared to all gastrointestinal NET (23.8% stage I, 23.8% stage IV) underscores a high percentage of incidental NET in our IBD population.[36]

Whether a relationship exists between chronic mucosal inflammation and NET development could not be extracted from our data. The significantly higher colonic NET prevalence in UC may indicate a role of inflammation. By contrast, most of reported IBD cases with NET in the literature arose in areas of uninflamed intestine suggesting absence of a firm correlation between local inflammation and NET development.[5] However, patients could have previously had inflammation in these areas, for example before start of medical therapy, or distant inflammatory mediators might play a role.

NET usually have an excellent prognosis if diagnosed at an early stage and treated adequately.[37] Although rare, NET may clinically simulate IBD, especially in CD patients with ileal involvement. Thus, an accurate and timely diagnosis of NET is extremely important.[21] NET are often detected incidentally during surgery and a different approach might have been considered if NET was already suspected clinically. Results of our study may improve the awareness of NET coexistence in IBD patients, especially in those who need to undergo intestinal surgery. Furthermore, the increased tumor risk in IBD patients as a consequence of incidental findings could also be investigated in future research for other (extra)-intestinal malignancies in IBD patients.

Strengths of this study include the nationwide approach and the comparison of NET prevalence across patient groups with frequent colonic resections. Although the size of our IBD cohort with NET is limited (n = 551), we established to our best knowledge the largest cohort thus far. This study also has some limitations. First, diagnoses of IBD, diverticulitis and ischemia were made on the basis of individual pathology reports rather than on clinical and endoscopic features. Reasons for surgery were unknown and thus it was unclear whether a NET was detected as an incidental finding. However, these limitations consistently applied to all cases, controls and total populations. Furthermore, NET diagnosis could be missed as a result of sampling bias. Since IBD is already associated with CRC, pathologists may have a higher cancer suspicion when assessing colonic specimens, with subsequently less sampling bias compared to diverticulitis and ischemia. Third, colonic resection types differed among case and control groups, which may influence NET risk. To address this issue, we performed a multivariate analysis adjusting for this confounder. Third, bias may be introduced by the extrapolation of data. However, due to feasibility reasons this was inevitable to determine total IBD, diverticulitis and ischemia populations and thus to address our research question. Finally, NET criteria and WHO grading systems changed during the inclusion period impeding the opportunity to analyze well differentiated NET and poorly differentiated neuroendocrine carcinomas separately.

In conclusion, we identified an increased colonic NET prevalence in IBD patients in comparison with the general population, resulting in a PRR between 2.8 and 4.1. This finding

may be attributed to a high rate of incidental NET as IBD patients frequently undergo intestinal surgery. A lower adjusted 20-year NET prevalence for IBD compared with ischemia and diverticulitis supports this hypothesis.

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CHAPTER 4

BETTER SURVIVAL OF RENAL CELL CARCINOMA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Immunosuppressive therapy may impact cancer risk in inflammatory bowel disease (IBD). Cancer specific data regarding risk and outcome are scarce and data for renal cell carcinoma (RCC) are lacking. We aimed (1) to identify risk factors for RCC development in IBD patients (2) to compare RCC characteristics, outcome and survival between IBD patients and the general population.

A PALGA (Dutch Pathology Registry) search was performed to establish a case group consisting of all IBD patients with incident RCC in The Netherlands (1991–2013). Cases were compared with two separate control groups: (A) with a population-based IBD cohort for identification of risk factors (B) with a RCC cohort from the general population to compare RCC characteristics and outcomes.

180 IBD patients with RCC were identified. Pancolitis (OR 1.8–2.5), penetrating Crohn's disease (OR 2.8), IBD related surgery (OR 3.7–4.5), male gender (OR 3.2–5.0) and older age at IBD onset (OR 1.0–1.1) were identified as independent risk factors for RCC development. IBD patients had a significantly lower age at RCC diagnosis ($p < 0.001$), lower N-stage ($p = 0.025$), lower M-stage ($p = 0.020$) and underwent more frequently surgical treatment for RCC ($p < 0.001$) compared to the general population. This translated into a better survival ($p = 0.026$; HR 0.7) independent of immunosuppression.

IBD patients with a complex phenotype are at increased risk to develop RCC. They are diagnosed with RCC at a younger age and at an earlier disease stage compared to the general population. This translates into a better survival independent of immunosuppressive or anti-TNFα therapy.

INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis is a chronic inflammatory disorder of the gastrointestinal tract. Patients with this disease have an increased risk for both intestinal and various extraintestinal malignancies.[1, 2] This risk is mainly attributed to two drivers: chronic inflammation and drug-induced immunosuppression.[3] Particularly immunosuppressive medication such as thiopurines and methotrexate may play a role in the development of extra-intestinal malignancies by impairing immunosurveillance of tumor cells or inducing DNA damage.[4-7] The potential associated cancer risk is an important growing concern given the need for prolonged immunosuppressive therapy in IBD, especially in view of the aging IBD population.

Various extra-intestinal malignancies, such as lymphoproliferative disorders and non-melanoma skin cancers occur more frequently in IBD patients compared to the general population, mainly in those using immunosuppression.[2, 6, 8-12] Although only limited evidence is available, it has been suggested that immunosuppression in IBD patients may increase the risk for a variety of solid malignancies, such as renal cell carcinoma (RCC). Indeed, RCC occurs more frequently in post-transplantation patients exposed to immunosuppressive medication.[13] In addition, the risk for urinary tract cancers in IBD patients on thiopurines seems to be elevated.[3]

It is unknown whether and how IBD therapy impacts risk of cancer recurrence, outcome and survival. Aggregate data failed to demonstrate an effect of immunosuppression and anti-TNFα agents on recurrence of any cancer in IBD patients.[5] By contrast, cancer specific data on recurrence and outcome are scarce. For example, only eight case reports of IBD patients with RCC have been described and led to speculation on a putative association with immunosuppressive therapy.[14-19] As such, more data are needed to estimate RCC risk and to guide the subsequent individual IBD therapy.

To this end we established a nationwide cohort of IBD patients with incident RCC. We had a dual aim: (1) to identify risk factors for RCC development, and in particular to investigate the impact of IBD therapy on RCC development (2) to compare RCC characteristics, outcome and survival between IBD patients and the general population, including the impact of immunosuppression and anti-TNFα agents.

MATERIALS AND METHODS

Study design and data sources

In order to study risk factors and the clinical course of RCC in IBD patients, we performed two retrospective nationwide case control studies. We established a case group consisting of all IBD patients who developed RCC in The Netherlands assembled over 22 years, using PALGA (Dutch nationwide network and registry of histo- and cytopathology).[34] Subsequently, these cases were included in the following two case control studies:

The first case control study aimed for the identification of risk factors to develop RCC. Controls were randomly sampled from IBDSL, a population-based IBD registry.[35]

The second case control study was performed to compare RCC characteristics and outcomes between IBD patients and the general population. Controls were identified from the ECR and included patients from the general population who developed RCC.[36]

The study was approved by the Privacy Commission and Scientific Council of PALGA and by the Medical Ethics Review Committee region Arnhem - Nijmegen (Registration number 2013/419).

Case identification

PALGA was searched in order to identify all IBD patients with concomitant RCC in The Netherlands from January 1991 until May 2013. The PALGA registry contains pathology reports generated in the Netherlands since 1971 and has complete national coverage since 1991 encompassing all pathology laboratories from all academic and non-academic hospitals in the Netherlands.[34] We performed a PALGA search with the following search terms: "*ulcerative colitis*", "*Crohn's disease*", "*indeterminate colitis*", or "*chronic idiopathic inflammatory bowel disease*" combined with all "*primary carcinomas of the kidney*" or "*metastasis of kidney cancer*". Cases were further confirmed or excluded after careful evaluation of the individual pathology reports and/or medical records (Figure 1).

All patients with UC, CD or indeterminate colitis who developed a histologically confirmed RCC following IBD diagnoses were included. The diagnosis of IBD was based on a combination of clinical, endoscopic, histological and radiographic criteria.[37] The following exclusion criteria were used: no diagnosis of IBD, no diagnosis of RCC, RCC diagnosis before IBD diagnosis and RCC diagnosis before 1991.

Controls (A) – IBD South Limburg cohort

Controls for the identification of risk factors to develop RCC were randomly selected from IBDSL. IBDSL is a prospectively followed, population-based IBD registry in an area in the southeast of The Netherlands between Germany and Belgium, called South-Limburg. This area has a population of approximately 645.000 inhabitants with a low migration rate and covers one academic and two general district hospitals.[38] Adult patients in this area with a diagnosis of UC or CD based on a combination of endoscopic, radiologic and histological evidence are included in this cohort since 1991.[38] It includes 2807 IBD patients (40.9% CD, 59.0% UC), which represents 93% of the regional IBD population.[35] We randomly included patients with an IBD diagnosis between 1991 and 2011. An unmatched study design was chosen given the relatively large number of cases, allowing adjustment for possible confounders as well as to avoid missing potential risk factors.[39]

Controls (B) – Eindhoven cancer registry

Controls to compare RCC characteristics and outcomes were identified from the ECR, maintained by the Netherlands Comprehensive Cancer Organization. The registry prospectively collects data on all newly diagnosed cancers in the southern part of The Netherlands since 1955.[36] This area includes 10 general hospitals and 6 regional pathology laboratories, comprising approximately 2.3 million inhabitants (15% of the Dutch population).[40] Tumor characteristics

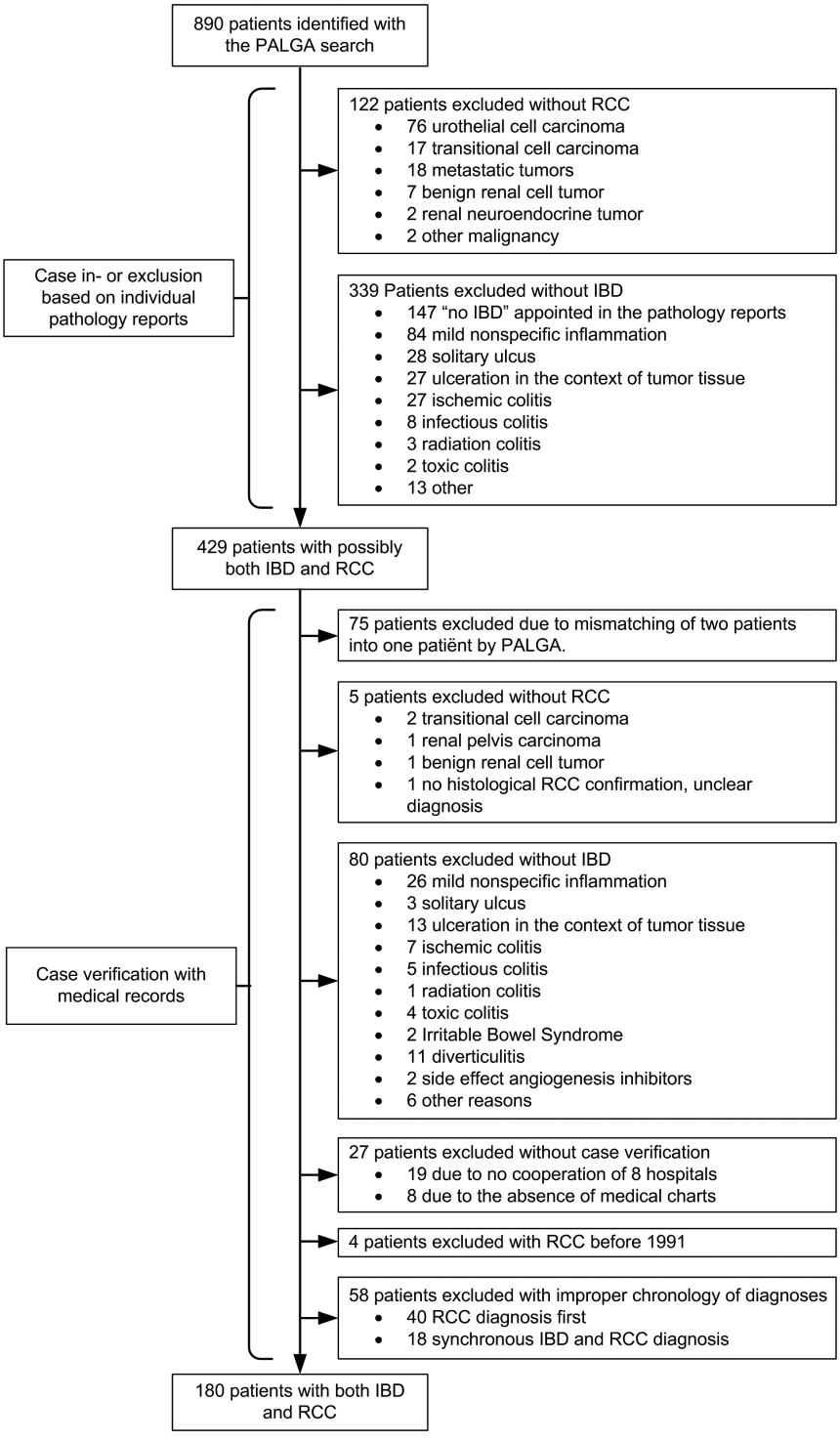

Figure 1. Patient inclusion flowchart.

and patient characteristics are routinely extracted from medical records by specially trained administrators of the cancer registry. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95%.[41] We included all patients with a histologically confirmed RCC between 1991 and 2010 from the ECR as controls.

Data extraction

Two authors (L.D and L.N) extracted demographic and clinical variables from anonymized medical records for patients included in the case group. Extracted data included gender, date of birth, smoking history (ever/never), primary sclerosing cholangitis, IBD characteristics and RCC characteristics. We collected the following IBD characteristics: type of IBD, date of diagnosis, phenotype according to the Montreal Classification, and medical and surgical treatment. Exposure to 5-ASA, thiopurines, anti-TNFα agents, cyclosporine or methotrexate was defined as "used" or "not used" since dosage/duration could not be reliably retrieved for all cases. RCC characteristics included: date of diagnosis, location, tumor stage according to the TNM classification (7th edition), differentiation grade according to Fuhrman[42], whether the tumor was incidentally detected or not, treatment, outcome and survival.

Incidentally diagnosed cancers were considered to be tumors discovered during investigations performed for reasons other than for RCC related symptoms including palpable tumor, haematuria (both macroscopic and microscopic), flank pain and signs of cachexia related to the disease.[21] RCC outcome included disease free survival (duration since RCC diagnosis until recurrence or death) and overall survival (duration since RCC diagnosis until death). Histopathological subtype could not be obtained reliably due to the great variability of morphology reporting standards since 1991. Similar variables with corresponding definitions were extracted from registries (IBDSL and ECR) for patients included in the control groups.

Statistics

For both case control studies we compared potential risk factors, RCC characteristics and/or outcomes between cases and controls with a univariable analysis. $\chi 2$ test or Fisher exact test (if expected cell counts were < 5) were used for categorical data and independent Student t test (if normally distributed) or Mann-Whitney U test (if not normally distributed) were used for continuous data. Variables with a *P* value of < 0.1 in univariable analyses were included in a multivariable model. As the control group in a case control study should reflect the entire source population that gave rise to the cases, we did not exclude IBD patients who developed RCC from the control groups.[43] These patients were in both models analyzed as cases.

For case control study A, identifying independent risk factors to develop RCC, we performed a multivariable logistic regression model with backward sampling. This model was adjusted for the duration of follow-up (fixed variable), which was defined as the time since IBD onset until the date of RCC diagnosis (cases) or the end of follow-up or death (controls). For case control study B, comparing RCC outcome between IBD cases and the general population, we made Kaplan Meier survival curves and performed log rank

analysis. Subsequently confounder correction was performed with Cox regression model with forward sampling. A covariate was considered as a confounder when the beta coefficient of the variable of interest (IBD yes/no) changed by 10% or more.[44] A *P* value of < 0.05 (2 sided) was considered to be statistically significant. All missing values were considered to be at random and were excluded from analyses. All statistical analyses were performed with IBM SPSS statistics version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient identification

We identified 180 IBD patients who developed RCC in 69 of 87 hospital organizations in the Netherlands (Figure 1).[20] Twenty-seven potential cases could not be verified and were excluded. To identify risk factors for RCC development we established a control group of 1800 IBD patients randomly selected from the IBD South Limburg Cohort (IBDSL; Case control study A). For the comparison of RCC characteristics and outcomes we identified a second control group using the Eindoven Cancer Registry (ECR). This search yielded 4388 patients with RCC in the general population (Case control study B).

Risk factors for RCC development - Case control study A

Potential clinical and demographic risk factors for RCC development were compared univariable between IBD cases who developed RCC and IBDSL control patients (Table 1). Male gender, Montreal E3 pancolitis, perianal disease activity, a stricturing and/or penetrating CD phenotype, and IBD related surgery occurred statistically significantly more frequent in the case group ($p < 0.001$ for all comparisons). Furthermore, cases had a statistically significantly longer duration of follow-up since IBD diagnosis ($p < 0.001$), but used less thiopurines ($p = 0.047$) and anti-TNFα agents ($p = 0.006$) during follow-up. We considered differences in inclusion period (IBD diagnosis since 1950 (cases) versus IBD diagnosis since 1991 (controls)) as a reason for these differences, since widespread use of thiopurines and the introduction of anti-TNFα therapy occurred in the last decade of inclusion. Using similar inclusion periods of IBD diagnosis for both cases and controls (since 1991) almost abolished treatment differences (5-aminosalicylic acids (5-ASA), 89.6% (cases) versus 89.8% (controls), $p = 0.954$; thiopurines, 35.6% versus 40.2%, $p = 0.432$; methotrexate, 0.0% versus 5.3%, $p = 0.049$; cyclosporine, 4.1% versus 1.5%, $p = 0.102$; anti-TNFα therapy, 15.1% versus 19.7%, $p = 0.326$).

A multivariable logistic regression model that took the duration of follow-up since IBD diagnosis into account was made separately for UC and CD patients to identify independent risk factors for RCC development. Included variables were: gender, age at IBD diagnosis, extend of UC and CD, perianal disease activity, CD phenotype and IBD related surgery. As prescribed medical therapy might be different and/or not reliable in early years of inclusion, we did not include these variables in this model. Therefore, we performed a sensitivity analysis including patients with an IBD diagnosis since 1991 in both the case and control group. Medical therapy was included in this logistic regression model.

Table 1. Univariable comparison of potential risk factors and confounders between cases (IBD patients who developed RCC) and controls (randomly selected IBD patients from IBDSL) for the identification of risk factors to develop RCC (case control study A).

Variable	IBD and RCC cases (n = 180)	IBDSL (n = 1800)	Missing values (cases/IBDSL)	P value
Male gender	114 (63.3)	837 (46.5)	0	< 0.001
Ever smoked[a]	38 (62.3)	421 (62.5)	11/122	0.979
Age at IBD diagnosis (y), median	43	39	3/1	0.106
IBD type[b]				
Ulcerative colitis	93 (56.4)	1004 (55.8)		
Crohn's disease	72 (43.6)	796 (44.2)	0	0.885
Ulcerative colitis				
Extend				
Proctitis (E1)	14 (17.5)	243 (24.4)		
Left-sided colitis (E2)	24 (30.0)	472 (47.5)		
Pancolitis (E3)	42 (52.5)	279 (28.1)	10/13	< 0.001
Crohn's disease				
Extend				
Ileum (L1)	27 (38.6)	223 (28.1)		
Colon (L2)	19 (27.1)	183 (23.0)		
Ileocolonic (L3)	24 (34.3)	389 (48.9)	2/1	0.054
Upper digestive (L4)	2 (2.8)	65 (8.2)	1/0	0.106
Perianal disease activity	21 (30.0)	119 (14.9)	2/0	0.001
Phenotype				
Non stricturing/penetrating (B1)	19 (27.9)	437 (54.9)		
Stricturing (B2)	16 (23.5)	171 (21.5)		
Penetrating (B3)	15 (22.1)	96 (12.1)		
Stricturing and penetrating	18 (26.5)	92 (11.6)	4/0	< 0.001
Medical therapy prior to RCC diagnosis				
5ASA	145 (94.2)	1605 (89.8)	26/13	0.083
Thiopurines	49 (32.0)	717 (40.2)	27/17	0.047
Methotrexate	3 (2.0)	95 (5.3)	29/10	0.074
Cyclosporine	5 (3.3)	26 (1.1)	27/10	0.091
Anti-TNFα therapy	16 (10.5)	350 (19.7)	28/25	0.006
IBD related surgery	86 (48.0)	508 (28.3)	1/8	< 0.001
Calendar year of IBD diagnosis, median	1989	2003	3/1	< 0.001
Duration of follow-up since IBD diagnosis (y), median	19	7	3/30	< 0.001

All values are expressed as n (%) unless otherwise noted.
[a] Smoking data were only available for patients with Crohn's Disease.
[b] Indeterminate colitis was not considered in this comparison since these patients were excluded from IBDSL.

Table 2 shows the final logistic regression models after backward elimination of the non-significant variables for both UC and CD patients. Patients with a more complex phenotype including Montreal E3 UC (OR 1.8–2.5, 95% CI 1.0–5.3), penetrating CD (OR 2.8, 95% CI 1.3–5.8) and/or IBD related surgery (OR 3.7–4.5, 95% CI 1.6–8.2) were at increased risk for RCC development. Furthermore, male gender (OR 3.2–5.0, 95% CI 1.7–13.2) and older age at IBD diagnosis but not age by itself (OR 1.0–1.1, 95% CI 1.0–1.1) were identified as independent risk factors. Use of 5-ASA (OR 0.2, 95% CI 0.0–0.7) protected against RCC development.

Table 2. Final multivariable regression model for the identification of independent risk factors to develop RCC.

Model	Variable	Coefficient β	Odds ratio (95% CI)	*P* value
Ulcerative colitis	Male gender	1.169	3.218 (1.715-6.040)	< 0.001
(all cases, n = 1061)	IBD related surgery	1.499	4.477 (2.433-8.238)	< 0.001
	Age at IBD diagnosis	0.023	1.023 (1.006-1.042)	0.009
	Montreal E3 colitis[a]	0.598	1.818 (1.045-3.163)	0.034
Ulcerative colitis	Male gender	1.609	4.999 (1.889-13.226)	0.001
(sensitivity analysis, n = 1015)	IBD related surgery	1.306	3.692 (1.578-8.641)	0.003
	Age at IBD diagnosis	0.028	1.029 (1.006-1.051)	0.011
	Montreal E3 colitis[a]	0.922	2.513 (1.2005.262)	0.015
	5-ASA	-1.746	0.174 (0.044-0.687)	0.013
Crohn's disease	Age at IBD diagnosis	0.035	1.035 (1.014-1.057)	0.001
(all cases, n = 845)	Penetrating disease	1.021	2.776 (1.320-5.836)	0.007
Crohn's disease	Age at IBD diagnosis	0.049	1.051 (1.028-1.074)	< 0.001
(sensitivity analysis, n = 811)				

Similar inclusion periods of IBD diagnosis (since 1991) for cases and controls were used in the sensitivity analysis (case control study A).
[a] Reference category is patients with Montreal E1 or E2 colitis.

RCC characteristics and survival - Case control study B

Univariable comparisons of RCC characteristics between IBD cases and the general population are shown in Table 3. IBD patients had a statistically significantly lower age at RCC diagnosis ($p < 0.001$), lower N-stage ($p = 0.025$), lower M-stage ($p = 0.020$) and underwent more frequently surgical treatment for RCC ($p < 0.001$). This may be attributed to a high percentage of incidentally diagnosed cancers in the case group (n = 80/180, 51.3%).

Figure 2 displays the overall survival curves of the case and control group. IBD patients had a statistically significant better overall survival compared to the general population ($p < 0.001$). However, age at RCC diagnosis, T-stage, M-stage, surgical treatment and calendar year of RCC diagnosis emerged as confounders in a Cox model. Adjusted for these confounders, a protective effect of IBD on overall survival was still present ($p = 0.026$; HR 0.7; 95% CI 0.5–1.0).

Table 3. Univariable comparison of RCC characteristics between cases (IBD patients who developed RCC) and controls (RCC patients in the general population derived from ECR) (case control study B).

Variable	IBD and RCC cases (n = 180)	ECR (n = 4388)	Missing values (cases/ECR)	*P* value
Male gender	114 (63.3)	2659 (60.6)	0	0.461
Age at RCC diagnosis (y), median	62 (27-83)	66	0	< 0.001
Location				
Left-sided	89 (50.6)	2119 (48.7)		
Right-sided	87 (49.4)	2230 (51.3)	4/39	0.631
Grade				
1-2	88 (72.7)	1214 (69.3)		
3-4	33 (27.3)	539 (30.7)	59/2635	0.442
T stage				
T1-T2	130 (76.9)	2509 (70.9)		
T3-T4	39 (23.1)	1032 (29.1)	11/847	0.089
N stage				
N0	160 (94.1)	3281 (88.6)		
N+	10 (5.9)	423 (11.4)	10/684	0.025
M stage				
M0	155 (87.1)	2962 (80.0)		
M1	23 (12.9)	742 (20.0)	2/684	0.020
Surgery	168 (93.9)	3318 (75.6)	1/0	< 0.001
Calendar year of RCC diagnosis, median	2003	2007	0	< 0.001

All values are expressed as n (%) unless otherwise noted.

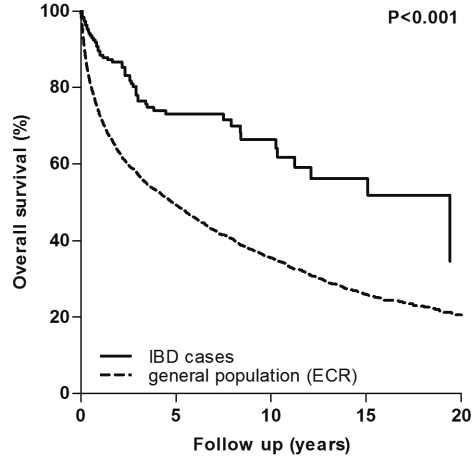

Figure 2. Overall survival curves of the general and IBD population following RCC diagnosis.

RCC survival related to medical IBD therapy

Based on received IBD medication, we performed subgroup survival analysis for IBD cases with RCC. Patients who used immunosuppression (including thiopurines, methotrexate and cyclosporine) and/or anti-TNFα therapy before or after RCC diagnosis had a statistically significantly better disease free survival following RCC diagnosis compared to those who did not (Figure 3). Especially patients who were treated with immunosuppression and/or anti-TNFα agents after RCC diagnosis, showed a better disease free survival. However, a multivariable Cox analyses adjusted for the confounders TNM stage and age at RCC diagnosis, abolished this protective effect of immunosuppressive and anti-TNFα therapy (immunosuppression before RCC diagnosis, p = 0.946; immunosuppression after RCC diagnosis, p = 0.386; anti-TNFα therapy before RCC diagnosis, p = 0.673; anti-TNFα therapy after RCC diagnosis, p = 0.502). Similar survival curves were found for the effect of IBD therapy on overall survival (data not shown).

Following a similar strategy as for the identification of risk factors we performed a sensitivity analysis focusing on patients who carried an IBD diagnosis since 1991. We determined the effect of medical therapy on disease free and overall survival. All survival analyses and Cox models showed similar results as shown above (data not shown).

DISCUSSION

One of the key findings of our study is that IBD patients with a complex phenotype (including Montreal E3 UC, penetrating CD and/or IBD related surgery) are at increased risk to develop RCC. They are younger at diagnosis and carry a lower RCC stage compared to the general population. This translates into a better disease free and overall survival. The second key finding of our study is that immunosuppressive and anti-TNFα therapy does not adversely affect disease free and overall survival in IBD patients following RCC diagnosis.

A better survival in our IBD cohort with RCC may be caused by frequent abdominal imaging in these patients, which leads to incidental findings such as RCC. Due to the widespread use of imaging techniques, the incidental detection of RCC in the general population significantly increased in recent decades to approximately 40%.[21-23] This compares to 51% for incidentally detected RCC in our IBD cohort. Previous studies have shown that patients with these incidentally detected RCC are diagnosed at an earlier stage, which is translated into a better survival after correction for confounders (TNM stage, age at RCC diagnosis, calendar year).[22-24] This is in line with our study in which IBD patients (including a high proportion of incidentally diagnosed cancers) received earlier RCC diagnosis and had a better survival.

We found that patients with a more complex IBD phenotype are at increased risk to develop RCC. A more frequent and intensive use of the health care system, including abdominal imaging, may be associated with this phenomenon. Indeed, another study found that IBD patients exposed to anti-TNFα agents (generally prescribed for patients with a more complex IBD phenotype) developed RCC at a younger age and received earlier RCC surgery compared to IBD patients unexposed to anti-TNFα therapy or patients having rheumatoid arthritis.[25] Other risk factors for RCC development were male gender and older age at IBD onset (not age by itself), but not the use of medical therapy. One could hypothesize that with

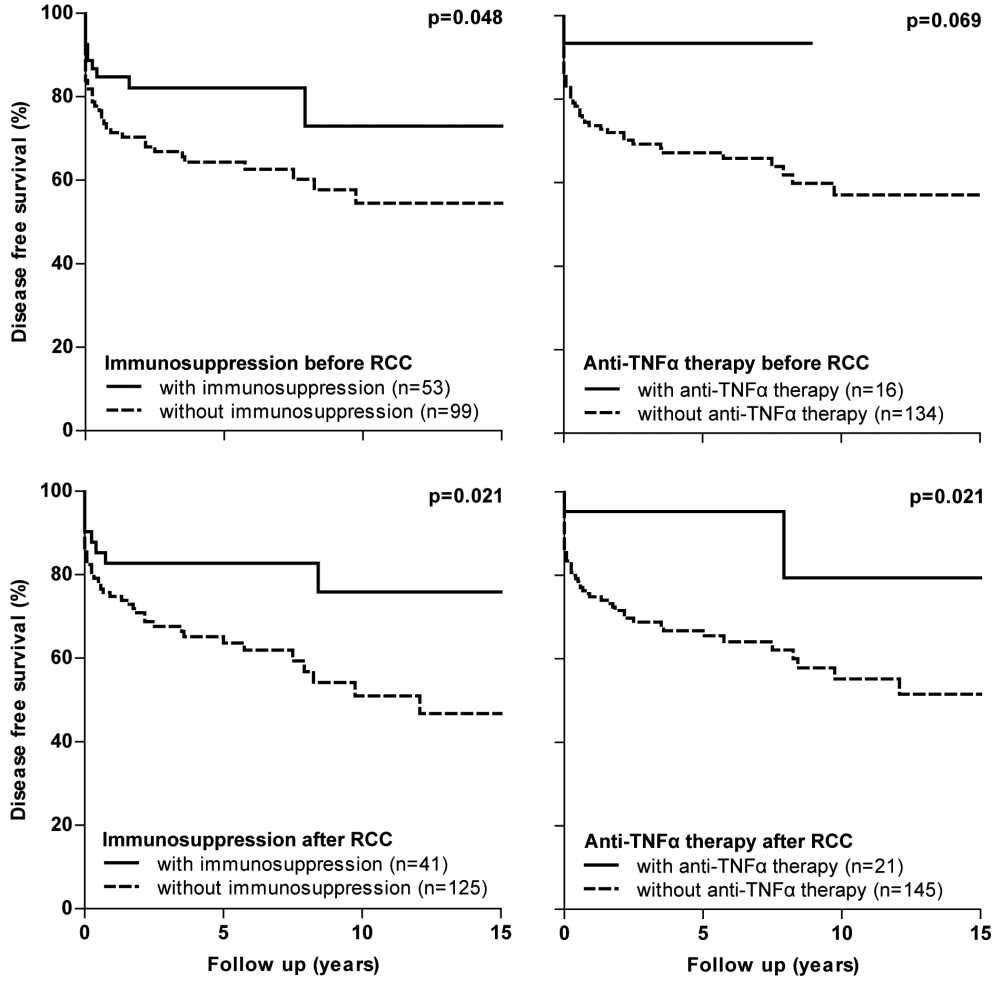

Figure 3. Disease free survival curves in IBD subgroups with RCC based on IBD medication received.

increasing age, potential cancer risk factors accumulate until IBD onset with subsequently accelerated carcinogenesis. As such, patients who develop IBD later in life are at increased risk to develop early colorectal cancer (< 8 y) and more widespread colorectal neoplasia.[26, 27] The role of immunosuppression and/or anti-TNFα agents in relation to cancer development remains to be clarified as the literature reports contradictory results.[3, 5, 28]

Results of our study demonstrated no adverse effect of immunosuppression and/or anti-TNFα therapy on both disease free and overall survival following RCC. These therapies were mainly (re)started or continued after RCC diagnosis in patients with low stage RCC and as a corollary these patients showed a better disease free and overall survival (Figure 3). For example, 32 out of 41 patients (82.1%) who used immunosuppressive therapy and 17 out of 21 patients (81.0%) with anti-TNFα therapy after RCC diagnosis had a T1 RCC. Adjustment for TNM stage abolished the protective effect of immunosuppressive and anti-TNFα therapy

and no differences on survival were subsequently found. These findings are in line with the only available, prospective study in IBD patients, which showed no negative impact of immunosuppressive agents on recurrent cancer of any type.[5] Other data originates from observational studies including patients with rheumatoid arthritis or solid organ transplants. No difference in any new or recurrent malignancy incidence was observed in rheumatoid arthritis patients exposed or unexposed to anti-TNFα agents.[7, 29] A study in post-transplant setting demonstrated a recurrence rate of 0% for incidentally diagnosed RCC and of 30% for symptomatic RCC, although a formal comparison to a control group was lacking.[30]

Despite concerns regarding a cancer inducing effect of anti-TNFα therapy, TNFα blockers have been previously considered as a therapeutic strategy for RCC.[31, 32] Previous studies showed that TNFα can act as an autocrine tumor growth factor and that its presence is associated with poor prognosis. Indeed, phase I/II trials in RCC demonstrated an anti-tumor effect of anti-TNFα treatment.[32] However, the most recent phase II trial in 2010 showed no beneficial effect of anti-TNFα therapy in metastatic RCC.[31] Similarly, results of our study did not show a better survival of metastatic RCC in patients treated with anti-TNFα agents (data not shown).

Our study has important clinical implications for the evidence-based management of IBD therapy in patients with a history of RCC. As no adverse effect of IBD therapy on disease free and overall survival was observed, our data suggest that these agents could be considered following RCC. Cancer specific data are lacking to date, although case-by-case management is encouraged based on the characteristics and expected evolution of the cancer, the probable impact of IBD therapy on cancer evolution, and IBD severity.[4, 7] The impact of dose, duration and time interval following RCC remains to be assessed in larger prospectively followed cohorts. In addition, more cancer specific data are needed for other types of cancer to develop individualized evidence-based management strategies in IBD patients with cancer.

The present study has several limitations. First, the retrospective nature of data collection could have influenced the completeness and accuracy of the extracted data. For example, medication use was difficult to ascertain from older medical records. To address this issue, we performed sensitivity analyses including patients with similar calendar years of IBD diagnosis or RCC diagnosis in the case and control group, disseminating missing values and errors across groups. Second, the use of multiple databases and registries resulted in different ways of data collection and the absence of some variables. For example, potential risk factors and confounders, such as smoking behavior, hypertension, body mass index and incidental detection of RCC, were not available in IBDSL or the ECR. Given this limitation some of our results need to be interpreted with caution. However, it was inevitable to use multiple databases to address our research questions. Finally, selection bias may have been introduced as we used different registries and databases. For example, cases were identified nationwide whereas controls with RCC and controls with IBD were ascertained from two different registries in the south of The Netherlands. However, previous studies confirmed that these population-based registries are representative of the Total Dutch population.[33]

In conclusion, we identified a complex IBD phenotype as a risk factor to develop RCC. IBD patients were diagnosed with RCC at a younger age and at an earlier disease stage compared to the general population, which translated into a better disease free and overall survival following RCC. Immunosuppressive and anti-TNFα therapy did not adversely affect this better survival. This observation may aid physicians in guiding IBD therapy following RCC diagnosis and treatment.

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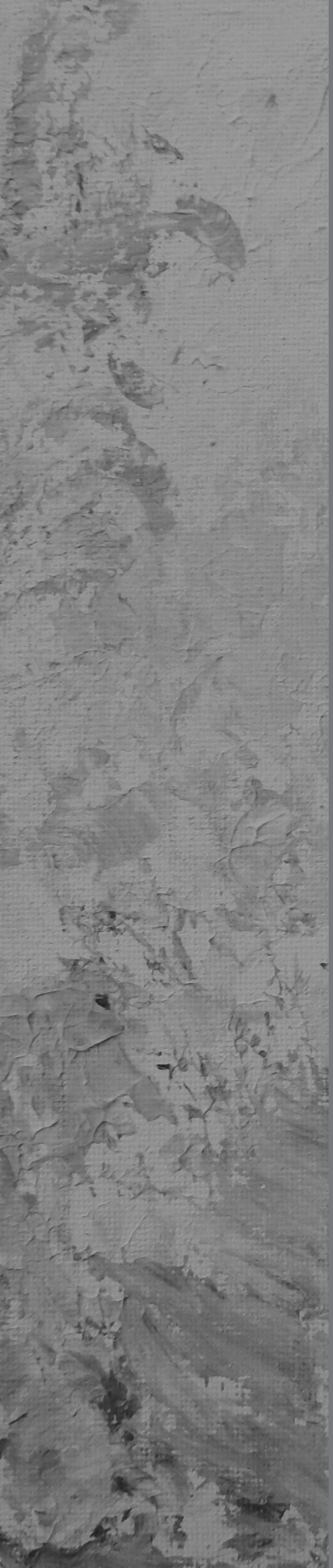

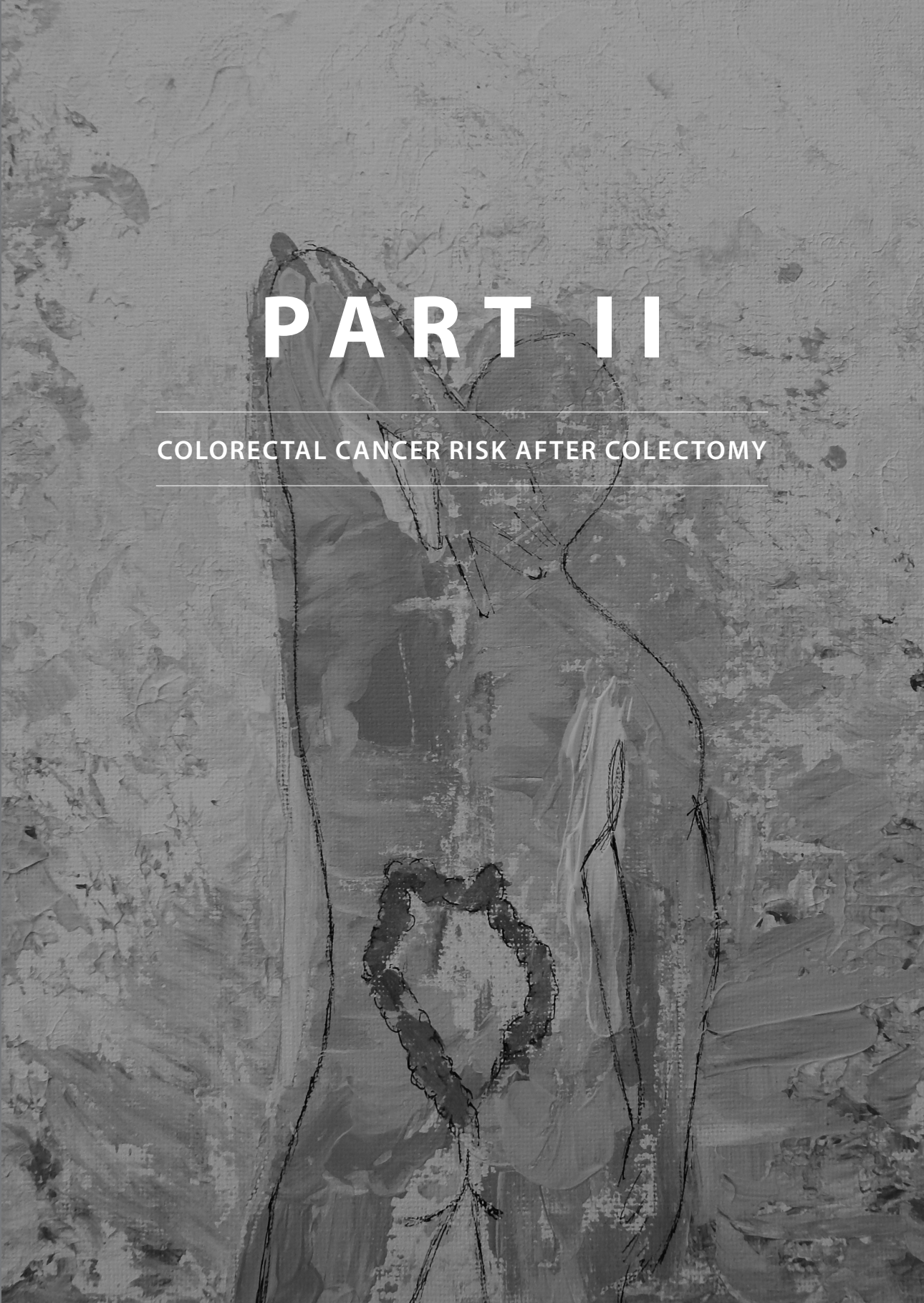

PART II

COLORECTAL CANCER RISK AFTER COLECTOMY

CHAPTER 5

PRIOR COLORECTAL NEOPLASIA IS ASSOCIATED WITH INCREASED RISK OF ILEOANAL POUCH NEOPLASIA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Although restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) substantially reduces the risk of colorectal cancer in patients with inflammatory bowel disease (IBD), subsequent pouch neoplasia can develop. There are few data on the incidence of and risk factors for neoplasia, so there is no consensus on the need for pouch surveillance. We aimed to determine the cumulative incidence of pouch neoplasia in patients with IBD and identify risk factors for developing pouch neoplasia.

We searched the Dutch Pathology Registry (PALGA) to identify all patients with IBD and IPAA in The Netherlands from January 1991 to May 2012. We calculated the cumulative incidence of pouch neoplasia and performed a case-control study to identify risk factors. Demographic and clinical variables were analyzed with univariable and multivariable Cox regression analyses.

We identified 1200 patients with IBD and IPAA; 25 (1.83%) developed pouch neoplasia, including 16 adenocarcinomas. Respective cumulative incidences at 5, 10, 15, and 20 years were 1.0%, 2.0%, 3.7%, and 6.9% for pouch neoplasia and 0.6%, 1.4%, 2.1%, and 3.3% for pouch carcinoma. A history of colorectal neoplasia was the only risk factor associated with pouch neoplasia. Hazard ratios were 3.76 (95% confidence interval, 1.39–10.19) for prior dysplasia and 24.69 (95% confidence interval, 9.61–63.42) for prior carcinoma.

The incidence of pouch neoplasia in patients with IBD without a history of colorectal neoplasia is relatively low. Prior dysplasia or colon cancer is associated with an approximate 4- and 25-fold increase in risk, respectively, of developing pouch neoplasia.

INTRODUCTION

Despite medical progress, approximately 30% of ulcerative colitis (UC) patients eventually require a colectomy because of refractory disease, intolerance to medication, or complications of the disease.[1] In those cases, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred surgical treatment to restore intestinal continuity and fecal continence. Dysplasia or cancer of the colon is one of the UC-related complications that may necessitate a colectomy. It is well established that the risk of colorectal cancer (CRC) is increased in patients with inflammatory bowel disease (IBD).[2] The risk of CRC is especially increased in cases of multi-focal low-grade dysplasia (LGD) or high-grade dysplasia (HGD), and these are generally well-accepted indications for proctocolectomy. Restorative proctocolectomy with IPAA substantially reduces the risk to develop CRC; however, malignant degeneration of the pouch may still arise.

The incidence and prevalence of pouch neoplasia in patients with IBD are probably low. According to the latest review, only 42 pouch adenocarcinomas have been described in the literature.[1] A previous study reported a cumulative incidence of pouch neoplasia of 1.9% after 15 years and 5.1% after 25 years.[3] However, these data were collected in a single tertiary pouch referral center and may not be representative of the general IBD population with IPAA. Furthermore, the relatively low incidence makes it difficult to assess risk factors for development of pouch neoplasia.

Given the paucity of data regarding the risk of pouch neoplasia, there is no consensus on the necessity and potential interval of pouch surveillance. The aim of our study was to establish the cumulative incidence of pouch neoplasia in a nationwide cohort of patients with IBD and IPAA. Furthermore, we aimed to identify risk factors for pouch neoplasia to contribute to a recommendation for a more targeted pouch surveillance program in patients with IBD.

Patients and methods

Design

We studied the cumulative incidence of pouch neoplasia using a nationwide established Dutch cohort of patients with IBD. Risk factors for developing pouch neoplasia were identified by adopting a case-control study approach.

Patient identification

PALGA, the nationwide network and registry of histopathology and cytopathology, was searched, with approval of their Privacy Commission and Scientific Council, to identify all patients with IBD and IPAA in The Netherlands. PALGA contains pathology reports generated in The Netherlands since 1971 and has complete national coverage since 1991 encompassing all pathology laboratories from all academic and nonacademic hospitals in The Netherlands.[4] A search of PALGA was performed with the following search terms: "*ulcerative colitis*", "*Crohn's disease*", "*indeterminate colitis*", and "*chronic idiopathic inflammatory bowel disease*" combined with "*pouch*" or a (Dutch) synonym. The search was performed from January 1991 to May

2012. Cases were further confirmed or excluded after careful evaluation of the individual pathology reports.

Verification cohort

To verify the coverage of our PALGA search, we compiled a verification cohort. This cohort consisted of patients with IBD and IPAA from the Radboud University Nijmegen Medical Centre who had at least one outpatient medical contact at the Department of Gastroenterology and Hepatology between 2004 and May 2012. Next, we verified whether pathology reports from examination of gastrointestinal tissue were available in the medical records. Using these pathology reports, we verified whether patients were likewise identified through the PALGA search.

Inclusion and exclusion criteria

Patients with IPAA were identified with PALGA, and those with a diagnosis of ulcerative colitis, indeterminate colitis, or Crohn's disease based on the colonic resection specimen were included. The following exclusion criteria were used: familial adenomatous polyposis, absence of a diagnosis of IBD or IPAA, Kock pouch, ileorectal anastomosis, ileoneorectal anastomosis, or missing follow-up. Furthermore, patients were excluded if the colectomy specimen was not available or if no distinction could be made for the type of pouch or anastomosis despite careful evaluation of the pathology reports. Of note, none of the exclusion groups contained patients with IPAA and pouch neoplasia.

Patients who developed pouch neoplasia, including pouch dysplasia and pouch adenocarcinoma, were identified as cases. Pouch malignancies other than adenocarcinomas were excluded from the case group. Controls for the case-control study were randomly selected (using a 1:3 ratio) from the entire population with IBD and IPAA (identified with PALGA) at the 6 centers that provided the majority (69%) of cases. Because the control group in a case-control study should reflect the entire source population that gave rise to the cases, we did not exclude patients with pouch neoplasia from the control group.[5]

Histopathologic assessment

Pouch neoplasia was defined as dysplasia or carcinoma in the pouch or anal transitional zone (ATZ; the area between the dentate line and anastomosis, with or without mucosectomy), classified according to Riddell as IND, LGD, HGD, or adenocarcinoma.[6] For the patients with a diagnosis of pouch dysplasia, the pouch biopsy specimens with dysplasia were reevaluated by an expert gastrointestinal pathologist (I.D.N.) blinded to clinical, endoscopic, and radiographic features. The gradation of dysplasia was reassessed, and eventually revised results were used for analysis. The category IND after reevaluation was excluded from the case group in the analysis.

Statistics

Cumulative incidences were counted with 1 minus Kaplan–Meier curves. Time to event was calculated from the date of pouch construction to the development of pouch neoplasia

(cases) or the end of follow-up for patients who did not develop a neoplasia (controls). End of follow-up was defined as the last gastroenterology-related medical contact, pouch excision, or patient's death. The median time to develop pouch carcinoma and the median survival time, including a minimum to maximum range, were derived from

Kaplan–Meier curves. For the variables collected from the total cohort, log-rank analyses were performed to compare the incidence of pouch neoplasia in those subgroups.

$\chi 2$ test or Fisher exact test (if expected cell counts were < 5) for categorical data and independent Student t test for continuous data were used to compare cases and controls on all selected possible risk factors. Variables with a *P* value of < 0.1 in univariate analyses were included in a multivariate Cox proportional hazard model with backward sampling to determine which risk factors are independently associated with developing a pouch carcinoma. A *P* value of < 0.05 (2 sided) was considered to be statistically significant. Cases in the control group were analyzed as cases in the Cox model, resulting in hazard ratios that can be interpreted as relative risks. All missing values were considered to be completely at random and were excluded from analyses. All statistical analyses were performed with IBM SPSS statistics version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients

We identified 1200 patients with IBD and IPAA with a median follow-up time of 6.5 years using PALGA. Fortyfive of the 1200 patients (3.75%) had an initial histological diagnosis of pouch neoplasia (Figure 1). This group consisted of 12 patients with IND, 17 patients with LGD, and 16 patients with adenocarcinoma. In the latter group, 4 carcinomas were considered to be recurrence of CRC and 2 carcinomas arose after pouch excision. One of the patients with a recurrence previously underwent an incomplete CRC resection and a pouch carcinoma was detected 1 month after pouch construction. In the other 3 cases, recurrences occurred within 1 to 2 years after treatment of CRC. The 2 patients with adenocarcinoma after pouch excision for chronic pouchitis or perianal symptoms developed carcinomas 5 and 6 years after pouch excision. Identified pouch malignancies other than adenocarcinoma included one B-cell non-Hodgkin lymphoma, and this case was excluded from the analysis. The control group was established by random selection of 100 patients from the nationwide cohort. The medical record of one patient could not be retrieved, which resulted in a final control group of 99 patients. This control group included 4 cases with a diagnosis of pouch neoplasia.

Verification cohort

Our verification cohort consisted of 93 patients with IBD and IPAA who visited the outpatient clinic at the Radboud University Nijmegen Medical Centre between 2004 and May 2012. Eighty-eight of the 93 patients (95%) were identified on the initial search of PALGA, and the remaining 5 patients (5%) escaped identification by our search. These 5 patients never underwent a pouch biopsy or the PALGA search terms were not mentioned in the pathology reports.

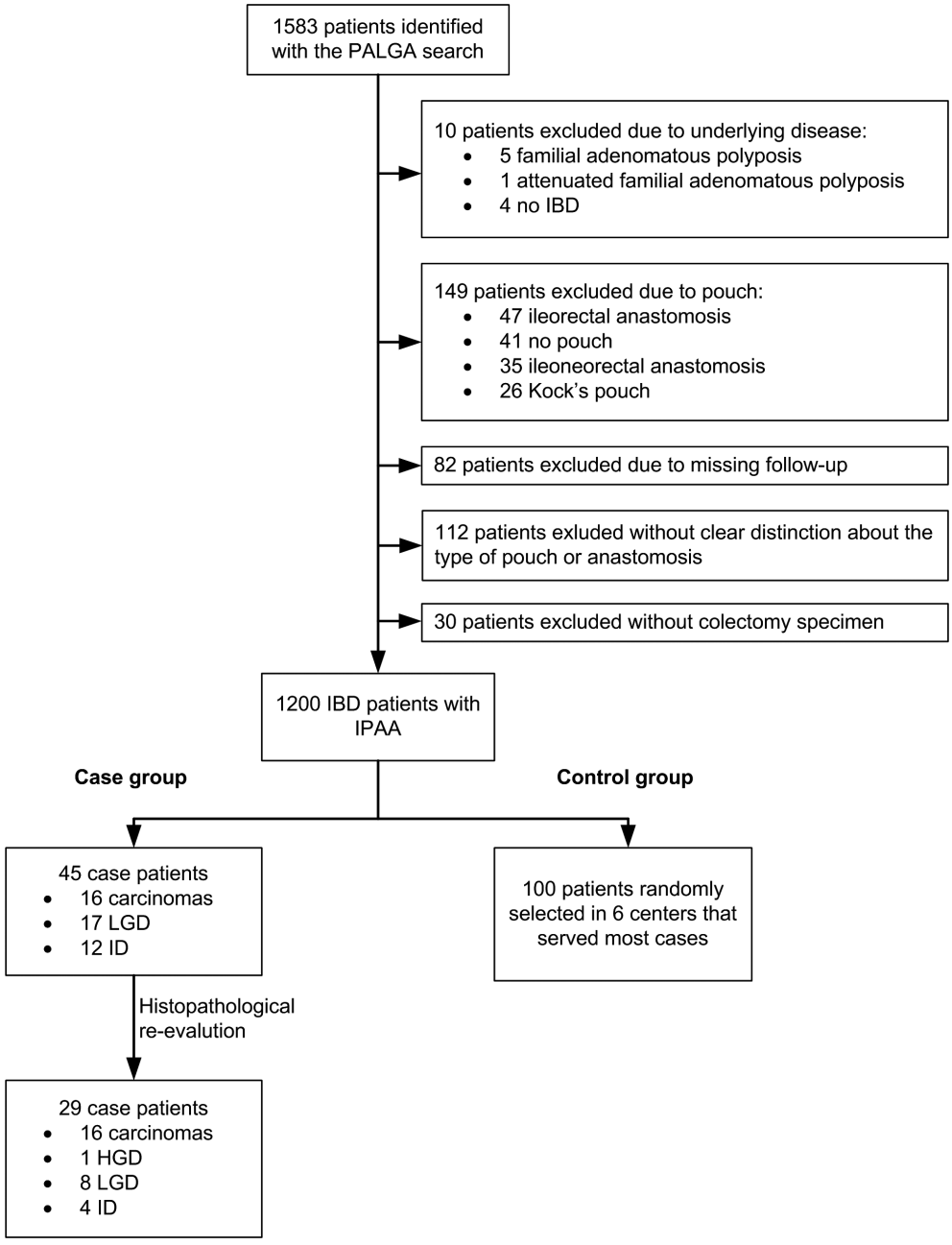

Figure 1. Flowchart showing patient inclusion.

Histopathologic reassessment

All pouch biopsy specimens with dysplasia except one were available for reassessment. Re-review of the specimens shifted the grades of dysplasia in 22 of 29 cases. Reassessment

resulted in downgrading of dysplasia in 18 patients and upgrading in 4 patients. This resulted in the identification of 4 cases with IND, 8 cases with LGD, 1 case with HGD, and 16 cases with adenocarcinoma (Figure 1).

Cumulative incidences

Figure 2 depicts the cumulative incidences of pouch neoplasia (both dysplasia and carcinoma), pouch dysplasia (LGD and HGD), and pouch carcinoma. The cumulative incidences of pouch neoplasia were 1.0%, 2.0%, 3.7%, and 6.9% at 5, 10, 15, and 20 years, respectively. The respective cumulative incidences at 5, 10, 15, and 20 years for pouch dysplasia were 0.3%, 0.5%, 1.6%, and 3.7% and for pouch carcinoma were 0.6%, 1.4%, 2.1%, and 3.3%.

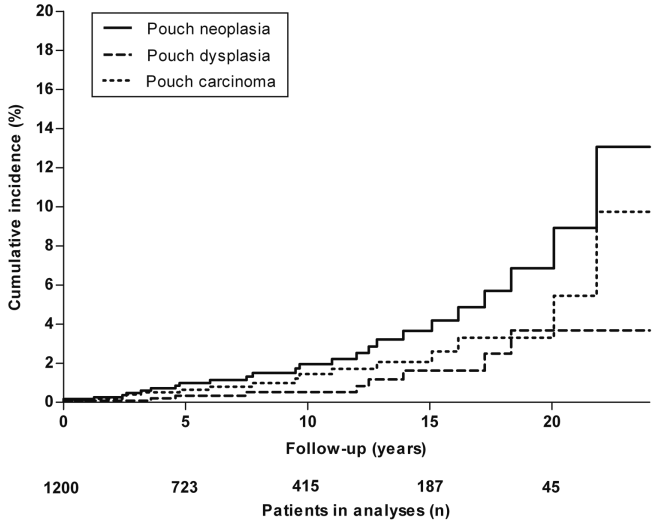

Figure 2. Cumulative incidences of pouch neoplasia (both carcinoma and dysplasia), pouch carcinoma, and pouch dysplasia.

Risk factors for pouch neoplasia

Table 1 lists the basic variables extracted from PALGA, including age at colectomy, sex, type of IBD, and prior colorectal neoplasia. A history of colorectal neoplasia significantly differed between cases and controls. For this variable, we performed log-rank analyses. Patients with prior colorectal dysplasia or carcinoma had higher cumulative incidences of pouch neoplasia compared with patients without a history of colorectal neoplasia ($P < 0.001$, log-rank test, Figure 3). After 15 years, the combined cumulative incidence of pouch dysplasia and carcinoma was 29.5% in the subgroup with prior CRC and 2.2% in the subgroup without prior neoplasia (Figure 3).

Clinical and demographic characteristics that were derived from the medical records are described in Table 2. Age at pouch construction, duration of IBD, primary sclerosing

Table 1. Comparison of the extracted variables from PALGA between patients with pouch neoplasia (both carcinoma and dysplasia) and patients without pouch neoplasia.

Variable	Pouch neoplasia (n = 25)	Without pouch neoplasia (n = 1175)	Univariate analyses (*P* value)	Missing value (n)
Age at colectomy (y), mean + SD	39.7 ± 9.9	35.9 ± 12.4	0.123	0
Female sex	8 (32.0)	559 (47.6)	0.157	0
IBD type				
Ulcerative Colitis	20 (80.0)	1033 (87.9)		
Crohn's disease	2 (8.0)	44 (3.7)		
Indeterminate colitis	3 (12.0)	98 (8.3)	0.190	0
Prior colorectal neoplasia				
Without	10 (40.0)	1026 (87.4)		
Dysplasia	6 (24.0)	107 (9.1)		
Adenocarcinoma	9 (36.0)	41 (3.5)	< 0.001	1

All values are expressed as n (%) unless otherwise noted.

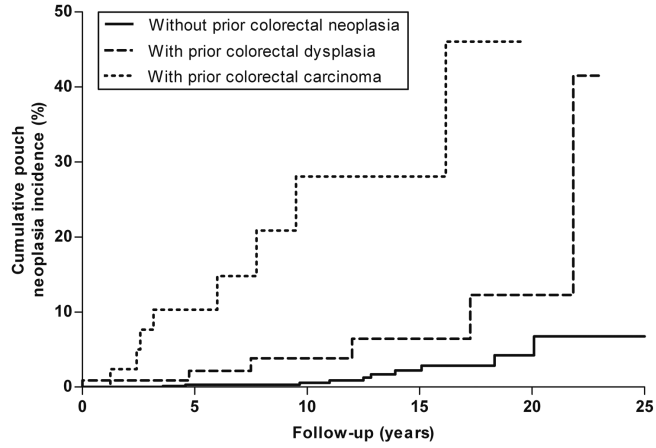

Figure 3. Cumulative incidences of pouch neoplasia of subgroups categorized by the presence or absence of prior colorectal dysplasia or cancer, which differ significantly with log-rank analyses (p < 0.001).

cholangitis, and again a history of colorectal neoplasia were significantly different between patients with and without pouch neoplasia (p = 0.019, p = 0.001, p = 0.030, and p < 0.001, respectively). Table 3 shows the results of the multivariate Cox model with all hazard ratios before elimination of nonsignificant variables as well as the final model after backward elimination. Both prior colorectal dysplasia and carcinoma emerged as risk factors with respective hazard ratios of 3.76 (95% confidence interval, 1.39–10.19; p = 0.009) and 24.69 (95% confidence interval, 9.61–63.42; p < 0.001). Most cases of prior colorectal neoplasia were located in the rectosigmoid colon (Table 4).

Inclusion of patients with a recurrence of CRC and thus a prior CRC may give a distorted picture of the identified risk factor "prior colorectal neoplasia." Patients who developed

Table 2. Comparison between patients with pouch neoplasia (both carcinoma and dysplasia) and the control group for possible risk factors and confounders extracted from the medical records.

Variable	Pouch neoplasia (n = 25)	Control group (n = 99)	Univariate analyses (*P* value)	Missing value (n)
Female sex	8 (32.0)	41 (41.4)	0.494	0
Age at IBD diagnosis (y), mean ± SD	25.7 ± 11.6	25.7 ± 12.5	0.984	10
Age at pouch construction (y), mean ± SD	39.8 ± 9.9	33.0 ± 13.3	0.019	0
IBD type				
Ulcerative Colitis	20 (80.0)	89 (89.9)		
Crohn's Disease	2 (8.0)	3 (3.0)		
Indeterminate colitis	3 (12.0)	7 (7.1)	0.296	0
Extended colitis (Montreal E3)	22 (91.7)	78 (89.7)	1.000	13
IBD duration from diagnosis to pouch construction (y), mean ± SD	13.3 ± 8.2	6.9 ± 6.1	0.001	10
Prior colorectal neoplasia (LGD, HGD, carcinoma)	15 (62.5)	12 (12.4)	< 0.001	3
J-pouch configuration	18 (85.7)	79 (85.9)	1.000	11
Anastomosis type				
Handsewn with mucosectomy	4 (19.0)	17 (18.7)		
Stapled without mucosectomy	17 (81.0)	74 (81.3)	1.000	12
Pouchitis (chronic or relapsing)	6 (24.0)	26 (26.3)	1.000	0
Cuffitis	4 (16.0)	10 (10.1)	0.479	0
Crohn's disease of the pouch	2 (8.0)	2 (2.0)	0.181	0
Primary sclerosing cholangitis	4 (16.0)	3 (3.0)	0.030	0
Ever smoked	8 (38.1)	17 (23.6)	0.262	31
Family history of colorectal carcinoma	0 (100)	0 (100)	Not computable	54
Pouch duration (y)[a], mean ± SD	8.6 ± 6.1	8.4 ± 7.0	0.883	0
Surveillance frequency (average/year)	0.43 ± 0.42	0.52 ± 0.57	0.470	15
Surveillance intervals				
No surveillance pouchoscopy	3 (12.0)	14 (14.1)		
≥ 1 pouchoscopy every 3 y	8 (32.0)	26 (26.3)		
≥ 1 pouchoscopy every 5 y	3 (12.0)	12 (12.1)		
≥ 1 pouchoscopy every 10 y	3 (12.0)	29 (29.3)		
< 1 pouchoscopy every 10 y	8 (32.0)	18 (18.2)	0.332	0

All values are expressed as n (%) unless otherwise noted.
[a] Pouch duration of cases and controls was calculated from the date of proctectomy to the development of pouch neoplasia (cases) or end of follow-up (controls). End of follow-up for controls was defined as the last gastroenterology-related medical contact, pouch excision, or patient's death.

adenocarcinoma after pouch excision may contribute to this effect. To verify the identified risk factors, we performed a sensitivity analysis excluding these patients. A new Cox model confirmed our earlier findings and showed prior colorectal dysplasia and carcinoma as the only risk factors, with respective hazard ratios of 4.17 (95% confidence interval, 1.50–11.62; p = 0.006) and 20.28 (95% confidence interval, 6.71–61.30; p < 0.001).

Table 3. Cox proportional hazard model to identify risk factors for developing pouch neoplasia.

	Cox model before backward elimination of non-significant variables			Final Cox model after backward elimination of non-significant variables		
	Coefficient β	**HR (95% CI)**	***P* value**	**Coefficient β**	**HR (95% CI)**	***P* value**
Prior colorectal neoplasia[a]						
Dysplasia (LGD and HGD)	0.63	1.87 (0.52-6.76)	0.341	1.33	3.76 (1.39-10.19)	0.009
Carcinoma	2.69	14.74 (4.96-43.78)	< 0.001	3.21	24.69 (9.61-63.42)	< 0.001
IBD duration	0.03	1.03 (0.97-1.10)	0.279			
Primary sclerosing cholangitis	0.93	2.54 (0.53-12.17)	0.244			
Age at pouch construction	0.03	1.03 (0.99-1.06)	0.137			

n = 112 patients (12 excluded from analyses due to missing variables).
[a] Reference category is patients without prior colorectal neoplasia.

Table 4. Overview of all patients with pouch carcinoma.

Case no.	Type of IBD	Age at IBD diagnosis (y)	IBD duration (y)	Age at IPAA (y)	Indication procto-colectomy	Type of anastomosis	Pouch duration until carcinoma (y)	Tumor location	Tumor stage at diagnosis		Endoscopic features	Treatment	Follow-up
Pouch carcinomas													
1	UC	17	15	33	2xLGD (location NA)	Stapled without mucosectomy	4	ATZ	T4N2M1	IV	Ulcerative inflammation	Chemoradiation Surgical resection	No recurrence at 11 months
2	UC	17	17	35	CRC (T3N1, rectosigmoid colon)	Stapled without mucosectomy	3	ATZ	T4N1M1	IV	No endoscopic abnormalities	Incidental finding in the pouch excisionspecimen. Chemoradiation	Metastases Died at 7 months
3	CD	5	28	34	CRC (T4N1, sigmoid colon)	Stapled without mucosectomy	9	ATZ	T2N0MX	I	No endoscopic abnormalities	Radiotherapy Surgical resection	Local recurrence at 38 months Treated with chemoradiation and surgical excision No recurrence at 10,5 years after pouch carcinoma
4	CD	28	25	53	Medically refractory	Stapled without mucosectomy	11	Pouch	T4N2M0	III	Cobbled lesion	Radiotherapy	Metastases Died at 11 months
5	UC	31	4	36	Medically refractory	Stapled without mucosectomy	12	ATZ	T3N0MX	II	Ulcerative inflammation with stenosis and fibrosis	Chemoradiation Surgical resection	Metastases Died at 13 months

Table 4. (continued)

Case no.	Type of IBD	Age at IBD diagnosis (y)	IBD duration (y)	Age at IPAA (y)	Indication procto-colectomy	Type of anastomosis	Pouch duration until carcinoma (y)	Tumor location	Tumor stage at diagnosis		Endoscopic features	Treatment	Follow-up
6	UC	24	6	31	Medically refractory	Stapled without mucosectomy	15	ATZ	T4N0M0	II	Masslike lesion (diameter 4 cm)	Chemoradiation Surgical resection	No recurrence at 25 months
7	UC	21	8	30	Medically refractory, incidental CRC(T2N0, rectosigmoid colon)	Stapled without mucosectomy	7	NA	NA	Masslike lesion	Surgical resection (irradical)	Died at 3 months	
8	UC	38	10	48	CRC (T1N0, rectum)	Stapled without mucosectomy	15	ATZ	T2N0M0	I	Masslike lesion (diameter 3 cm)	Chemoradiation Surgical resection	No recurrence at 12 months
9	UC	4	22	26	2xHGD (rectum)	Handsewn with mucosectomy	11	ATZ	T4N0M1	IV	No endoscopic abnormalities	Radiotherapy	Died at 20 months
10	UC	16	4	20	Medically refractory	NA	22	Pouch	T4N2M1	IV	Circular growing mass	Chemoradiation	Died at 12 months
Recurrences colorectal carcinoma													
11	UC	29	27	56	CRC (T2N0, rectum)	Stapled without mucosectomy	2	ATZ	T4N2M0	III	Polypoid lesion	Surgical resection	Died at 4 months
12	UC	33	14	47	CRC (T1N0, rectum)	Handsewn with mucosectomy	1	ATZ	T3N1MX	III	NA	Chemoradiation	Metastases Lost to follow-up

Table 4. (continued)

Case no.	Type of IBD	Age at IBD diagnosis (y)	IBD duration (y)	Age at IPAA (y)	Indication procto-colectomy	Type of anastomosis	Pouch duration until carcinoma (y)	Tumor location	Tumor stage at diagnosis		Endoscopic features	Treatment	Follow-up
13	UC	28	18	46	CRC (T3N1, rectum)	NA	2	Between pouch en vagina back wall	NA	No endoscopy performed	Chemoradiation surgical resection	Local recurrence at 8 months Treated with chemoradiation Died at 13 months	
14	UC	10	20	31	CRC (T3N2, ascending colon)	NA	0	NA	Extended disease	No endoscopy performed	Tumor debulking Chemotherapy	Died at 10 months	
Adenocarcinomas after pouch excision													
15	IC	44	5	49	Medically refractory	Stapled without mucosectomy	9 (pouch excision after 3.5 years, pouch carcinoma 5.5 years later)	Prior pouch location, originating from pouch remnant	NA	Masslike lesion and abscess	Radiotherapy Surgical resection	Metastases Lost to follow-up	
16	IC	21	20	42	CRC (T2N0, rectum)	Handsewn with mucosectomy	6 (pouch excision after 0.5 years, pouch carcinoma 5.5 years later	Remnant anal canal	TisN0M0	0	Inflammation	Incidental finding in the anorectal remnant excision specimen No further treatment	Lost to follow-up

NA, not available.

Characteristics and outcomes of pouch neoplasia

The identified cases of pouch carcinoma and dysplasia were further analyzed, and an overview is presented in Table 4 and Supplementary Table 1. The median time to develop a pouch carcinoma after diagnosis of IBD was 20 years (range, 14–38 years) and 7.0 years (range, 0–22 years) after pouch construction. LGD developed at a median time of 19 years (range, 9–34 years) after diagnosis of IBD and 7.0 years (range, 0–18 years) after pouch construction. Ten of 16 pouch carcinomas were located at the ATZ, and 3 of 8 cases of pouch dysplasia arose at the ATZ.

The endoscopic characteristics at the time of detection of pouch neoplasia were not consistent. Dysplasia and cancer were seen in patients with ulcerated lesions, polypoid lesions, and mass-like lesions, but patients without endoscopic abnormalities also had neoplasia (Table 4 and Supplementary Table 1). For instance, 4 of 16 patients with pouch carcinoma did not have any visible lesions on endoscopy.

Pouch dysplasia rarely progressed during follow-up, and as a result only 3 carcinomas (19%; stage I, n = 2; stage II, n = 1) were preceded by HGD, LGD, and/or IND. In patients with IND or LGD, only 2 of 14 patients progressed to carcinoma during follow-up, whereas 9 of 14 patients with dysplasia had regression on subsequent biopsy specimens. One patient with HGD also showed regression, and no dysplasia was found on subsequent biopsy specimens. In our cohort, 3 patients with pouch dysplasia were not followed up by pouchoscopy. In one patient in the latter group, LGD was detected in the excised pouch specimen.

Most pouch carcinomas were detected at an advanced stage of disease, resulting in a high mortality rate (Table 4). Nine of 16 patients died with a median survival of 11 months (range, 1–20 months) after diagnosis of pouch carcinoma. Three additional patients were lost to follow-up. Two of these patients had metastatic disease at last followup. Pouch carcinomas did not recur in 4 patients during a median follow-up of 12 months (range, 11–124 months) after diagnosis of pouch carcinoma.

DISCUSSION

The key finding of our study is the relatively low incidence of pouch carcinoma, especially in patients without a history of colorectal neoplasia. Only 16 of 1200 patients with IPAA (1.3%) were identified with pouch carcinoma in our nationwide IBD cohort. Of note, most of these carcinomas developed at the ATZ (63%). The cumulative incidence of developing pouch carcinoma reached 3.3% after 20 years. Furthermore, a history of colorectal dysplasia and carcinoma raised the risk of pouch neoplasia by 4- and 25-fold, respectively. After 15 years, the cumulative incidence of pouch neoplasia was 29.5% in the subgroup with a prior CRC and 2.2% in the subgroup without a prior neoplasia.

The relatively low incidence of pouch carcinoma (cumulative incidence of 3.3% after 20 years) in IBD is in line with the findings of another large cohort study. This study evaluated

3202 patients with IBD and IPAA and reported a cumulative incidence of pouch carcinoma of 2.4% after 20 years.[3] Similarly, this cohort study detected 23 patients (0.72%) with pouch dysplasia, while a meta-analysis showed a pooled prevalence of pouch dysplasia of 1.13% in 2040 patients.[3, 9] This is in line with data presented in the current study (pouch dysplasia in 9 of 1200 patients [0.75%]).

Prior colorectal neoplasia is a risk factor for development of pouch neoplasia.[3, 10–12] The majority of cases identified in our cohort (69%) as well as by the most recent review[1] (57%) had a history of colorectal neoplasia. Most pouch carcinomas (63% in our cohort) developed at the ATZ. Although it seems reasonable to remove colonic tissue by mucosectomy, this strategy does not protect against pouch neoplasia.[3, 13, 14] A possible explanation is the presence of residual colonic mucosa islets that may remain even after "complete" mucosectomy.[15] It could be hypothesized that this residual colonic mucosa bears an increased risk of malignant degeneration, especially in patients with prior colorectal neoplasia. The short interval between pouch construction and development of carcinoma in some patients and the ATZ location of most pouch carcinomas raises the issue whether some pouch carcinomas represent recurrence of CRC rather than a primary pouch carcinoma. Other previously purported risk factors for developing pouch neoplasia include pouchitis,[3, 15–17] long duration of IBD,[3, 10–12] and primary sclerosing cholangitis.[3, 18, 19] None of these factors were identified as a risk factor in our study.

A thorough understanding of the natural history of pouch neoplasia is fundamental to the development of an effective strategy for pouch surveillance. In colonic IBD, the surveillance strategy is based on the concept of an inflammation-dysplasia-carcinoma sequence.[20] Whether this sequence also applies to pouch neoplasia is unknown. The fact that pouchitis was not identified as a risk factor as well as the high regression rates and low progression rates of pouch dysplasia both in the literature and in our study suggest that this hypothesis does not hold for pouch carcinogenesis.[1, 21] On the other hand, one study identified concurrent LGD or HGD in 10 of 11 (90.9%) pouch carcinomas in the pouch excision specimens.[3] In addition, many clinicopathological and molecular features in pouch carcinoma are shared with IBD-associated CRC, which is in favor of the inflammation-dysplasia-carcinoma sequence.[22]

The underlying purpose of our study was to contribute to a recommendation for a more targeted pouch surveillance program in patients with IBD. Importantly, our nationwide study provides the opportunity to generate data that reflect the IPAA population at large, in contrast to prior studies that stem from tertiary referral centers. Data from the present study suggest that pouch surveillance with close inspection of the ATZ should be considered in patients with IPAA who have a history of colorectal neoplasia. However, it is unknown whether surveillance will indeed detect carcinoma at a less advanced stage and result in an improved prognosis. Most pouch carcinomas in our study were not preceded by dysplasia, and resection of dysplastic lesions might not contribute to the prevention of pouch carcinoma. Furthermore, our data suggest a limited role for pouch surveillance in patients without a history of colorectal neoplasia. This is supported by the relatively low incidence of pouch neoplasia in patients without prior colorectal neoplasia (cumulative incidence of 2.2% after 15 years), especially in comparison with the lifetime incidence of approximately 5% for developing CRC in the general population.[23]

The present study has some limitations. First, the retrospective nature of the study and use of data primarily not intended for research resulted in missing variables. Second, the relatively small number of cases might result in a type II error in determining risk factors. In addition, the current study could represent a slight overestimation of the actual cumulative

incidences. The exclusion of patients because of incomplete documentation of the presence of IPAA, as well as pouch patients who never underwent pouch biopsies (and thus escaped identification by our search), could contribute to this effect. However, our verification cohort suggests that only few patients were missed and none of these patients had a diagnosis of pouch neoplasia. It is debatable whether patients with recurrences of CRC and pouch carcinomas after pouch excision should be part of the case group. Because we aimed to formulate a comprehensive surveillance strategy that identifies all pouch carcinomas, we included these carcinomas in our case group. This may influence the identification of risk factors, but sensitivity analyses excluding these patients resulted in identification of similar risk factors. Finally, patients were not subjected to a standardized endoscopic surveillance program. Pouchoscopies were performed by both gastroenterologists and surgeons without standardized biopsy protocol and well-defined intervals. Although the average pouchoscopy rate was once per 5 years and the surveillance intervals were the same between the case and control groups, it is unknown whether a more standardized surveillance program would have picked up more cases of pouch dysplasia in general and before pouch carcinoma. Many cases of dysplasia regressed; this, combined with the absence of a standardized endoscopic surveillance strategy, may have contributed to missed cases of pouch dysplasia. The slightly larger sample size of the pouch carcinoma group compared with the pouch dysplasia group might also reflect missed detection of dysplasia. Patients with a prior CRC could have had a pouchoscopy more frequently; however, this was not seen in the patients included in the case-control study (data not shown).

In conclusion, the incidence of pouch neoplasia in patients with IBD without prior colorectal neoplasia is relatively low. A history of dysplasia and CRC raises the risk of pouch neoplasia significantly. Our data suggest that a limited surveillance program is sufficient for patients with IPAA without a history of colorectal neoplasia. A targeted surveillance program should be considered in patients with a prior colorectal neoplasia. However, prospective studies are required to evaluate the effects of such a surveillance strategy.

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Table S1. Overview of all patients with pouch dysplasia.

Case no.	Type of IBD	Age at IBD diagnosis (y)	IBD duration (y)	Age at IPAA (y)	Indication procto-colectomy	Type of anastomosis	Pouch duration until dysplasia (y)	Dysplasia location	Highest grade of dysplasia	Endoscopic features	Treatment	Follow-up
17	UC	26	11	38	LGD and IND	Handsewn with mucosectomy	0	multiple foci (location NA)	LGD	No endoscopy performed	Incidental finding in pouch excision specimen. No further treatment	Pouch excision
18	IC	NA	NA	48	Medically refractory, incidental ID (rectum)	Stapled without mucosectomy	4	ATZ	LGD	Polypoid lesion	Watchful waiting	Refinding of dysplasia at 3 months Lost to follow-up
19	UC	29	20	49	Carcinoma in situ (sigmoid colon)	Stapled without mucosectomy	12	pouch	LGD	2 erosive lesions	Watchful waiting	Regression of dysplasia at 11, 23 and 35 months
20	UC	18	17	35	Multifocal HGD	Stapled without mucosectomy	17	Pouch and in random biopsies	LGD	No endoscopic abnormalities	Watchful waiting	Refinding of dysplasia at 7 and 24 months Regression of dysplasia at 34 months
21	IC	52	1	53	Iatrogenic bowel perforation	Stapled without mucosectomy	18	ATZ	LGD	Ulcerative inflammation	Watchful waiting	Regression of dysplasia at 3 months
22	UC	34	15	50	Repeatedly LGD	Stapled without mucosectomy	7	Pouch	LGD	Solitary ulcer	Watchful waiting	Regression of dysplasia at 3 months
23	UC	38	5	44	Toxic megacolon	NA	3	ATZ	LGD	NA	Watchful waiting	Refinding of dysplasia at 13 months Lost to follow-up

Table S1. (continued)

Case no.	Type of IBD	Age at IBD diagnosis (y)	IBD duration (y)	Age at IPAA (y)	Indication procto-colectomy	Type of anastomosis	Pouch duration until dysplasia (y)	Dysplasia location	Highest grade of dysplasia	Endoscopic features	Treatment	Follow-up
24	UC	32	3	35	NA	Stapled without mucosectomy	13	NA	LGD	Inflammation	Watchful waiting	Lost to follow-up
25	UC	21	4	25	Medically refractory	Stapled without mucosectomy	12	NA	HGD	Inflammation	Watchful waiting	Regression of dysplasia at 2 months No endoscopically visible lesions (biopsies not taken) at 21, 49 and 52 months.

NA, not available.

CHAPTER 6

NEOPLASIA RISK AFTER COLECTOMY IN INFLAMMATORY BOWEL DISEASE PATIENTS – A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Colorectal neoplasia can still develop after colectomy for inflammatory bowel disease. However, data on this risk are scare, and there have been few conclusive findings, so no evidence-based recommendations have been made for postoperative surveillance. We conducted a systematic review and meta-analysis to determine the prevalence and incidence of and risk factors for neoplasia in patients with inflammatory bowel disease who have undergone colectomy, including the permanent-end ileostomy and rectal stump, ileorectal anastomosis (IRA), and ileal pouch-anal anastomosis (IPAA) procedures.

We searched PubMed, Embase, Web of Science, and Cochrane Library through May 2014 to identify studies that reported prevalence or incidence of colorectal neoplasia after colectomy or specifically assessed risk factors for neoplasia development. Studies were selected, quality was assessed, and data were extracted by 2 independent researchers.

We calculated colorectal cancer (CRC) prevalence values from 13 studies of patients who underwent rectal stump surgery, 35 studies of IRA, and 33 studies of IPAA. Significantly higher proportions of patients in the rectal stump group (2.1%; 95% confidence interval [CI], 1.3%–3.0%) and in the IRA group (2.4%; 95% CI, 1.7%–3.0%) developed CRC than in the IPAA group (0.5%; 95% CI, 0.3%–0.6%); the odds ratio (OR) for CRC in the rectal stump or IRA groups compared with the IPAA group was 6.4 (95% CI, 4.3–9.5). A history of CRC was the most important risk factor for development of CRC after colectomy (OR for patients receiving IRA, 12.8; 95% CI, 3.31–49.2 and OR for patients receiving IPAA, 15.0; 95% CI, 6.6–34.5).

In a meta-analysis of published studies, we found the prevalence and incidence of CRC after colectomy to be less than 3%; in patients receiving IPAA it was less than 1%. Factors that increased risk of cancer development after colectomy included the presence of a residual rectum and a history of CRC. These findings could aid in development of individualized strategies for post-surgery surveillance.

INTRODUCTION

Although the magnitude of the colorectal cancer (CRC) risk in inflammatory bowel disease (IBD) patients is still under debate, it is well-established that both ulcerative colitis (UC) and Crohn's disease (CD) patients with colonic involvement have an increased risk to develop CRC. It is one of the most detrimental complications of IBD, with significant morbidity and an associated mortality rate of approximately 15%.[1] To reduce CRC risk, endoscopic surveillance guidelines have been developed that allow detection and potential removal of precancerous lesions. This strategy might reduce the increased CRC incidence in IBD patients and improve mortality rates.[2] However, IBD surveillance guidelines have been written on the basis of research in patients with an intact colon.[3, 4]

Although therapeutic options have expanded during the last decade, bowel surgery still plays an important role in the management of IBD. Indeed, the cumulative risk of intestinal surgery for UC patients is 25%–30% and even higher for CD patients (70%–80%).[5, 6] For UC or extensive colorectal CD, staged restorative proctocolectomy is the surgical treatment of choice. The series of surgical procedures start with subtotal colectomy and ileostomy with a residual rectum left in situ. This initial approach will keep options for reconstructive surgery open.[1] Ileal pouch-anal anastomosis (IPAA) is the preferred reconstructive procedure after colectomy in UC patients.[1, 5] In patients with extensive colonic CD, ileorectal anastomosis (IRA) is the first restorative option to consider.[6] For several reasons including comorbidities and concerns about fertility, treating physicians and patients may reconsider restorative surgery, and these patients usually continue with a permanent ileostomy and rectal stump.

Colectomy, with or without reconstructive surgery, substantially reduces the risk to develop colorectal neoplasia. However, neoplasia of the residual rectum or ileoanal pouch may still arise and is associated with a poor prognosis. The latter underlines the importance of preventative strategies such as endoscopic surveillance. In recent years, data have expanded regarding prevalence, incidence, and risk factors for colorectal neoplasia after colectomy. Lack of a comprehensive approach and interpretation of these data has led to the absence of endoscopic surveillance recommendations for these patients. Thus, integrated data on CRC risk in postsurgical IBD patients are needed to further aid development of surveillance guidelines. We therefore conducted a systematic review and meta-analysis that aimed to determine prevalence, incidence, and risk factors regarding colorectal dysplasia and cancer after colectomy in 3 groups of IBD patients including (1) patients with a permanent ileostomy and rectal stump, (2) patients with IRA, and (3) patients with IPAA.

METHODS

Search strategy

Medline, Embase, the Cochrane Library, and Web of Science were independently searched with the help of a clinical librarian until May 2014 by 2 authors (L.D., L.N.) to identify studies that evaluated the colorectal neoplasia risk after colonic resection in IBD patients. We used the medical subject headings (MeSH) "*Inflammatory bowel disease*" OR "*Ulcerative colitis"* OR *"Crohn's disease*", combined with "*Surgical anastomosis*" OR "*Colectomy*" OR "*Restorative*

proctocolectomy" and combined with "*Colorectal neoplasms"* OR "*Rectal neoplasms"* OR "*Colon neoplasms"* OR "*Anus neoplasms"*. Simultaneously, a title/abstract search was performed with similar search terms and synonyms. The full search strategy is described in Supplementary Table 1. No restrictions regarding language, year of publication, or publication type were imposed. A manual search for references in the initially selected articles (Figure 1) was performed to identify additional relevant articles. The reporting checklist proposed by the Meta-analysis of Observational Studies in Epidemiology was used as a guideline in this systematic review and meta-analysis.

Inclusion and exclusion criteria

Studies were eligible for inclusion if the authors reported a series of IBD patients who underwent colonic resection and if occurrence of postoperative neoplasia in the residual rectum or pouch was described. In addition, we included studies that specifically assessed risk factors for neoplasia development after colectomy. Studies including patients with a Hartmann procedure or segmental resection and studies not defining the total IBD patient group were excluded. Furthermore, we excluded case reports, case series, studies including < 20 patients, and conference abstracts because these might not be representative for the target population. In case of duplicate publication or similar data from same institutions, the most recent and complete data sets were considered. Multiple studies from one institution were both considered if less than 25% of the inclusion years overlapped.

Quality assessment of retrieved articles

On the basis of the guidelines for critically appraising studies of prevalence or incidence, we composed a list of parameters for quality judgment.[7] These comprise whether the study was single center or population based, the number of patients (more or less than 100; a calculated sample size of 114 patients would be needed to show a prevalence of 5% with an error rate of 4%; a smaller sample size would give a higher risk of bias), duration of follow-up (cutoff mean or median 1 year), proctectomy or pouch excision rate, whether a clear pathologic classification system was used for grading neoplasia, whether the study was retrospective or prospective, and whether the study was consecutive. Two authors (L.D., L.S.) independently determined a quality score for each study, with a maximum of 7 points. Disagreement was resolved by discussion and consensus with a third reviewer (F.H.).

Data extraction

Different parameters were independently extracted by 2 authors (L.D., L.S., in consensus with F.H.) from the original articles including demographics, IBD characteristics, neoplasia prevalence and incidence, and risk factors such as a history of preoperative colorectal neoplasia, primary sclerosing cholangitis (PSC), pouchitis, and type of pouch anastomosis. IBD characteristics included the type and duration of IBD. For each group of IBD patients (rectal stump, IRA, and IPAA), the prevalence of colorectal neoplasia was calculated by dividing the cases by the total patient group at risk. Patients with either adenocarcinoma, including carcinoma in situ, or dysplasia were included as cases. The first group with a rectal

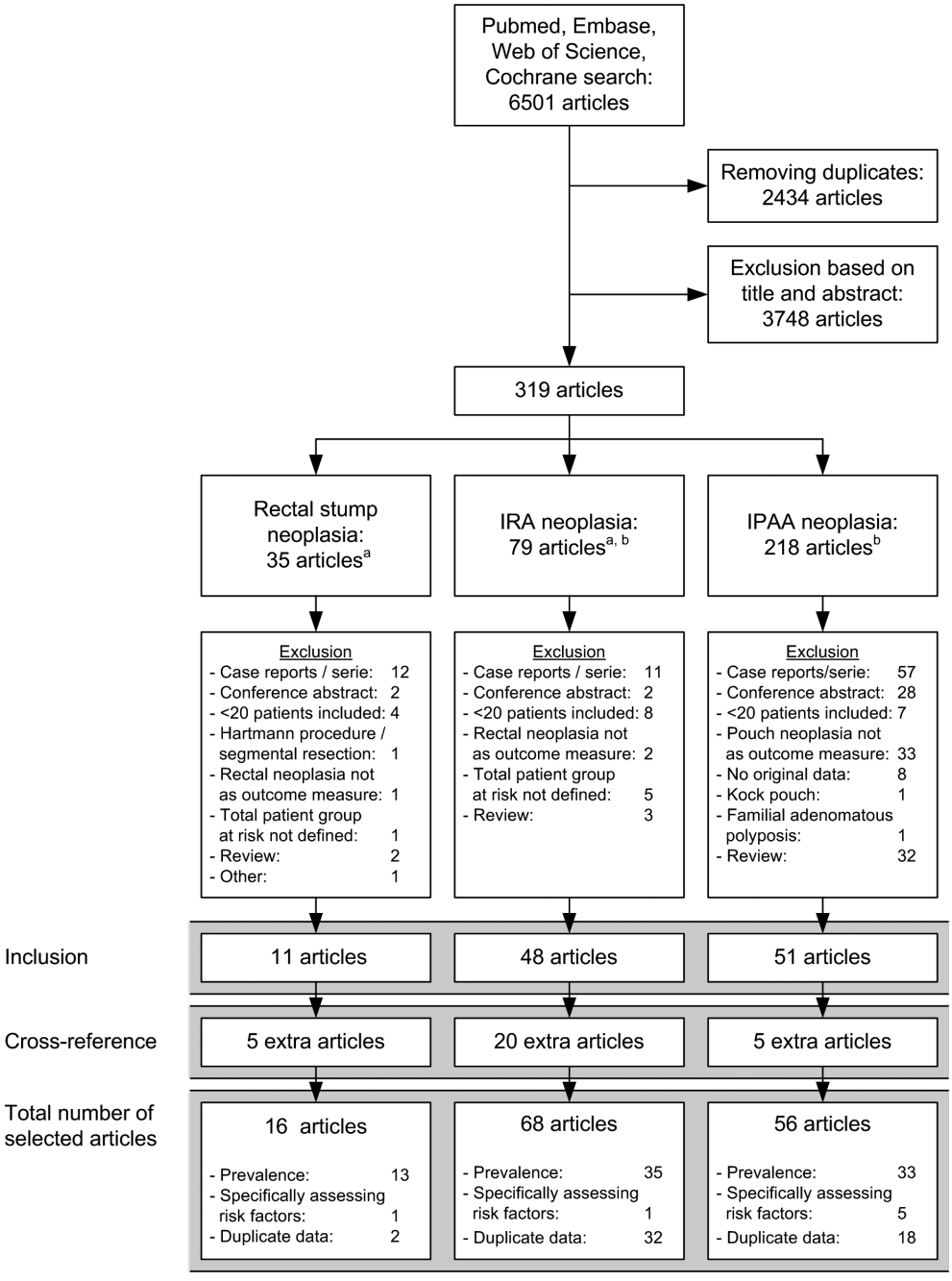

Figure 1. Flowchart showing inclusion of articles for analysis.

[a] Twelve articles are included in both the rectal stump group and the IRA group.

[b] One article is included in both the IRA group and the IPAA group.

stump was defined as the group of patients who underwent a colonic resection including the hepatic and splenic flexure and who received a permanent ileostomy. A rectal or rectosigmoidal stump was still in situ and at risk for neoplasia development. Patients who were lost to follow-up, postoperatively deceased, or undergoing secondary reconstruction of IRA or IPAA were not included in this group. The IRA and IPAA groups included all patients who underwent IRA or IPAA in 1 or more stages, respectively. Patients with an ileosigmoidal or cecorectal anastomosis were also included in the IRA group. In accordance with the rectal stump group, patients who were lost to follow-up or postoperatively deceased were excluded from the IRA and IPAA groups.

Statistics

We performed a meta-analysis to estimate pooled prevalences and cumulative incidences of colorectal neoplasia after colectomy. Random-effect models were used because of heterogeneity of studies. We assessed publication bias with the visual inspection of a funnel plot and used the Egger test to analyze funnel plot asymmetry.[8] Subsequently, we compared prevalences between subgroups (for example UC versus CD) with a logistic regression model calculating odds ratios (ORs).

To analyze potential risk factors for developing CRC after colectomy, ORs were separately calculated for each study and subsequently pooled with a random-effect model. Risk factors that comprised continuous data were analyzed in a pooled model by calculating a weighted mean difference.

To compare equality of follow-up duration between the 3 groups, we used one-way analysis of variance. Correlations between duration of follow-up and prevalence were analyzed with Spearman correlation coefficient. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed by using StatsDirect Statistical Software version 2.8.0 (StatsDirect, Sale, Cheshire, UK), Statistical Analysis Software version 9.2 (SAS Institute, Cary, NC), or IBM SPSS statistics version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Study selection

The systematic study selection flowchart is depicted in Figure 1. Sixteen, 68, and 56 articles were included in the rectal stump group, the IRA group, and the IPAA group, respectively. Because of duplicate data, 2 studies in the rectal stump group, 32 studies in the IRA group, and 18 studies in the IPAA group were not used for prevalence calculations (references for excluded studies are listed in Supplementary Material). For both the rectal stump group and the IRA group we included 1 article and for the IPAA group 5 articles that specifically assessed risk factors.

Study characteristics and quality assessment

Summarized quality scores for all included studies are depicted in Supplementary Tables 2–4 for the rectal stump group, IRA group, and IPAA group. Full quality assessment is displayed in Supplementary Tables 5–7.

The mean quality score of selected studies in the rectal stump group was 2.3 out of 7. All studies included retrospective, single-center cohort studies. Sample sizes were insufficient, and none of the studies mentioned the pathologic classification system that was used to evaluate rectal neoplasia. Proctectomy rates differed between 46% and 95%, resulting in a reduced number of patients at risk to develop rectal neoplasia. However, there was no correlation between proctectomy rates and cancer prevalence (P = 0.510).

Studies included in the IRA group had better overall quality, with average quality score of 4.0. This was mainly caused by better documentation and longer duration of follow-up, lower proctectomy rate, and larger number of included patients per study. Higher proctectomy rates were not correlated with lower cancer prevalence (P = 0.311).

Included articles on the IPAA group had a mean quality score of 3.0. The difference in quality score with the IRA group might be attributed to absence of the pouch excision rate, which was not reported in most articles. No correlation between follow-up duration and prevalence was observed (P = 0.515).

Ileostomy and rectal stump

Prevalence and incidence

A pooled analysis including 1011 IBD patients demonstrated a carcinoma prevalence of the rectal stump of 2.1% (95% confidence interval [CI], 1.3–3.0; Supplementary Table 2, Supplementary Figures 1 and 4). This value represents the prevalence in a variable duration of reported follow-up between 0.25 and 40 years. None of the included studies evaluated dysplasia development. One study specifically assessed the cumulative rectal cancer incidence in UC patients with a rectal stump or secondary IRA (constructed in 2 stages), resulting in an incidence of 12.6% after 24 years after surgery.[9]

Risk factors

Only 1 study assessed risk factors for the development of rectal stump cancer.[10] This retrospective case-control study included 12 rectal stump carcinomas and 18 control patients without rectal stump neoplasia and identified PSC and IBD duration until subtotal colectomy as risk factors. The study design of this case-control study was not sufficient to identify a history of colorectal neoplasia as risk factor because these patients were excluded from the control group.

We detected no difference in carcinoma prevalence of the rectal stump between UC and CD (2.2%, 95% CI, 1.3%–3.4% versus 2.1%, 95% CI, 0.6%–4.4%; OR 1.4, 95% CI, 0.4–5.0, p = 0.574).

Ileorectal anastomosis

Prevalence and incidence

A pooled rectal carcinoma prevalence of 2.4% (95% CI, 1.7%–3.3%) was calculated in the IRA group, including 2762 patients with a variable duration of reported follow-up between 1 and 35 years (Supplementary Table 3, Supplementary Figures 2 and 5). Development of rectal dysplasia after IRA was described in 16 studies including 1425 patients, resulting in

a pooled dysplasia prevalence of 2.5% (95% CI, 1.2%–4.2%). Because the year of publication and the duration of follow-up may influence the prevalence, we performed subgroup analysis on the basis of these variables. There was a statistically significant lower carcinoma prevalence (OR, 2.3; 95% CI, 1.3–4.1; p = 0.003) in studies published after 1990 (1.6%; 95% CI, 0.8%–2.6%) compared with earlier studies (3.2%; 95% CI, 2.1%–4.4%). No differences were found between studies with a duration of follow-up of at least 8 years (start surveillance colonoscopies), compared with studies with a shorter duration of follow-up (2.0%, 95% CI, 0.9%–3.4% versus 2.4%, 95% CI, 1.3%–3.7%; OR, 1.1, 95% CI, 0.5–2.2; p = 0.899).

Three studies reported a cumulative incidence of rectal carcinoma in the IRA group after onset of IBD.[11–13] A pooled analysis showed cumulative incidences of 0%, 5% (95% CI, 3.0%–7.5%), and 10% (95% CI, 7.0%–12.0%) after 10, 20, and 25 years after IBD onset, respectively. One study estimated cumulative incidences after IRA construction. After 5, 10, 15, and 20 years, respectively, cumulative incidences were 0%, 2%, 5%, and 14% for rectal carcinoma and 7%, 9%, 20%, and 25% for rectal dysplasia.[14]

Risk factors

UC, a history of CRC, and IBD duration emerged as risk factors for developing rectal carcinoma after IRA construction. None of the included studies specifically evaluated PSC as a risk factor. UC patients, including patients with indeterminate colitis, were more likely to develop rectal carcinoma after IRA construction compared with CD patients. A higher pooled carcinoma prevalence of the rectum was estimated in UC patients versus CD patients (3.2%, 95% CI, 2.3%–4.3% versus 0.7%, 95% CI, 0.2%–1.6%) with OR of 10.3 (95% CI, 2.5–41.9; p = 0.001).

A forest plot evaluating prior CRC as a risk factor to develop rectal carcinoma after IRA construction is displayed in Figure 2A. Three studies were available for meta-analysis because they reported prior CRC both in the patients who developed rectal carcinoma and in the patients who did not.[11, 12, 15] A pooled OR of 12.8 (95% CI, 3.3–49.2) favors prior CRC as risk factor to develop rectal carcinoma in patients with IRA. This is further supported by another study that described rectal neoplasia after subtotal colectomy in 17 CD patients with a history of CRC.[16] Six of 17 patients (28.6%) developed rectal carcinoma after subtotal colectomy, which is significantly higher than a pooled prevalence of 2.4% (P < 0.001). A history of colorectal dysplasia could not be assessed as risk factor because of insufficient data.

A longer duration of IBD also predisposes development of rectal carcinoma after colectomy and IRA. Others have reported an increasing risk over time in which none of the 22 rectal carcinomas after IRA developed within IBD duration of 10 years (3534 patient-years of follow-up). Beyond 10 years, the risk was 1 in 185 patient-years between 10 and 20 years of IBD duration and 1 in 117 patient-years in patients with IBD history of more than 20 years.[12] Furthermore, 1 study showed that patients who developed rectal cancer had a statistically significant longer duration of IBD compared with patients who did not develop rectal cancer (P = 0.030).[14] Nine studies reported IBD duration until rectal carcinoma development, and none of the 49 patients developed cancer within 10 years of IBD duration.[9, 12, 14, 17–22]

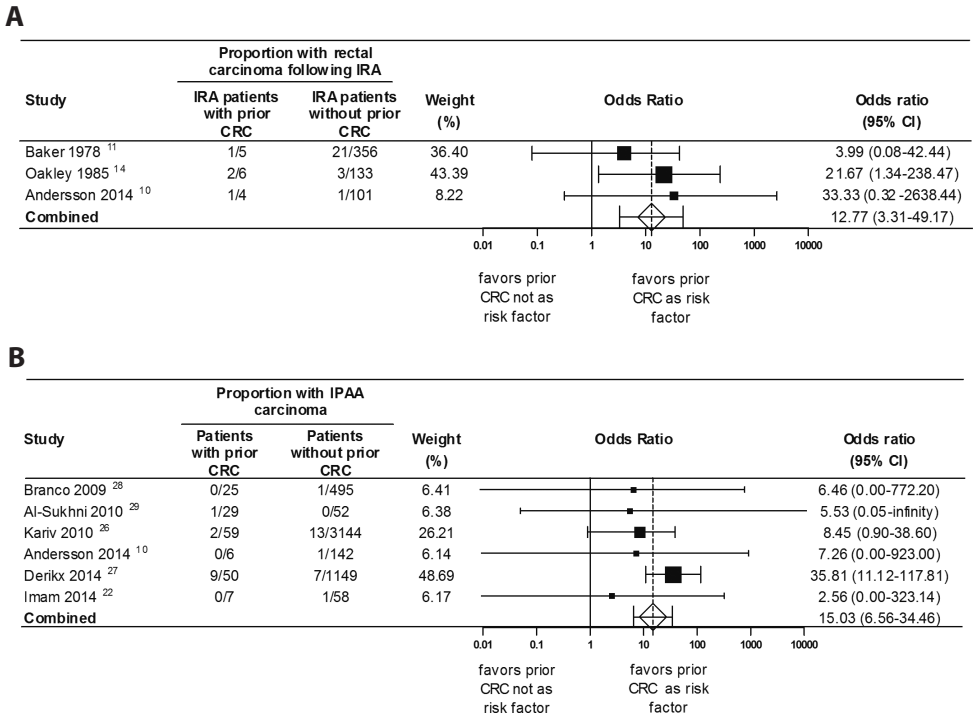

Figure 2. (A) Forest plot displaying effect of CRC before colectomy on development of rectal carcinoma after IRA. I2 (inconsistency) = 0%. (B) Forest plot displaying effect of CRC before colectomy on development of IPAA carcinoma. I2 (inconsistency) = 7.1%.

Ileal pouch-anal anastomosis

Prevalence and incidence

The pooled prevalence of carcinoma in the ileoanal pouch was 0.5% (95% CI, 0.3%–0.6%; Supplementary Table 4, Supplementary Figures 3 and 6). This analysis included 8403 patients with a variable duration of follow-up. Thirty-one articles including 7647 patients reported pouch dysplasia development, resulting in a pooled pouch dysplasia prevalence of 0.8% (0.5%–1.3%). Even studies that only included high-risk patients, such as patients with chronic pouchitis, prior CRC, long pouch duration (> 8 years), or PSC, showed relatively low pouch neoplasia prevalence (0.9%–4.6%).[23–26]

Three studies reported cumulative incidences of pouch carcinoma after IPAA construction, resulting in a pooled cumulative incidence of 0.4% (95% CI, 0.1%–0.9%), 0.9% (95% CI, 0.2%–1.9%), 1.4% (95% CI, 0.04%–3.0%), 2.7% (95% CI, 2.1%–3.4%), and 3.4% (95% CI, 2.8%–4.0%) after 5, 10, 15, 20, and 25 years, respectively.[11, 27, 28] Cumulative incidences of pouch dysplasia were reported in 2 of these studies. A pooled analysis showed cumulative incidences of pouch dysplasia after IPAA of 0.6% (95% CI, 0.2%–1.2%), 0.9% (95% CI, 0.8%–1.8%), 1.5% (95% CI, 1.2%–1.9%), and 3.0% (95% CI, 2.0%–5.0%) after 5, 10, 15, and 20 years, respectively.[27, 28]

Risk factors

Risk factors for pouch neoplasia development are a history of colorectal neoplasia and IBD duration. There was insufficient evidence available to evaluate a stapled anastomosis, PSC, and pouchitis as risk factors.

Prior colorectal neoplasia is the most important risk factor for developing pouch neoplasia. A pooled analysis including 5216 patients showed that patients with prior CRC had a statistically significant increased risk to develop pouch carcinoma (OR, 15.0; 95% CI, 6.6–34.5; Figure 2B) compared with patients without a history of CRC.[11, 23, 27–30] Moreover, an analysis excluding patients with prior CRC showed that prior colorectal dysplasia was also a risk factor for developing pouch carcinoma (OR, 4.4; 95% CI, 1.9–10.1; Supplementary Figure 7).[11, 23, 27–29] A systematic review of all described pouch carcinoma cases in IBD patients reported that 57.1% of these cases (28 of 49) had prior colorectal neoplasia.

IBD duration might also be considered as a risk factor because patients who developed pouch neoplasia had a significantly longer IBD duration before pouch construction compared with patients who did not develop pouch neoplasia in the univariate analysis of the 2 largest cohort studies. A pooled analysis of these 2 studies including 4403 patients showed that patients with pouch neoplasia had 5.1 years (95% CI, 2.5–7.6) longer IBD history before pouch construction ($P < 0.001$).[27, 28] Mean pouch duration before cancer was 10.8±7.3 years in all cases described in the literature.[31]

Patients with a hand-sewn anastomosis with mucosectomy carry a higher risk to develop pouch carcinoma compared with patients with a stapled anastomosis as shown in a pooled meta-analysis (OR, 2.9; 95% CI, 1.3–6.6; Supplementary Figure 8). However, no statistical difference was reached when comparing stapled and hand-sewn anastomosis for pouch neoplasia development (OR, 1.7; 95% CI, 1.0–3.1; Supplementary Figure 9).

Less conclusive evidence is available regarding the role of PSC and pouchitis in pouch neoplasia development. One small study including 22 patients with IPAA found that patients with PSC had a higher risk to develop atrophic pouch mucosa.[32] Pouchitis was associated with atrophic pouch mucosa development in 2 other studies.[33, 34] These patients with PSC or pouchitis might indirectly carry an increased risk to develop pouch neoplasia because atrophic pouch mucosa is associated with pouch neoplasia development.[35] By contrast, both PSC and pouchitis were not identified as risk factors for pouch neoplasia development in the 2 largest IBD cohorts with IPAA ($n = 1200$[28] and $n = 3203$[27]).

Comparison of rectal and pouch neoplasia in the rectal stump, ileorectal anastomosis, and ileal pouch-anal anastomosis

A summary of the prevalence, incidence, and risk factors for each group is shown in Figure 3. Pooled prevalences of both rectal carcinoma and rectal dysplasia in patients with a residual rectum (rectal stump or IRA) were significantly higher compared with pouch carcinoma and pouch dysplasia (IRA and rectal stump carcinoma versus pouch carcinoma, OR, 6.4, 95% CI, 4.3–9.5, $p < 0.001$; IRA carcinoma versus pouch carcinoma, OR, 7.1, 95% CI, 4.8–10.7, $p < 0.001$; IRA dysplasia versus pouch dysplasia, OR, 3.3, 95% CI, 2.1–5.2, $p < 0.001$; rectal stump carcinoma versus pouch carcinoma, OR, 4.5, 95% CI, 2.5–7.9, $p = 0.049$). Prevalence

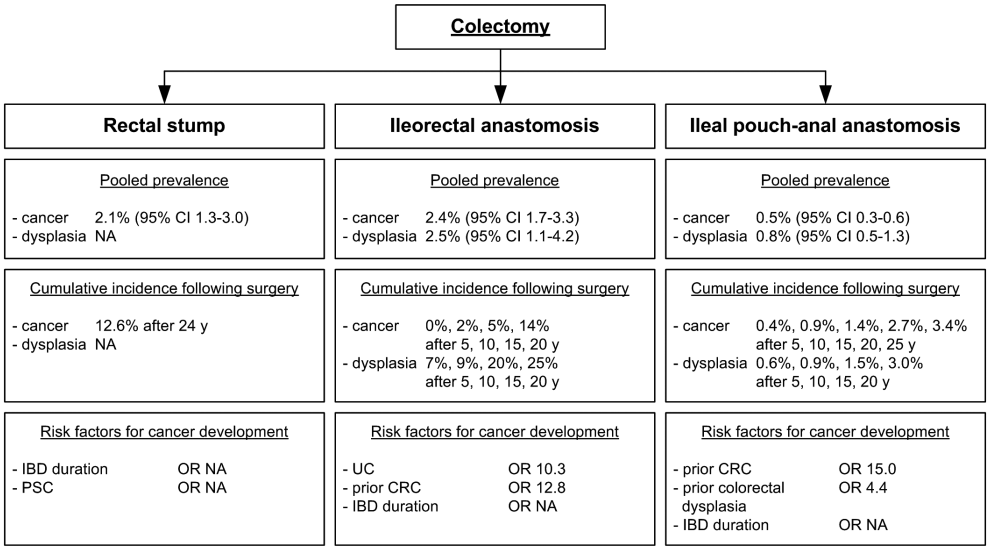

Figure 3. Summary chart of prevalence, incidence, and risk factors for colorectal neoplasia in the rectal stump, IRA, and IPAA. NA, not available.

of rectal carcinoma in the rectal stump group versus the IRA group did not show significant differences (OR, 0.6, 95% CI, 0.4–1.0, p = 0.074). Because the duration of follow-up after colectomy might influence the prevalence, we compared this between the 3 groups. No differences in ollow-up duration were observed between the rectal stump, IRA, and IPAA groups (p = 0.544). In addition, no increasing trend of pooled prevalences over time was observed when analyzed per 5-year mean or median duration of follow-up (Figure 4).

DISCUSSION

One of the key findings that can be derived from our systematic review is a low overall carcinoma prevalence and incidence in IBD patients after (reconstructive) colonic surgery. The cancer prevalence appeared to be dependent on the type of surgery and was highest in IRA patients (2.4%), followed by patients with a rectal stump (2.1%), and lowest in IPAA patients (0.5%). Prior CRC was the most important risk factor for developing rectal or pouch carcinoma (IRA group: OR, 12.8; IPAA group: OR, 15.0). Furthermore, we identified IBD duration and a diagnosis of UC as risk factors.

The calculated prevalences and cumulative incidences of rectal and pouch carcinoma need to be placed in perspective. The lifetime incidence for developing CRC in the general population approaches 5%.[36] Although the cumulative incidence of rectal carcinoma after IRA is based on only 1 study, 5% equals the cumulative rectal carcinoma risk 15 years after IRA construction. The pooled cumulative incidence of pouch carcinoma 25 years after IPAA construction (3.4%) is below the general lifetime CRC risk. None of the reported rectal carcinomas in the IRA group developed within 10 years after IBD onset. Pouch carcinomas

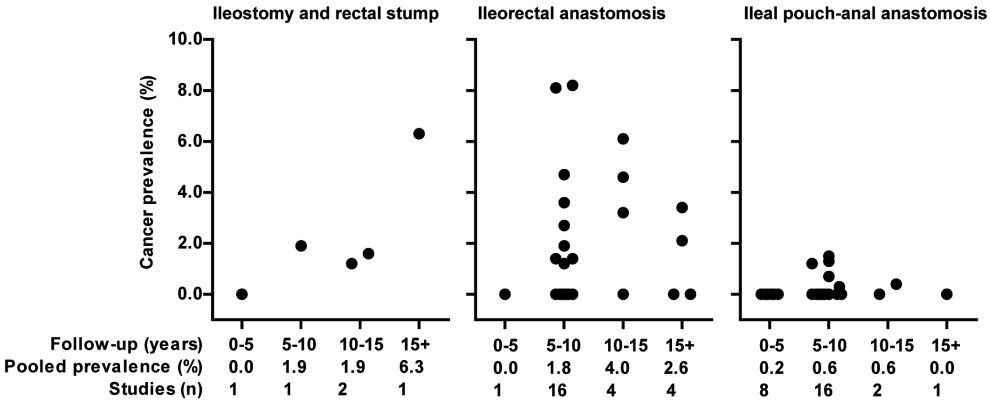

Figure 4. Pooled prevalences of carcinoma in the rectal stump, IRA, and IPAA groups when analyzed per 5-year mean or median duration of follow-up after colectomy.

developed after mean 10.8 years after IPAA. Furthermore, for proper interpretation of prevalences and incidences we should take a declining CRC risk over time into account because of improved IBD treatment strategies and advanced endoscopic procedures. This may have resulted in lower CRC prevalences and incidences for rectal stump, IRA, and IPAA patients in recent years. Moreover, prevalences and incidences may even be lower because mainly single-center studies rather than population-based cohorts were available for analysis.

A history of colorectal neoplasia before IRA or IPAA surgery is the most important risk factor for subsequent development of rectal and pouch carcinoma (IRA: OR, 12.8; IPAA: OR, 15.0). This is underlined by a shorter pouch duration before cancer diagnosis in IPAA patients with prior dysplasia or cancer compared with those without prior pouch neoplasia.[31] Furthermore, the majority of the carcinomas in the IPAA group arose from therectal mucosa rather than from the ileal pouch mucosa.[31] Therefore, it could be speculated that residual colonic mucosa is the main contributor to an increased risk to develop colorectal neoplasia, especially in patients with prior colorectal neoplasia.

As a corollary, one may hypothesize that the total amount of colorectal mucosa in situ may correlate with the subsequent risk to develop rectal or pouch carcinoma. The significantly lower cancer prevalence in the IPAA group compared with the groups with a rectum in situ fuels this hypothesis. In line with this, patients with a complete colon in situ may bear an even higher risk for colorectal neoplasia. This is supported by other authors who showed a lower risk of CRC per patient-year in patients after IRA compared with patients with an intact colon.[12] On the other hand, patients with a stapled anastomosis, leaving a few centimeters rectal mucosa in situ, were not carrying a higher risk compared with patients with a hand-sewn anastomosis with mucosectomy. The presence of residual colonic mucosal islands that remain even after "complete" mucosectomy might form an explanation for this latter observation.[37]

UC patients had approximately 10-fold increase in risk to develop rectal carcinoma after IRA construction in comparison with CD patients. This might suggest an association with the inflammatory process, because the rectum is more frequently involved in UC patients. On the other hand, pouchitis, inflammation of the pouch, was not identified as a risk factor. However, pouchitis is variable and often poorly defined, making it difficult to assess this potential risk factor.

Our findings may impact clinical practice because they could provide guidance in developing a postsurgical endoscopic surveillance strategy. Similar to the guidelines for CRC screening, direct evidence regarding the benefit of colorectal surveillance is not available.[3, 4] To this end, the identified risk factors may assist in recommendations on surveillance. The current British surveillance guidelines distinguish low-risk (no high-risk factors) and high-risk groups (PSC, prior colorectal neoplasia, atrophic mucosa) after colectomy and recommend surveillance intervals of 5 years and 1 year, respectively.[4] On the basis of our findings, we believe that the presence of a residual rectum after surgery is the major determinant for cancer development. Furthermore, the cancer risk is determined by a history of preoperative colorectal neoplasia, the duration of IBD, and a UC rather than a CD diagnosis. All these factors should be assessed by the clinician and taken into account in a postoperative surveillance strategy. IPAA patients, especially those without prior colorectal neoplasia, have a low cancer risk, and a very limited surveillance program might be sufficient for these patients.

One of the limitations of this review is that the included studies have a high risk of bias, especially those in the rectal stump group. Most studies were retrospective single-center studies introducing selection and recall bias. Furthermore, neoplasia development was often one of the secondary outcomes, and study heterogeneity was significant across studies. For example, some studies offered routine surveillance after colectomy, whereas other studies only performed an endoscopic procedure on indication. In addition, the included studies had a highly variable duration of follow-up, and the year of publication of the included studies varied between 1956 and 2014, which may also introduce bias. In older studies, diagnosis of IBD, detection of dysplasia and carcinoma, and IBD treatment differed from current practice. More recent treatment strategies such as thiopurines and biologicals may have decreased the burden of chronic colonic inflammation and have led to a reduction of cancer risk. In addition, advancing endoscopic visualization techniques may have further reduced cancer rates over time. Indeed, we observed statistically lower carcinoma prevalence in studies published after 1990.

In conclusion, we found significantly lower carcinoma prevalence in the IPAA group (0.5%) compared with the rectal stump group (2.1%) and IRA group (2.4%). A history of CRC was the most important risk factor, with 15.0-fold (IPAA) and 12.8-fold (IRA) increase in risk. Furthermore, IBD duration and UC rather than a diagnosis of CD emerged as risk factors for rectal or pouch neoplasia. These findings may aid in developing individualized postsurgical endoscopic surveillance strategies to optimize prevention of CRC development in IBD patients.

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SUPPLEMENTARY MATERIAL

Reference lists of excluded duplicate publications by same institutions

Rectal stump

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Ileorectal anastmosis

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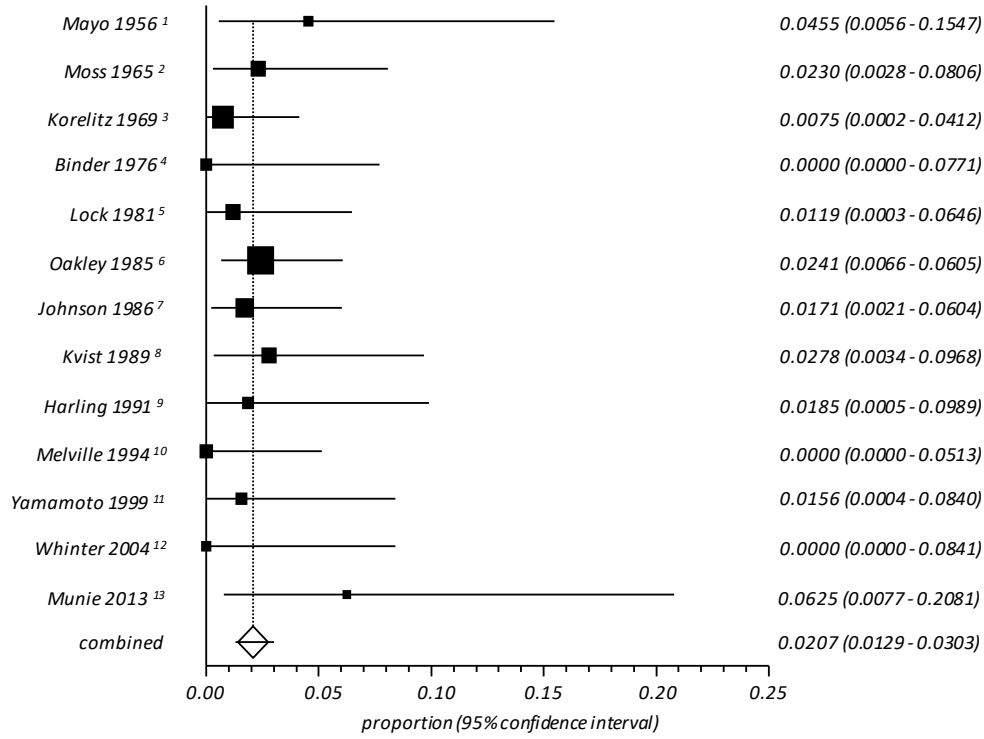
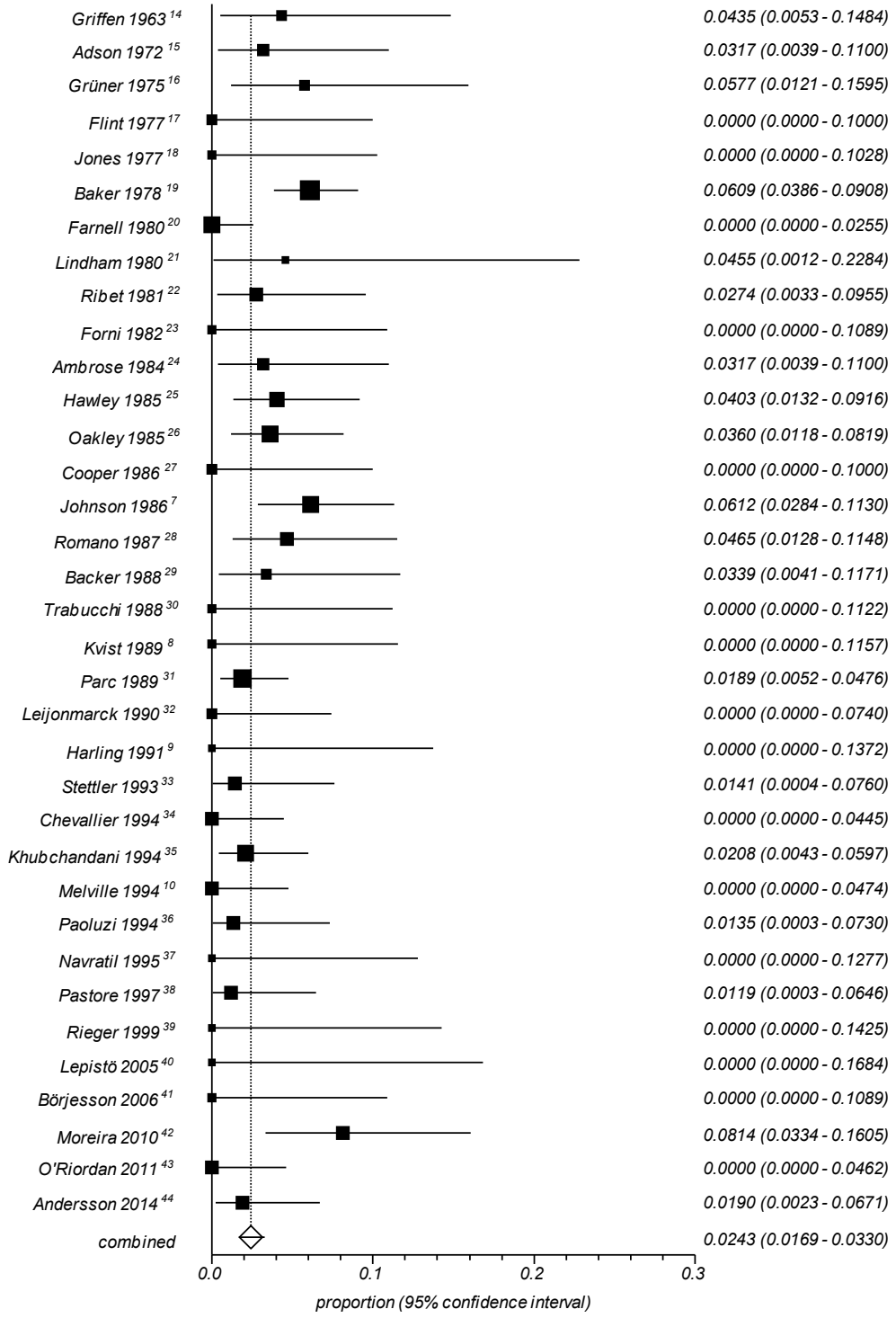
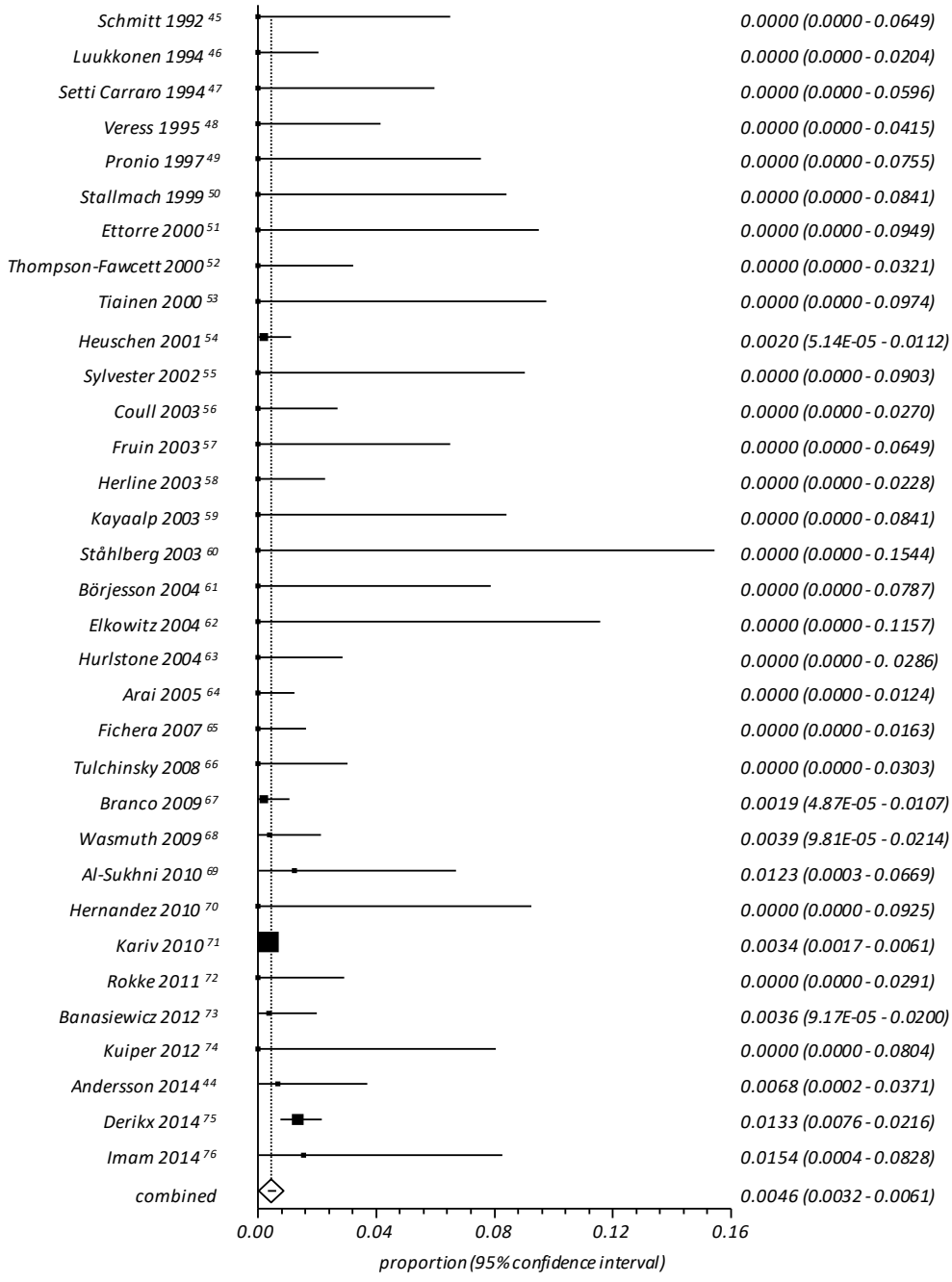


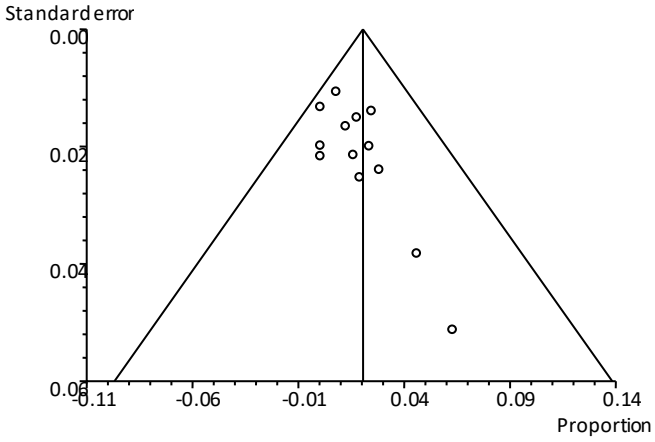
Supplementary Figure 1. Forest plot displaying pooled carcinoma prevalence in the rectal stump of IBD patients.



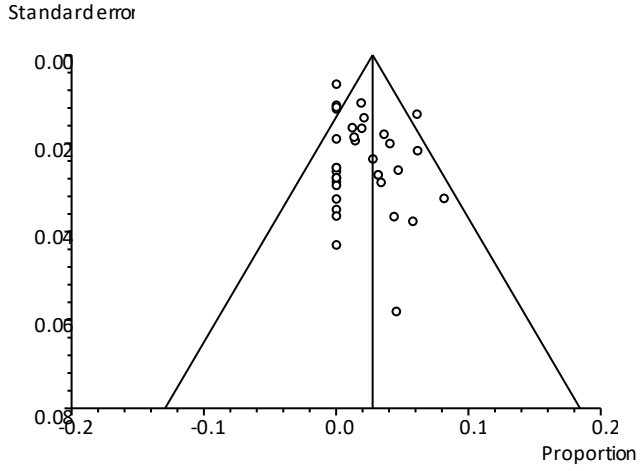
Supplementary Figure 2. Forest plot displaying pooled carcinoma prevalence for IBD patients with IRA.



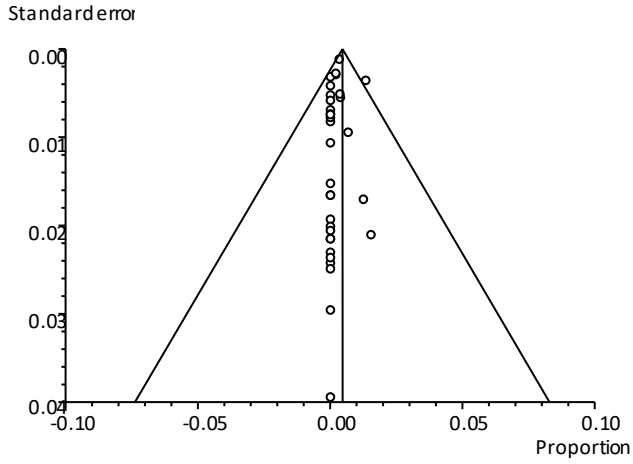
Supplementary Figure 3. Forest plot displaying pooled carcinoma prevalence for IBD patients with IPAA.



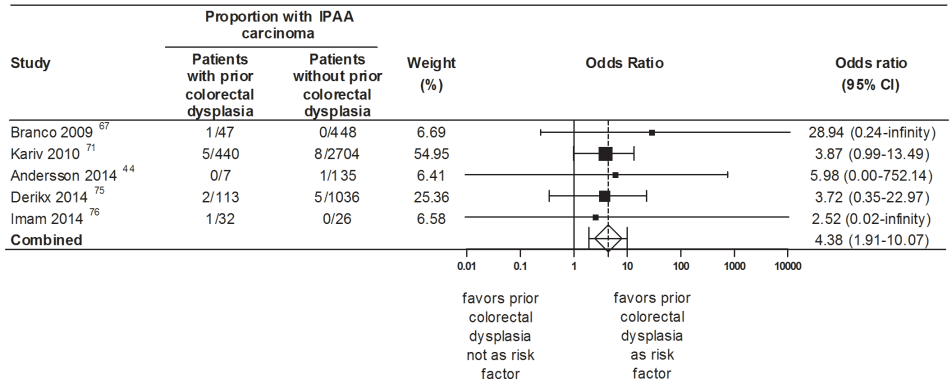
Supplementary Figure 4. Funnel plot analyzing publication bias of prevalence studies regarding rectal cancer in IBD patients with a rectal stump. Visual inspection of the funnel plot may indicate that some low prevalence studies are missing. Indeed, asymmetry of the plot is confirmed with the Egger test. However, because prevalence cannot extend below "0", some asymmetry of the funnel plot may be expected. In addition, there are no outliers.
Egger test: bias = 1.02 (95% CI, 0.05–2.00); p = 0.042.



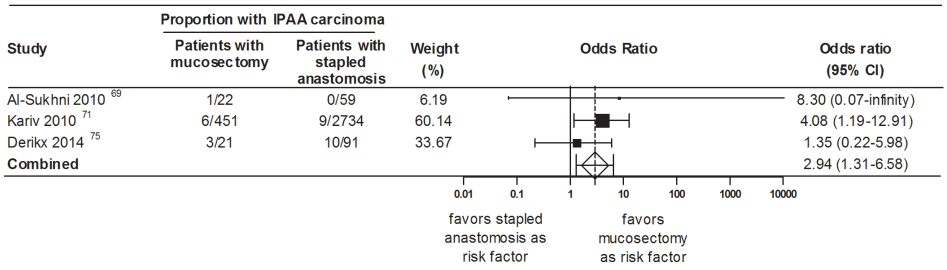
Supplementary Figure 5. Funnel plot analyzing publication bias of prevalence studies regarding rectal cancer in IBD patients with IRA. Visual inspection of the funnel plot does not indicate publication bias, although the Egger test showed some asymmetry of the funnel plot. Many low prevalence studies are included contradicting publication bias.
Egger test: bias = 0.79 (95% CI, 0.00–1.57); p = 0.049.



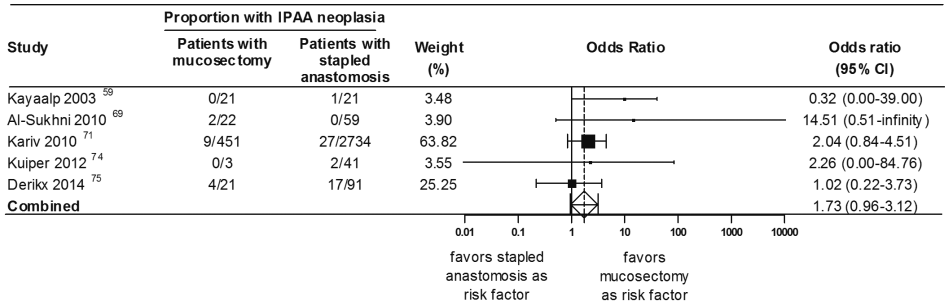
Supplementary Figure 6. Funnel plot analyzing publication bias of prevalence studies regarding pouch cancer in IBD patients with IPAA. Both visual inspection of the funnel plot and the Egger test showed no indication for publication bias.
Egger test: bias = –0.14 (95% CI, –0.45 to 0.16); p = 0.346.



Supplementary Figure 7. Forest plot displaying effect of colorectal dysplasia before colectomy on development of IPAA carcinoma. I2 (inconsistency) = 0%.



Supplementary Figure 8. Forest plot displaying effect of type of anastomosis on development of IPAA carcinoma. I2 (inconsistency) = 0.1%.



Supplementary Figure 9. Forest plot displaying effect of type of anastomosis on development of IPAA neoplasia. I2 (inconsistency) = 0%.

Supplementary Table 1. Full search strategy that was used to identify studies for inclusion.

MeSH terms	(inflammatory bowel diseases OR colitis, ulcerative OR Crohn disease) **AND** (anastomosis, surgical OR colectomy OR proctocolectomy, restorative OR colonic Pouches OR ileostomy) **AND** (colorectal neoplasms OR rectal neoplasms OR colonic neoplasms OR anus neoplasms)
Emtree terms	(inflammatory bowel disease (exploded) OR ulcerative colitis OR Crohn disease OR colon Crohn disease) **AND** (colon resection (exploded) OR proctocolectomy (exploded) OR ileum pouch OR ileostomy OR continent ileostomy) **AND** (colorectal tumor (exploded) OR anus tumor (exploded))
Title/abstract words	(inflammatory bowel OR IBD OR ulcerative colitis OR colitis ulcerosa OR indeterminate colitis OR Crohn* OR idiopathic proctocolitis OR regional Enteritis OR granulomatous enteritis OR granulomatous colitis OR ileocolitis OR terminal ileitis OR regional ileiti*) **AND** (colectom* OR ileostom* OR restorative proctocolectom* OR pouch* OR IPAA OR ileoana* OR ileo-ana* OR ileal stoma* OR ileorect* OR ileo-rect* OR ileosigmoid OR ileo-sigmoid OR IRA OR rectoileal) **AND** (neoplas* OR dysplasia* OR tumor* OR tumour* OR carcinoma* OR cancer* OR malignanc* OR adenocarcinoma)

PubMed, Web of Science, and Cochrane search strategies were based on MeSH terms and title/abstract words. Emtree terms combined with title/ abstracts words were used for the Embase search.
MeSH, Medical Subject Headings.

Supplementary Table 2. Overview of included articles that assessed prevalence of carcinoma in rectal stump after colectomy in IBD patients.

Author/Year of publication	Center	Inclusion period	Type of IBD	Rectal cancer/ total patients at risk		Proctectomy rate		Duration to proctectomy since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Mayo 1956 [1]	Mayo Clinic, Rochester	1949-1953	UC	2/44	4.6	25/44	56.8	range 3-28 mo	NS	2
Moss 1965 [2]	Massachusetts General Hospital, Boston	1940-1950	UC	2/87	2.3	67/87	77.0	median 1-2 y, 89% < 5y	range 13-25 y	2
Korelitz 1969 [3]	Mount Sinai Hospital, New York	1952-1963	UC	1/133	0.8	126/133	94.7	median 1-2 y (0-16) 40% < 1 y, 90% < 3 y	NS	2
Binder 1976 [4]	Tufts New England Medical Centre, Boston	1953-1974	IBD	0/46	0.0	36/46	78.3	median 1-2 y	range 1-14 y	2
Lock 1981 [5]	Cleveland Clinic Foundation, Cleveland	1955-1973	CD	1/84	1.2	46/84	54.8	NS	mean 11.3 y	3
Oakley 1985 [6]	Cleveland Clinic Foundation, Cleveland	1960-1982	UC	4/166	2.4	129/166	77.7	mean 39 mo (4days-22y)	NS	2
Johnson 1986 [7]	Monash University Medical School, Melbourne	1950-1981	UC	2/117	1.7	87/117	74.4	NS	range 0.25-40 y	1
Kvist 1989 [8]	University Hospital of Copenhagen, Copenhagen	1964-1982	UC	2/72	2.8	NS		median 11 y (0-54)	NS	1
Harling 1991 [9]	University Hospital of Copenhagen, Copenhagen	1964-1989	CD	1/54	1.9	25/54	46.3	median 6-7 y	median 7.7 y (0.5-24.1)	3
Melville 1994 [10]	St Mark's Hospital, London	1976-1990	UC, IC	0/70	0.0	45/70	64.3	NS	NS	2
Yamamoto 1999 [11]	Queen Elizabeth Hospital, Birmingham	1962-1997	CD	1/64	1.6	37/64	57.8	median 2 y (1 mo-23.4 y)	median 10 y (1.2-36)	3
Whinter 2004 [12]	University Hospital of Copenhagen, Copenhagen	NS	IBD	0/42	0.0	0/42	0.0	n/a	UC: median 2.5 y (0.5-10.0) CD: median 4.0 y (0.8-16.6)	4
Munie 2013 [13]	University of Vermont college of Medicine, Burlington	1990-2010	UC	2/32	6.3	19/32	59.4	12/19: median 2.6 y 7/19: median 9.0 y	13.8 y (5.5-20.5)	3

IC, indeterminate colitis; NS, not stated.

Supplementary Table 3. Overview of included articles that assessed prevalence of carcinoma in the rectum after subtotal colectomy with IRA in IBD patients.

Author/Year of publication	Center	Inclusion period	Type of IBD	Rectal cancer/ total patients at risk		Proctectomy rate		Duration to proctectomy since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Griffen 1963 [14]	University of Minnesota Medical School, Minneapolis	1940-1961	UC	2/46	4.4	3/46	6.5	NS	median 10-19.9 y (1-23)	2
Adson 1972 [15]	Mayo Clinic, Rochester	1950-1964	IBD	2/63	3.2	20/63	31.7	NS	range 5-18 y	3
Grüner 1975 [16]	Rigshospitalet, Oslo	1959-1973	UC	3/52	5.8	17/52	32.7	NS	NS	2
Flint 1977 [17]	Long Island Jewish-Hillside Medical Centre, New York	1956-1976	IBD	0/35	0.0	5/35	14.3	3 y	mean 6 y (1-18)	3
Jones 1977[18]	Woodend General Hospital, Aberdeen	1958-1976	IBD	0/34	0.0	3/34	8.8	median 2 y (2-3)	range 1-18 y	3
Baker 1978 [19]	Gordon Hospital, London	1952-1976	UC	22/361	6.1	41/361	11.4	NS	median 10-14 y	4
Farnell 1980 [20]	Mayo Clinic, Rochester	1961-1973	IBD	0/143	0.0	38/143	26.6	NS	median 8.2 y (5-17)	4
Lindham 1980 [21]	Karolinska Hospital, Stockholm	1953-1968	UC	1/22	4.6	9/19	47.4	mean 6.5 y (3 mo-14 y)	mean 14 y (9-23)	3
Ribet 1981 [22]	Centre Hospitalier Universitaire de Lille, Lille	1962-1980	UC	2/73	2.7	9/73	12.3	NS	median 7.3 y	3
Forni 1982 [23]	University of Pavia, Pavia	1969-1980	UC	0/32	0.0	0/32	0.0	n/a	range 6 mo – 10 y	0
Ambrose 1984 [24]	General Hospital, Birmingham	1951-1981	CD	2/63	3.2	15/63	23.8	NS	mean 9.5 y (2 mo-29.3 y)	3
Hawley 1985 [25]	St Mark's Hospital, London	1953-1984	UC	5/124	4.0	33/124	26.6	NS	NS	3
Oakley 1985 [26]	Cleveland Clinic, Cleveland	1960-1982	UC	5/139	3.6	30/139	21.6	NS	mean 7.8 y (1-22)	3
Cooper 1986 [27]	General Infirmary, Leeds	1955-1982	CD	0/35	0.0	7/35	20.0	NS	median 7 y (3 mo-20 y)	3
Johnson 1986 [7]	Monash University, Melbourne	1950-1981	UC	9/147	6.1	22/147	15.0	NS	range 0.25-40 y	2
Romano 1987 [28]	Università di Napoli, Napoli	1960-1985	UC	4/86	4.7	12/86	14.0	NS	mean 7.2 y (3-20)	3
Backer 1988 [29]	Bispebjerg Hospital, Copenhagen	1951-1979	UC	2/59	3.4	NS		NS	median 15 y	2

Supplementary Table 3. (continued)

Author/Year of publication	Center	Inclusion period	Type of IBD	Rectal cancer/ total patients at risk		Proctectomy rate		Duration to proctectomy since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Trabucchi 1988 [30]	Univeristy of Milan, Milan	1972-1986	UC	0/31	0.0	0/31	0.0	n/a	mean 8.8 y	5
Kvist 1989 [8]	University Hospital of Copenhagen, Copenhagen	1964-1982	UC	0/30	0.0	NS		NS	NS	1
Parc 1989 [31]	Hospital St Antoine, Paris	1961-1982	UC	4/212	1.9	35/212	16.5	NS	range 1-24 y	4
Leijonmarck 1990 [32]	Stockholm county	1955-1984	UC	0/48	0.0	29/48	60.4	mean 4.5 y (1 mo-15 y)	mean 13 y (4-27)	4
Harling 1991 [9]	University Hospital of Copenhagen, Copenhagen	1964-1989	CD	0/25	0.0	4/25	16.0	median 6-7 y	median 7.7 y (0.5-24.1)	3
Stettler 1993 [33]	Bichat-Claude Bernard Hospital, Paris	1948-1987	UC	1/71	1.4	2/71	2.8	NS	median 7.5 y (1-35)	4
Chevallier 1994 [34]	Hospital St Antoine, Paris	1960-1988	CD	0/81	0.0	14/81	17.3	mean 4.1 y (2 mo-14.5 y)	mean 8 y (2 mo-28.5 y)	3
Khubchandani 1994 [35]	Lehigh Valley Hospital Centre, Allentown	1960-1992	IBD	3/144	2.1	15/144	10.4	mean 8 y (2-10)	mean 22 y (6 mo-30 y)	4
Melville 1994 [10]	St Mark's Hospital, London	1976-1990	UC, IC	0/76	0.0	10/76	13.2	NS	NS	2
Paoluzi 1994 [36]	University of Rome, Rome	1966-1987	UC	1/74	1.4	9/74	12.2	median 16 mo (2 mo-16 y)	median 9.5 y (3-25)	4
Navratil 1995 [37]	Bichat-Claude Bernard Hospital, Paris	1991-1992	UC	0/27	0.0	0/27	0.0	n/a	median 9.3 y (1-28)	5
Pastore 1997 [38]	Mayo Clinic, Rochester	1974-1990	IBD	1/84	1.2	17/84	20.2	mean 3.2 y	mean 6.5 y (6 days-18.9 y)	3
Rieger 1999 [39]	St Vincent's Hospital, Melbourne	1968-1994	CD	0/24	0.0	5/24	20.8	median 2 y (1-25)	median 7 y (1-29)	3
Lepistö 2005 [40]	Helsinki University Central Hospital, Helsinki	1978-2000	UC	0/20	0.0	7/20	35.0	median 8 y (7 days-23 y)	mean 18 y (3.7-25.2)	3
Börjesson 2006 [41]	Sahlgrenska University Hospital, Göteborg	1997-2003	UC	0/32	0.0	4/32	12.5	NS	median 42 mo (28-48 mo)	2

Supplementary Table 3. (continued)

Author/Year of publication	Center	Inclusion period	Type of IBD	Rectal cancer/ total patients at risk		Proctectomy rate		Duration to proctectomy since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Moreira 2010 [42]	Cleveland Clinic, Cleveland	1971-2006	UC, IC	7/86	8.1	46/86	53.5	median 10 y (1-33)	median 9 y (1-36)	2
O'Riordan 2011 [43]	Mount Sinai Hospital, Toronto	1982-2010	CD	0/78	0.0	18/78	23.1	mean 8.3 mo	mean 8.5 y	3
Andersson 2014 [44]	Linköping University Hospital, Linköping	1192-2006	IBD	2/105	1.9	6/105	5.7	NS	mean 5.4 y	4

IC, indeterminate colitis; NS, not stated.

Supplementary Table 4. Overview of included articles that assessed prevalence of pouch carcinoma after restorative proctocolectomy with IPAA in IBD patients.

Author/Year of publication	Center	Inclusion period	Type of IBD	IPAA cancer/ total patients at risk		Pouch excision rate		Duration to pouch excision since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Schmitt 1992 [45]	Cleveland Clinic Florida, Fort Lauderdale	1988-1992	UC	0/55	0.0	0/55	0.0	NS	mean 8.6 mo (1.5-29)	3
Luukkonen 1994 [46]	University Central Hospital, Helsinki	1985-1992	UC	0/179	0.0	NS		NS	median 27 mo (6-80)	4
Setti Carraro 1994 [47]	St Mark's Hospital, London	1976-1985	UC	0/60	0.0	NS		NS	median 97 mo (19-173)	1
Veress 1995 [48]	Huddinge University Hospital, Huddinge	1980-1992	UC	0/87	0.0	1/87	1.1	NS	mean 6.3 y (3-14)	4
Pronio 1997 [49]	University of Rome, Rome	1984-1994	IBD	0/47	0.0	NS		NS	NS	3
Stallmach 1999 [50]	Saarland University, Homburg	1996-1997	UC	0/42	0.0	NS		NS	range 3 mo-8 y, median < 3 y	2
Ettorre 2000 [51]	Villa Claudia Hospital, Rome	1995-1996	IBD	0/37	0.0	NS		NS	median 85 mo (7-198)	4
Thompson-Fawcett 2000 [52]	John Radcliffe Hospital, Oxford	NS	UC	0/113	0.0	NS		NS	mean 2.5 y (0-10)	4
Tiainen 2000 [53]	Tampere University Hospital, Tampere	1985-1990	UC	0/36	0.0	NS		NS	median 9.8 y (7.8-11.9)	2
Heuschen 2001 [54]	University of Heidelberg, Heidelberg	1982-1998	UC	1/493	0.2	16/493	3.2	NS	NS	3
Sylvester 2002 [55]	Bristol Royal Infirmary, Bristol	NS	UC	0/39	0.0	NS		NS	NS	0
Coull 2003 [56]	Glasgow Royal Infirmary, Glasgow	1988-1998	UC	0/135	0.0	10/135	7.4	NS	median 56 mo (12-145)	5
Fruin 2003 [57]	Boston University School of Medicine, Boston	NS	UC	0/55	0.0	NS		NS	mean 6.2 y (5-9)	2
Herline 2003 [58]	Lahey Clinic, Burlington	1983-2001	UC	0/160	0.0	NS		NS	mean 8.4 y	2
Kayaalp 2003 [59]	Turkey Yuksek Ihtisas Hospital, Ankara	1992-2000	UC	0/42	0.0	NS		NS	mean 42 mo (16-108)	2

Supplementary Table 4. (continued)

Author/Year of publication	Center	Inclusion period	Type of IBD	IPAA cancer/ total patients at risk		Pouch excision rate		Duration to pouch excision since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Ståhlberg 2003 [60]	Huddinge University Hospital, Stockholm	1994-1999	UC	0/22	0.0	NS		NS	mean 151.5 mo	2
Börjesson 2004 [61]	Sahlgrenska University Hospital, Gothenburg	1982-1987	UC	0/45	0.0	NS		NS	median 16 y (14-18)	2
Elkowitz 2004 [62]	New York University School of Medicine, New York	NS	UC	0/30	0.0	NS		NS	median 1-2 y (0-5)	2
Hurlstone 2004 [63]	Royal Hallamshire Hospital, Sheffield	2001-2003	IBD	0/127	0.0	NS		NS	median 6.5 y (2-12)	4
Arai 2005 [64]	Yokohama City Hospital, Yokohama	1993-2003	UC	0/296	0.0	NS		NS	mean 4.38 y	3
Fichera 2007 [65]	University of Chicago Hospitals, Chicago	1992-2006	UC	0/225	0.0	NS		NS	median 36 mo (3-132)	3
Tulchinsky 2008 [66]	Tel Aviv Sourasky Medical Centre, Tel Aviv	1986-2005	UC	0/120	0.0	NS		NS	mean 65 mo (2-258)	4
Branco 2009 [67]	Mount Sinai School of Medicine, New York	1978-2008	UC	1/520	0.2	NS		NS	NS	2
Wasmuth 2009 [68]	St Olavs Hospital, Trondheim	1984-2006	IBD	1/258	0.4	20/258	7.8	NS	mean 10 y (1-22)	4
Al-Sukhni 2010 [69]	Mount Sinai Hospital, Toronto	1981-2009	UC	1/81	1.2	NS		NS	median 76.1 mo	1
Hernandez 2010 [70]	University of Puerto Rico School of Medicine, San Juan	2000-2006	UC	0/38	0.0	NS		NS	NS	3
Kariv 2010 [71]	Cleveland Clinic, Cleveland	1983-2009	IBD	11/3203	0.3	NS		NS	mean 8.2 y	4
Rokke 2011 [72]	University Hospital, Oslo	1988-2002	UC	0/125	0.0	9/125	7.2	NS	mean 6.8 y (0.8-15.3)	4
Banasiewicz 2012 [73]	Poznan University of Medical Scienes, Poznań	1984-2009	UC	1/276	0.4	5/276	1.8	NS	median > 5 y	4

Supplementary Table 4. (continued)

Author/Year of publication	Center	Inclusion period	Type of IBD	IPAA cancer/ total patients at risk		Pouch excision rate		Duration to pouch excision since colectomy	Duration of follow-up since colectomy	Overall quality assessment
				(n)	(%)	(n)	(%)			
Kuiper 2012 [74]	Amsterdam Medical Centre, Amsterdam	1988-2008	UC	0/44	0.0	0/44	0.0	NS	mean 8.6 y	4
Andersson 2014 [44]	Linköping University Hospital, Linköping	1992-2006	UC	1/148	0.7	7/148	4.7	NS	mean 6.3 y	4
Derikx 2014 [75]	Radboud University Medical Centre, Nijmegen	1991-2012	IBD	16/1200	1.3	NS		NS	median 6.5 y	5
Imam 2014 [76]	Mayo Clinic, Rochester	1995-2012	IBD	1/65	1.5	1/65	1.5	NS	median 6 y (3.6-248.4)	3

IC, indeterminate colitis; NS, not stated.

Supplementary Table 5. Quality assessment table for included studies in group with ileostomy and rectal stump.

Author/Year of publication	Single center (= 0) / population based (= 1)	Retrospective (= 0) / prospective (= 1)	Consecutive (0 = no; 1 = yes)	Number of patients (> 100 = 1)	Duration of follow-up (> 1 y = 1)	Proctectomy rate (< 70% = 1)	Pathological classification system for grading Neoplasia	Overall quality assessment
Mayo 1956 [1]	0	0	1	0	0	1	0	2
Moss 1965 [2]	0	0	1	0	1	0	0	2
Korelitz 1969 [3]	0	0	1	1	0	0	0	2
Binder 1976 [4]	0	0	1	0	1	0	0	2
Lock 1981 [5]	0	0	1	0	1	1	0	3
Oakley 1985 [6]	0	0	1	1	0	0	0	2
Johnson 1986 [7]	0	0	0	1	0	0	0	1
Kvist 1989 [8]	0	0	1	0	0	0	0	1
Harling 1991 [9]	0	0	1	0	1	1	0	3
Melville 1994 [10]	0	0	1	0	0	1	0	2
Yamamoto 1999 [11]	0	0	1	0	1	1	0	3
Whinter 2004 [12]	0	1	0	0	1	1	1 (Riddell [77])	4
Munie 2013 [13]	0	0	1	0	1	1	0	3

Supplementary Table 6. Quality assessment table for included studies in IRA group.

Author/Year of publication	Single center (= 0) / population based (= 1)	Retrospective (= 0) / prospective (= 1)	Consecutive (0 = no; 1 = yes)	Number of patients (> 100 = 1)	Duration of follow-up (> 1 y = 1)	Proctectomy rate (< 70% = 1)	Pathological classification system for grading Neoplasia	Overall quality assessment
Griffen 1963 [14]	0	0	0	0	1	1	0	2
Adson 1972 [15]	0	0	1	0	1	1	0	3
Grüner 1975 [16]	0	0	1	0	0	1	0	2
Flint 1977 [17]	0	0	1	0	1	1	0	3
Jones 1977[18]	0	0	1	0	1	1	0	3
Baker 1978 [19]	0	0	1	1	1	1	0	4
Farnell 1980 [20]	0	0	1	1	1	1	0	4
Lindham 1980 [21]	0	0	1	0	1	1	0	3
Ribet 1981 [22]	0	0	1	0	1	1	0	3
Forni 1982 [23]	0	0	0	0	0	0	0	0
Ambrose 1984 [24]	0	0	1	0	1	1	0	3
Hawley 1985 [25]	0	0	1	1	0	1	0	3
Oakley 1985 [26]	0	0	0	1	1	1	0	3
Cooper 1986 [27]	0	0	1	0	1	1	0	3
Johnson 1986 [7]	0	0	0	1	0	1	0	2
Romano 1987 [28]	0	0	1	0	1	1	0	3
Backer 1988 [29]	0	0	1	0	1	0	0	2
Trabucchi 1988 [30]	0	1	1	0	1	1	1 (Riddell [77]; Morson [78])	5
Kvist 1989 [8]	0	0	1	0	0	0	0	1
Parc 1989 [31]	0	0	1	1	1	1	0	4
Leijonmarck 1990 [32]	1	0	1	0	1	1	0	4
Harling 1991 [9]	0	0	1	0	1	1	0	3
Stettler 1993 [33]	0	0	1	0	1	1	1 (Riddell [77])	4
Chevallier 1994 [34]	0	0	1	0	1	1	0	3
Khubchandani 1994 [35]	0	0	1	1	1	1	0	4
Melville 1994 [10]	0	0	1	0	0	1	0	2

Supplementary Table 6. (continued)

Author/Year of publication	Single center (= 0) / population based (= 1)	Retrospective (= 0) / prospective (= 1)	Consecutive (0 = no; 1 = yes)	Number of patients (> 100 = 1)	Duration of follow-up (> 1 y = 1)	Proctectomy rate (< 70% = 1)	Pathological classification system for grading Neoplasia	Overall quality assessment
Paoluzi 1994 [36]	0	0	1	0	1	1	1 (Riddell [77])	4
Navratil 1995 [37]	0	1	1	0	1	1	1 (Riddell [77])	5
Pastore 1997 [38]	0	0	1	0	1	1	0	3
Rieger 1999 [39]	0	0	1	0	1	1	0	3
Lepistö 2005 [40]	0	0	1	0	1	1	0	3
Börjesson 2006 [41]	0	0	1	0	1	0	0	2
Moreira 2010 [42]	0	0	0	0	1	1	0	2
O'Riordan 2011 [43]	0	0	1	0	1	1	0	3
Andersson 2014 [44]	0	0	1	1	1	1	0	4

Supplementary Table 7. Quality assessment table for included studies in IPAA group.

Author/Year of publication	Single center (= 0) / population based (= 1)	Retrospective (= 0) / prospective (= 1)	Consecutive (0 = no; 1 = yes)	Number of patients (> 100 = 1)	Duration of follow-up (> 1 y = 1)	Pouch excision rate (< 70% = 1)	Pathological classification system for grading Neoplasia	Overall quality assessment
Schmitt 1992 [45]	0	0	1	0	1	1	0	3
Luukkonen 1994 [46]	0	0	1	1	1	0	1 (De Silva [79])	4
Setti Carraro 1994 [47]	0	0	0	0	1	0	0	1
Veress 1995 [48]	0	0	1	0	1	1	1 (Riddell [77])	4
Pronio 1997 [49]	0	1	1	0	0	0	1 (Riddell [77])	3
Stallmach 1999 [50]	0	1	1	0	0	0	0	2
Ettorre 2000 [51]	0	1	1	0	1	0	1 (Riddell [77])	4
Thompson-Fawcett 2000 [52]	0	1	1	1	1	0	0	4
Tiainen 2000 [53]	0	0	1	0	1	0	0	2
Heuschen 2001 [54]	0	0	1	1	0	1	0	3
Sylvester 2002 [55]	0	0	0	0	0	0	0	0
Coull 2003 [56]	0	0	1	1	1	1	1 (Melville [80])	5
Fruin 2003 [57]	0	0	0	0	1	0	1 (Riddell [77])	2
Herline 2003 [58]	0	0	0	1	1	0	0	2
Kayaalp 2003 [59]	0	0	1	0	1	0	0	2
Ståhlberg 2003 [60]	0	0	0	0	1	0	1 (Riddell [77])	2
Börjesson 2004 [61]	0	0	0	0	1	0	1 (Riddell [77])	2
Elkowitz 2004 [62]	0	0	0	0	1	0	1 (Riddell [77])	2
Hurlstone 2004 [63]	0	1	0	1	1	0	1 (Vienna criteria [81])	4
Arai 2005 [64]	0	0	1	1	1	0	0	3
Fichera 2007 [65]	0	1	0	1	1	0	0	3
Tulchinsky 2008 [66]	0	1	1	1	1	0	0	4
Branco 2009 [67]	0	0	1	1	0	0	0	2
Wasmuth 2009 [68]	0	0	1	1	1	1	0	4
Al-Sukhni 2010 [69]	0	0	0	0	1	0	0	1

Supplementary Table 7. (continued)

Author/Year of publication	Single center (= 0) / population based (= 1)	Retrospective (= 0) / prospective (= 1)	Consecutive (0 = no; 1 = yes)	Number of patients (> 100 = 1)	Duration of follow-up (> 1 y = 1)	Pouch excision rate (< 70% = 1)	Pathological classification system for grading Neoplasia	Overall quality assessment
Hernandez 2010 [70]	0	1	1	0	0	0	1 (Riddell [77])	3
Kariv 2010 [71]	0	0	1	1	1	0	1 (Riddell [77])	4
Rokke 2011 [72]	0	0	1	1	1	1	0	4
Banasiewicz 2012 [73]	0	0	1	1	1	1	0	4
Kuiper 2012 [74]	0	1	0	0	1	1	1 (Vienna criteria [81])	4
Andersson 2014 [44]	0	0	1	1	1	1	0	4
Derikx 2014 [75]	1	0	1	1	1	0	1 (Riddell [77])	5
Imam 2014 [76]	0	0	0	0	1	1	1 (Riddell [77])	3

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CHAPTER 7A

CUFF AND POUCH CANCER IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: WHAT SURVEILLANCE STRATEGY SHOULD BE RECOMMENDED?

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TO THE EDITOR

With great interest, we read the systematic review by Selvaggi et. al.[1] regarding cuff and pouch cancer in patients with ulcerative colitis (UC). Using clear study selection criteria, the authors evaluated epidemiology and risk factors of pouch-related malignancies after ileal pouch-anal anastomosis (IPAA) for UC. Main findings were a low pooled cumulative incidence of pouch and cuff cancer (0.35%, 20 y after IPAA) and the identification of prior colorectal neoplasia as the predominant risk factor (odds ratio, 8.8) for developing pouch-related carcinoma. The authors then propose an endoscopic surveillance strategy of the pouch but based on our interpretation of the data, we suggest an alternative approach.

First, the authors recommended routine surveillance pouchoscopy starting 10 years after UC diagnosis followed by annual surveillance. However, the risk of pouch-related cancer is low and should be placed in perspective. For example, cumulative colorectal cancer risk from birth to 75 years is 1.96% in the general population, compared with a defined pooled cumulative incidence of pouch-related malignancies of 0.33% for 50 years after UC diagnosis and 0.35% for 20 years after IPAA.[1] The early starting point and subsequent high surveillance frequency as recommended is at odds with the low risk.

Second, the authors suggest a delayed surveillance strategy in patients who underwent mucosectomy. This proposed risk stratification for pouch surveillance does not take into account the single most important risk factor, neoplasia of the colectomy specimen. In our opinion, patients with prior colorectal neoplasia do require an intensified pouch surveillance program.

Third, no surveillance strategy was proposed for patients with Crohn's disease or indeterminate colitis because these subgroups were excluded from analyses. We advocate a pouch surveillance program for all patients with inflammatory bowel disease. Crohn's disease and indeterminate colitis patients do carry a pouch-related cancer risk,[2] and no evidence is available to support a separate surveillance strategy.

We applaud the efforts by Selvaggi et. al. because this will contribute toward the development of evidence-based pouch surveillance programs. By contrast, we favor a limited pouch surveillance program for all patients with inflammatory bowel disease with IPAA given the low pouch-related carcinoma incidence. Patients with prior colorectal neoplasia should be subjected to a more intensified pouch surveillance strategy with special attention for the anal transitional zone where most carcinomas are localized. Whether pouch surveillance prevents pouch and cuff cancer or improves clinical outcomes remains an area of future research.

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CHAPTER 7B

CONTROVERSIES IN POUCH SURVEILLANCE FOR PATIENTS WITHIN INFLAMMATORY BOWEL DISEASE

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CLINICAL VIGNETTE

Case 1

Following 2 years of rectal blood loss, a 31-year-old male was diagnosed with ulcerative pancolitis in 1978. Initial treatment consisted of both topical and systemic 5-aminosalicylic acids (5-ASA), and remission was achieved. In both 1984 and 1986 he was hospitalised due to exacerbations necessitating treatment with intravenous corticosteroids. The following years went well, without disease activity, under treatment with 5-ASA. In 1997, at the age of 50 years, a surveillance colonoscopy showed a stenotic process with a macroscopic irregularity in the sigmoid region. Histology revealed at least high-grade dysplasia (HGD) and signs of an invasive growth pattern which could indicate colorectal cancer (CRC). The patient underwent restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). Histology of the resection specimen confirmed active inflammation in the colon and rectum and a carcinoma in situ was identified in the sigmoid colon without invasive growth. This patient did not have significant comorbidities, for example primary sclerosing cholangitis (PSC), and the CRC family history was negative. What pouch surveillance strategy should be recommended?

Case 2

A 34-year-old man presented at our inflammatory bowel disease (IBD) center with ulcerative proctitis. Ten years later, after an initially mild disease course, his disease progressed to a pancolitis. An 11-year period with multiple exacerbations (on average every 2 year, including hospitalization followed and treatment consisted of topical and systemic 5-ASAs with intermittent corticosteroids. In 1998, at the age of 65 years, a two-stage restorative proctocolectomy with IPAA was performed due to disease activity refractory to systemic corticosteroids. The colectomy specimen confirmed the diagnosis of ulcerative pancolitis without evidence for colorectal dysplasia or carcinoma. Other than steroid-induced diabetes mellitus, this patient had no comorbidities. His father died from CRC at unknown age. What pouch surveillance strategy should be recommended?

BACKGROUND

Although clear and well-accepted surveillance guidelines exist for inflammatory bowel disease (IBD) patients with an intact colon, several controversies exist with respect to endoscopic surveillance of the ileal pouch-anal anastomosis IPAA. Following from our clinical vignettes, it could be questioned whether pouch surveillance is necessary at all, whether and how risk stratification should be performed, and which pouch surveillance intervals should be followed. Both the British Society of Gastroenterology (BSG) and American Gastroenterology Association (AGA) recommend regular surveillance in IBD patients with an intact colon, tailored to the individual patient's risk profile.[1, 2] These strategies may reduce colorectal cancer (CRC) incidence and mortality.[3, 4] However, for IBD patients who had undergone a colectomy, guidance is less clear.

Pouch surveillance recommendations in the current IBD surveillance guidelines are lacking (AGA guideline), incomplete (American Society for Gastrointestinal Endoscopy (ASGE) guideline) or not up to date in the light of new available evidence (BSG guideline; European Crohn's and Colitis Organisation (ECCO) guideline) as shown in Table 1.[1, 2, 5, 6] The British surveillance guidelines distinguish low (no high risk factors) and high risk (primary sclerosing cholangitis (PSC), previous colorectal neoplasia, atrophic mucosa) groups following colectomy, and recommend surveillance intervals of 5 years and 1 year, respectively.[1] However, new data with respect to risk factors for pouch carcinoma development became available in recent years. The ECCO guidelines only identify previous CRC as a very important risk factor, but subsequently propose surveillance based on risk factors as in the BSG guidelines.[5]

Lack of clear, updated, and consistent guidelines in pouch surveillance has resulted in a wide variation in daily practice. Some physicians adopt very short surveillance intervals, which may lead to unnecessary burden for patients and increased costs. In contrast, longer surveillance intervals may result in interval carcinomas. The recently updated evidence to support pouch surveillance is limited and requires careful interpretation and discussion.

Table 1. Overview of pouch surveillance guidelines.

Guideline	Year of publication	Risk stratification		Surveillance strategy
		Yes/no	Risk categories	
AGA[2]	2010	n/a	n/a	No recommendations
BSG[1]	2010	Yes	High risk: • Previous rectal dysplasia • Dysplasia/cancer at the time of pouch surgery • Primary sclerosing cholangitis • Type C pouch mucosa[a]	Yearly
			Low risk: • Absence of high risk factors	5-Yearly
ASGE[6]	2015	Yes	Highest risk: • History of dysplasia or cancer.	Yearly surveillance should be considered
			High risk: • Primary sclerosing cholangitis • Type C pouch mucosa[a] • Refractory pouchitis	Yearly surveillance may be considered
			Other patients	No recommendations
ECCO[5]	2015	Yes	High risk: • Dysplasia/cancer at the time of pouch surgery • Primary sclerosing cholangitis • Type C pouch mucosa[a] • Unremitting pouchitis	Yearly
			Absence of high risk factors	No evidence that support routine surveillance

[a]Type C pouch mucosa is defined as exhibiting permanent persistent atrophy and severe inflammation.

Here, we aim to discuss controversies regarding IPAA surveillance based on the currently available literature and suggest an approach to pouch surveillance based on up-to-date risk stratification.

IS POUCH SURVEILLANCE NECESSARY IN IBD PATIENTS?

Pro

One of the main factors that determine the benefit of a pouch surveillance strategy is the risk of developing pouch cancer. For example, it would be more useful to screen a population of which 50% will develop pouch cancer compared with a population containing almost no patients who will develop pouch cancer. As such, pouch surveillance may be of benefit in subgroups that carry a high pouch cancer risk, whereas in subgroups with a low risk profile, surveillance pouchoscopies will not be worthwhile.

The major determinant for pouch cancer development is the presence of colorectal dysplasia or carcinoma before colectomy. A recent meta-analysis showed that IBD patients with a history of colorectal dysplasia or CRC had a respectively 4.4- and 15.0-fold increase in pouch cancer risk.[7] In addition, 57.1% of pouch cancer cases in the literature had preceding colorectal neoplasia.[8] The high cumulative pouch neoplasia incidence in subgroups with previous colorectal neoplasia (29.5% after 15 years in patients with previous CRC) supports regular surveillance in these patients.[9]

The poor outcome of pouch carcinomas may also support pouch surveillance. In a previous study, 9 out of 16 patients with pouch carcinoma died within a median follow-up of 11 months (range 1–20 months).[9] Three additional patients had metastatic disease at the end of follow-up. This is in line with another study, in which 3 of 11 patients with pouch carcinoma died within 1 year of follow-up. Furthermore, alarm symptoms for pouch carcinoma can be masked due to already altered defaecation patterns, which may contribute to delayed detection and worsened outcome. Earlier detection of pouch cancers by regular endoscopic surveillance may improve the outcome.

Contra

The low overall incidence and prevalence of pouch carcinoma in IBD argues against routine pouch surveillance in all IPAA patients. A meta-analysis showed a pooled cumulative incidence of pouch cancer of 3.4% 25 years after IPAA construction, which is below the general lifetime CRC risk.[7] IPAA cancers are mostly located at the anal transitional zone, and the cumulative incidence of pouch cancers originating from ileal mucosa will be even lower.[8] In addition, the incidence of precancerous lesions such as low-grade dysplasia (LGD) and high-grade dysplasia (HGD) is also low (3.0% after 20 years).[7]

When incorporating risk stratification in a pouch surveillance strategy, only those with a history of colorectal neoplasia could be identified as high risk patients. Evidence for other risk factors is less conclusive or pronounced and a combined cumulative dysplasia and carcinoma incidence of 2.2% after 15 years was shown in those without a history of colorectal neoplasia.[9] Patients with a longer IBD duration and a hand-sewn IPAA may carry

an increased pouch cancer risk, but the impact of these risk factors is much lower.[7] Current factors that guide the ECCO and BSG pouch surveillance guidelines, including PSC and an atrophic pouch mucosa or pouchitis, were not identified as risk factors in the two largest IBD cohorts with IPAA reported (n = 3203 and n = 1200).[9, 10] In addition, studies that only included patients with PSC pouchitis or a long-standing pouch (≥ 12 years) showed relatively low pouch carcinoma prevalences (1.5%–2.4%).[11, 12, 13] This advocates against regular surveillance in these subgroups.

A low absolute risk for detecting pouch cancer and precancerous lesions will result in a high number needed to screen, questioning cost-efficiency of a surveillance strategy in those with a low risk profile. Many patients will need to undergo surveillance, but in most cases pouch neoplasia will not be detected. This will result in significant disadvantages, such as a financial burden for patients and health care providers, and discomfort for patients due to preparation and the endoscopic procedure. Furthermore, studies that show an improved detection and prognosis of pouch neoplasia with surveillance are lacking, and may never be performed due to the limited size of available cohorts.

DOES POUCH SURVEILLANCE IMPROVE THE OUTCOME OF POUCH NEOPLASIA?

Pro

In long-standing colonic IBD, current surveillance strategies are based on the concept of an inflammation-dysplasia-carcinoma sequence.[14] This sequence may also apply to the pathogenesis of pouch carcinoma, since patients with subsequent LGD, HGD, and pouch carcinoma have been described previously.[15] Regular pouch surveillance may result in earlier pouch neoplasia detection, with potential improved prognosis and outcome. Supportive evidence for this hypothesis is derived from a tertiary pouch referral center performing regular surveillance pouchoscopies every 1 to 3 years at the discretion of the treating physician.[10] Of 9 patients with pouch carcinoma detected in this surveillance programme, only 1 (11%) had a stage IV cancer diagnosis, whereas in a nationwide study without routine endoscopic surveillance, 4 of 12 (33%) primary pouch carcinomas were diagnosed with stage IV disease.[9]

Contra

Although regular surveillance may result in earlier pouch neoplasia detection, it is unknown whether this strategy is sufficient to find more lesions at a precancerous stage. Typical endoscopic features of pouch neoplasia are lacking, and in many cases there are no endoscopic abnormalities at all.[9, 16] Difficulties with detection of dysplasia in the pouch were confirmed by a tertiary pouch referral center: despite regular surveillance, only 3 out of 11 patients (27.3%) were detected with dysplastic lesions preceding pouch cancer, whereas in 10 (90.9%) concurrent dysplasia was subsequently identified in the pouch excision specimen.[10]

Furthermore, it is unknown whether detection of pouch neoplasia at an earlier stage will improve outcome. For example, many dysplastic lesions never show progression to cancer or even show spontaneous regression. A previous study reported on 22 patients with LGD of the pouch. Only 3 patients demonstrated persistent LGD and 3 showed progression after a median time of 9.5 years, whereas 16 patients showed regression of LGD.[15] Similarly another study, including 21 patients with lesions of the pouch categorized as indefinite for dysplasia (IND), only showed progression to LGD in 1 patient and progression to HGD in 1 other patient during a mean follow-up of 19.3 months. In contrast, IND was not re-detected in 12 patients and 7 had persistent IND.[17]

DISCUSSION

As in colorectal surveillance, direct evidence for the benefit of a pouch surveillance strategy is lacking. There are no studies evaluating the yield and the number of interval carcinomas of a particular pouch surveillance strategy, in contrast to previous studies on

colorectal surveillance in IBD.[18] Furthermore, studies comparing surveillance strategies, which is for example done for colorectal surveillance recommended by the BSG and AGA guidelines, are lacking for pouch surveillance.[19] There is a need to establish a clear and well-accepted pouch surveillance guideline, reducing the wide variation in practice and allowing prospective evaluation in coming years.

Our pro-con debate has resulted in a proposed pouch surveillance strategy which is outlined in Figure 1. Given the available data, we propose a strategy based on risk stratification. Risk stratification should be based only on the presence of a history of colorectal neoplasia before colectomy which is the dominant risk factor for pouch cancer in recent studies.[7] The low absolute and relative pouch carcinoma risk in patients without

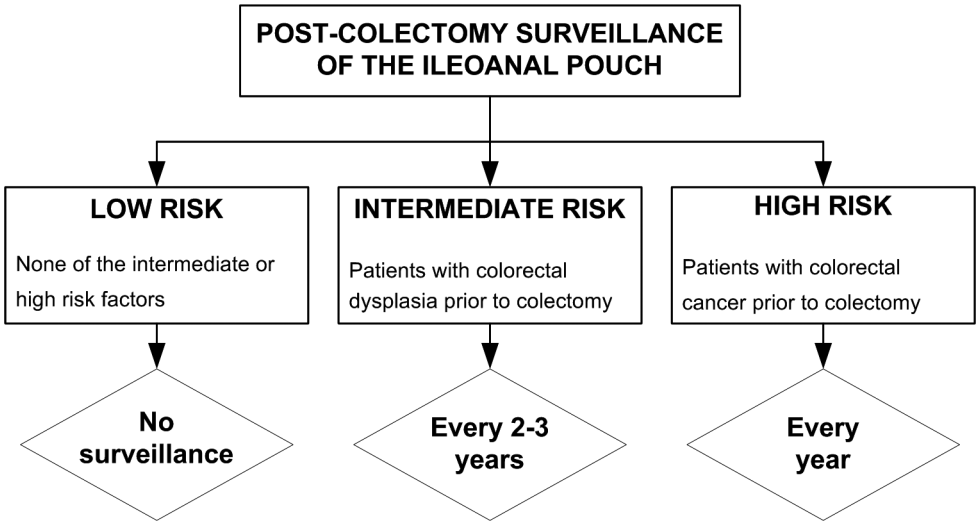

Figure 1. Proposed pouch surveillance strategy.

previous colorectal neoplasia allows us to propose forgoing surveillance in this subgroup. Thus, in line with the current ECCO recommendations, routine surveillance of the pouch is not recommended in low risk patients.[5] However, in contrast to the BSG and ECCO guideline, the presence of PSC, atrophic pouch mucosa, or pouchitis do not guide risk stratification.[1, 5] In our proposed strategy, patients with previous colorectal dysplasia or CRC are categorised into intermediate and high risk categories, respectively. The optimal surveillance interval for these categories still has to be defined. In our proposed strategy, surveillance intervals are derived from the BSG guideline for regular IBD surveillance.

One of the questions that remain is how surveillance pouchoscopy should be performed. We did not incorporate this in our procon debate, since data from well-designed studies are lacking. Only one study investigated chromoendoscopy in 44 IPAA patients and found no increased pouch neoplasia detection rate compared with white light endoscopy.[20] In addition, the preparation for pouchoscopy is often insufficient and residual stool is a disadvantage for chromoendoscopy. By contrast, both the AGA and the BSG guidelines recommend chromoendoscopy with targeted biopsies for regular IBD surveillance.[1, 2] Furthermore, evidence for a biopsy regimen in pouch surveillance is absent. Since most carcinomas arise at the anal traditional zone (67.3%), we endorse close and careful inspection of this region including random and targeted biopsies.[8] Targeted biopsies in the afferent and efferent limb and in the pouch body may be sufficient; however, evidence underlying such a strategy is currently lacking.

In addition to pouch surveillance endoscopy with biopsy, previous reports have suggested that biomarkers may also contribute to more accurate and earlier pouch neoplasia detection. As such, DNA abnormalities including aneuploidy, loss of heterozygosity, and mutations of p53, K-ras, and adenomatous polyposis coli genes have been studied as early biomarkers for pouch neoplasia.[21] Some studies reported DNA aneuploidy or loss of heterozygosity in patients with pouch dysplasia. However, these studies are small in size (≤ 5 patients with pouch dysplasia) and often lack a control group, not allowing us to draw clinically relevant conclusions from these data.

Several other questions are still open to debate with respect to pouch surveillance. For example, can we discontinue surveillance after a certain number of pouchoscopies without abnormalities? And what is the appropriate management of detected LGD or HGD? Although many questions remain, the implementation of a widely supported guideline for pouch surveillance is a first step towards improved surveillance in IBD patients following IPAA construction.

CLINICAL VIGNETTE

Case 1

Based on our proposed surveillance strategy, we would categorize this patient into the high risk category recommending yearly surveillance pouchoscopies. The history of a carcinoma in situ in his sigmoid colon justifies yearly surveillance.

Indeed, this patient was followed up with pouchoscopies. He underwent a pouchoscopy in 1997, in 2001, and yearly since 2009 until 2014 (except in 2013). A gap without surveillance

of respectively 4 and 8 years was left between the first three pouchoscopies. In 2009, LGD of the pouch body was found, which regressed to normal in all following pouchoscopies.

Case 2

This patient would be categorised in the low risk category not requiring pouch surveillance, according to our proposed algorithm. Even when other factors such as a long IBD history or PSC are present, we do not recommend surveillance, in view of the low pouch cancer risk in these subgroups.

Nevertheless, this patient was frequently followed up with pouchoscopies every 2 to 3 years. He developed pouchitis once, for which he was treated with metronidazole. This did not influence the surveillance intervals. During five follow-up pouchoscopies in 14 years, no dysplasia was detected.

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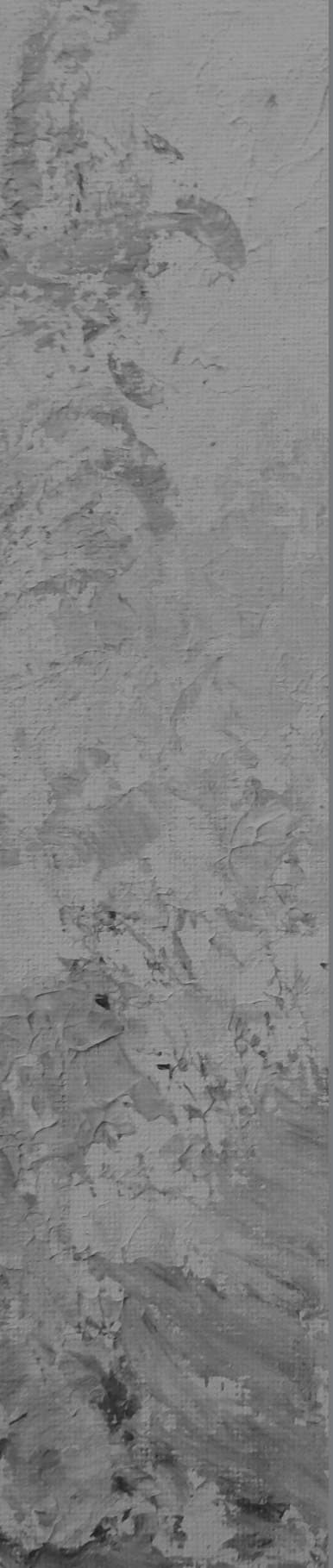

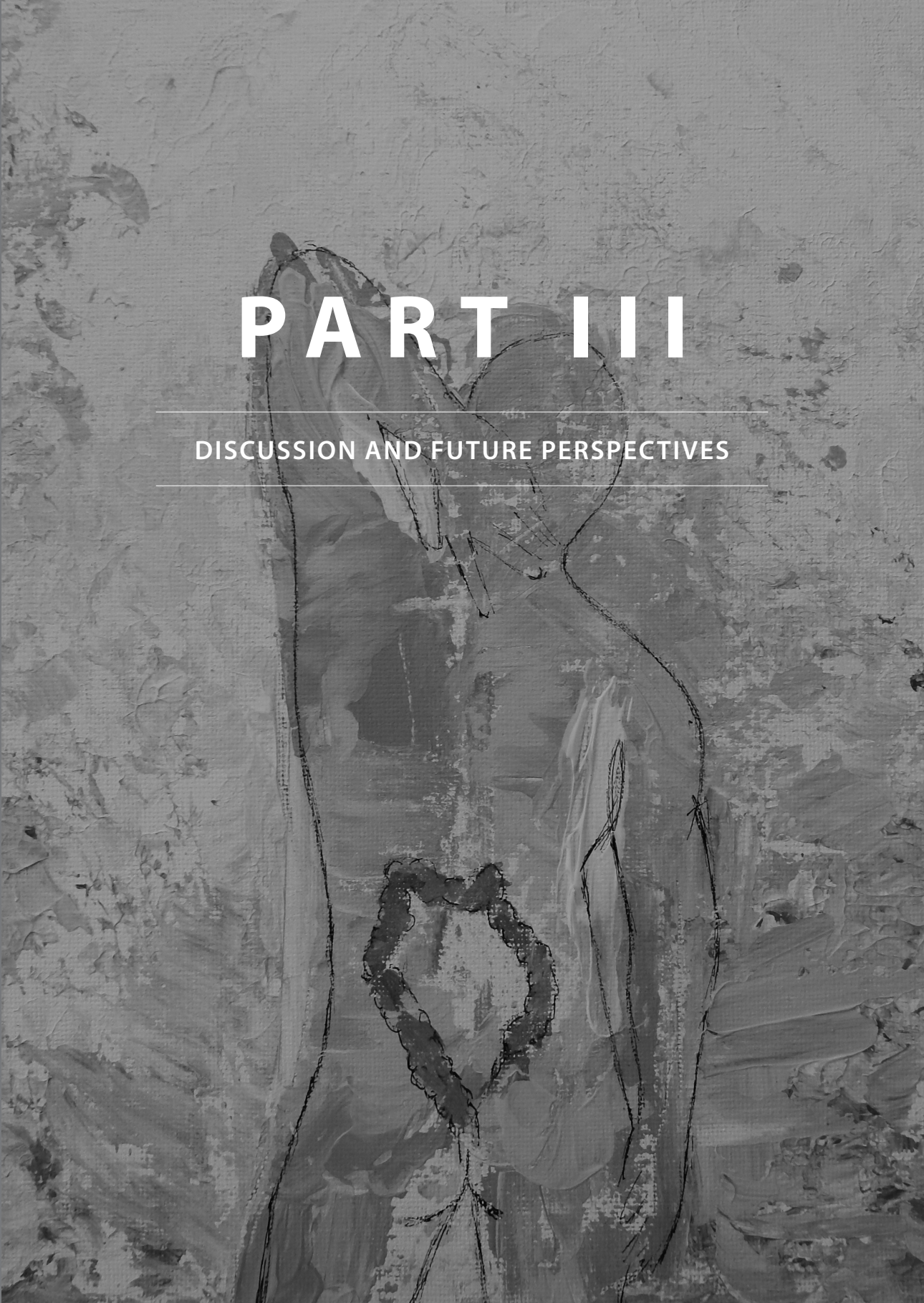

PART III

DISCUSSION AND FUTURE PERSPECTIVES

CHAPTER 8

GENERAL DISCUSSION

GENERAL DISCUSSION

The proportion of inflammatory bowel disease (IBD) patients with cancer is increasing. The aging population and improved IBD management clearly contribute to this trend. For IBD patients with cancer, a case-by-case approach for treatment of both cancer and IBD is encouraged based on the type and expected evolution of the cancer. Studies that evaluated the influence of IBD therapies on cancer course and treatment are scarce. As a consequence, the evidence that supports various strategies is limited at best.

This thesis investigated the risk of several solid cancers in patients with IBD in order to optimize and individualize prevention and treatment strategies for both IBD and cancer. It includes risk assessments and interpretation of data for different malignancies, such as pouch cancer, enabling case-by-case decision-making. In this chapter, our main findings are discussed and further interpreted. We will discuss how our findings affect daily practice and current thinking as well as the remaining gaps of knowledge that are open for further research.

INTESTINAL MALIGNANCIES – COLORECTAL CANCER

Since a wealth of data is available on colorectal (CRC) risk in IBD patients we applied our research questions to CRC in specific scenarios. First, we assessed the CRC risk in patients suffering from both Lynch syndrome (LS) and IBD. Second, we investigated the risk to develop CRC after colectomy in patients with IBD.

Results of this thesis – Risk assessment

We demonstrated that patients with both IBD and LS developed CRC at a younger age compared to LS patients without IBD, although cumulative CRC incidence was similar (**Chapter 2**). As such, patients with both LS and IBD developed CRC 10 years earlier. Our unique cohort highlights that CRC specifically developed in LS patients with ulcerative colitis rather than Crohn's disease and that this subgroup has a higher cumulative CRC incidence. One case series describing 12 LS patients with IBD confirms these results.[1] In addition, experimental models with MSH2 or MLH1 deficient mice, recapitulating human LS, also support an increased and/or accelerated carcinogenesis in those with inflammation.[2, 3]

In IBD patients who underwent a colectomy, we demonstrated in a systematic review a relatively low CRC risk with pooled prevalences varying between 0.5% and 2.4% for the different surgical scenarios (**Chapter 6**). The lowest CRC prevalence was observed in patients with an ileal pouch-anal anastomosis (IPAA, 0.5%), which was significantly lower compared to patients with a rectal stump (2.1%) or ileorectal anastomosis (IRA, 2.4%). Similarly, low cumulative incidences were found in IPAA patients with after 25 years a pooled cumulative incidence of 3.4%. This is in line with our study in which we identified all IBD patients with IPAA in The Netherlands and showed a cumulative pouch carcinoma incidence of 3.3% after 20 years (**Chapter 5**).

A history of CRC prior to colectomy is the most important risk factor for CRC development after colectomy. We showed in our Dutch cohort that IPAA patients with prior CRC had an

approximately 25-fold increase in risk to develop pouch neoplasia. Those with a history of colorectal dysplasia carried a 4-fold increased risk. Similarly, we found in our meta-analysis a respectively 15- and 13-fold increase in CRC risk for IPAA and IRA patients with a history of CRC. Other identified risk factors included a longer duration of IBD and a diagnosis of ulcerative colitis rather than Crohn's disease. Our analysis did not support previously suggested risk factors to develop pouch neoplasia, including a stapled anastomosis, primary sclerosing cholangitis and pouchitis.

Implications

Risk assessment for CRC development in IBD and LS is of major importance for endoscopic surveillance recommendations. As such, clear and well-accepted surveillance guidelines exist for IBD and LS patients with an intact colon, recommending regular surveillance tailored to the individual patients' risk profile.[4, 5] Compliance to these guidelines may reduce CRC incidence and mortality in IBD patients.[6, 7] Indeed LS patients subjected to regular surveillance may benefit from 7 additional life years.[4] However, endoscopic guidance is less clear in specific IBD subgroups including IBD patients who underwent colectomy or with concomitant LS. This has resulted in a wide variation in daily practice, which may lead to an excessive number of colonoscopies and pouchoscopies, increased costs and put unnecessarily burden on patients.[8] By contrast, insufficient surveillance intervals may result in increased CRC risks and even mortality.

Results of our CRC risk assessment in specific IBD populations may contribute to surveillance recommendations. To this end, we translated our findings into a pouch surveillance strategy (**Chapter 7**). A surveillance strategy based on risk stratification is proposed, including yearly surveillance in those with prior CRC and the withholding of surveillance in IBD patients without a history of colorectal neoplasia. Furthermore, our data may aid the development of surveillance recommendations in other specific IBD subgroups, such as those with IRA or a rectal stump. A history of colorectal neoplasia should also be the major determinant indicating surveillance since this factor is the most important post-colectomy CRC risk factor in these subgroups as well. The higher CRC incidence and prevalence in IBD patients with a residual rectum (including IRA and rectal stump) compared to IPAA, especially in those with ulcerative colitis, may allow more frequent surveillance in this subgroup rather than withholding surveillance. However, similarly to colorectal surveillance, direct evidence regarding the benefit of surveillance is lacking. To this end, the identified risk factors may only assist in recommendations on surveillance.

In addition to the implications for a surveillance strategy, our data emphasize the importance of careful compliance to existing surveillance guidelines. For example, one patient with both LS and IBD in our cohort developed multiple CRC following insufficient endoscopic follow-up (**Chapter 2**). This is underlined in the literature by the observation that inadequate bowel preparation and inadequate surveillance intervals were the most important risk factors for interval CRC despite endoscopic surveillance in general IBD patients.[9]

Finally, our findings may impact surgical decision-making. As the presence of colorectal neoplasia may predict new and/or recurrent CRC development post-colectomy, this may

guide the choice between different surgical scenarios. For example, an abdominoperineal resection could be preferable over IPAA construction or a residual rectum in IBD patients with prior CRC. Likewise, the younger age of CRC development in LS patients with IBD may justify a more aggressive surgical approach in these patients, although one case series described 4 LS patient with IBD and LGD who underwent prophylactic colectomy not revealing malignancy.[1]

Reflection

One of the main strengths of these studies are the unique, large cohorts that we established with PALGA. As such, we identified all IBD patients with IPAA in The Netherlands (n = 1200) and investigated which of them developed pouch cancer. Furthermore, we established a unique cohort of patients with both LS and IBD. PALGA enabled us to generate data that reflect the IBD population at large rather than data from single tertiary referral centers. Especially in rare disease entities, such as pouch cancer, proper methods for the identification of patients and for the establishment of a large cohort are of major importance. Another strength of this thesis is that we used multiple approaches to confirm and explain our findings. For example, a systematic review and meta-analysis, one of the highest grades of evidence, was performed to verify our findings regarding pouch cancer risk assessment from the Dutch IBD and IPAA cohort.

Our studies also come with some limitations. These include the retrospective nature of PALGA studies and the small number of patients that reached the primary outcome (for example pouch cancer: n = 16 out of 1200). Although we presented one of the largest series thus far, risk factors for pouch cancer development could be missed due to lack of power. To this end, a meta-analysis was performed that pooled data from several cohorts. However, the heterogeneity of included studies, with for example different durations of follow-up hampered the interpretation of cancer rates and other results. Currently, an individual patient data meta-analysis is performed including data from several North-American centers and our center. One large dataset with well defined consistent variables is being created in order to identify risk factors for pouch cancer development with sufficient power.

Future perspectives

One of the main purposes of our CRC risk assessment was to generate data that could aid surveillance recommendations. Since we both established a large nationwide cohort and performed a meta-analysis to assess pouch cancer risk, it is not expected that better epidemiological evidence will be available in the next years. To assess the need for and impact of potential evidence-based surveillance programs, large prospective trials with long-term follow-up are required. Therefore, clear, feasible and up to date post-colectomy surveillance guidelines with wide acceptance need to be established. This may reduce the high variation in practice and allows its future evaluation. Similarly as for colorectal surveillance is done, the yield and number of interval carcinomas of such a strategy could be assessed.[6, 7]

Several questions remain with respect to surveillance that may be of interest for future research. These questions are related to the type of endoscopy (white light or chromo),

the biopsy protocol (random or targeted) and the stop criteria for surveillance. Moreover, the best strategy after detection of low grade dysplasia is unknown. Current colorectal surveillance guidelines may guide clinical practice with respect to these topics. However, specific knowledge in the post-colectomy setting regarding these questions may in future optimize endoscopic surveillance strategies after colectomy.

Although a multi-factorial etiology of CRC development in IBD is acknowledged, the exact etiology and pathophysiology remains not elucidated yet. For rectal stump, IRA and IPAA patients, and for patients with both LS and IBD, a better understanding of CRC development is needed. The concept of field cancerization including premalignant mutated, but histologically normal fields may contribute to CRC development.[10, 11] To this end, we are currently assessing clonality of pro-oncogenic mutations between pouch neoplasia and prior colorectal neoplasia in IBD. Further elucidation of the specific genetic steps could serve the diagnostic process and may aid the prediction of CRC development. In extension, the inflammatory process may be another potential factor that contributes to CRC development. This process could drive pro-oncogenic mutations and may impede repair mechanisms. Our LS cohort with IBD provides a unique opportunity to investigate the contributions of the inflammatory process to CRC development by comparing them with LS only.

INTESTINAL MALIGNANCIES – NEUROENDOCRINE TUMORS

Results of this thesis – Risk assessment

Although the prevalence of colonic neuroendocrine tumors (NET) is relatively low, we demonstrated an increased NET prevalence in IBD patients compared to the general population (**Chapter 3**). This may be attributed to frequent colonic resections in IBD as most NET are detected by coincidence during surgery. The higher NET prevalences we found in colonic resection specimens from diverticulitis and ischemia patients compared to those from patients with IBD support this hypothesis. Similarly to NET in the general population, the appendix was one of the anatomical preference sites.

Implications

Since NET have an excellent prognosis if diagnosed at an early stage, awareness of NET coexistence in IBD is of major importance for an accurate and timely diagnosis. NET may clinically simulate IBD, especially in Crohn's disease patients with ileal involvement. By considering NET early in the diagnostic process, early detection of NET may be facilitated and prognosis may be improved. However, the low absolute NET prevalence does not support additional colonoscopies or abdominal imaging for early NET detection.

Reflection

Although we adopted a nationwide approach, there are several limitations. One of the major limitations is that the total numbers of patients in the total IBD, diverticulitis and ischemia

cohorts are estimates based on extrapolated data. In addition, sampling bias may be present and final diagnoses are only based on individual pathology reports. Although these biases were inevitable for feasibility reasons to address our research questions, results of this study should be interpreted with caution.

Our risk assessment for NET development in IBD is very concise and does not embrace all potential questions. For example, the risk of NET development in the small intestines is not incorporated, whereas this is the anatomical location with the highest NET prevalence in the general population. Furthermore, potential risk factors are not explored as this was not allowed by our study design.

Future perspectives

Despite all raised limitations, one conclusion that stands is the low NET prevalence in IBD patients, although an increased NET risk is present compared to the general population. Future studies that also aim NET risk assessment in IBD could refine these findings. The focus of future studies should be shifted towards underlying pathophysiological mechanisms and toward the outcome of IBD and NET. Inflammation may hyperstimulate entero-endocrine cells leading to hyperplasia and neoplasia, however studies that firmly approve this mechanism are lacking. Therefore, future studies that unravel the underlying NET mechanism in IBD and that predict the outcome may be beneficial to optimize treatment and prevention strategies.

EXTRA-INTESTINAL MALIGNANCIES

Results of this thesis – risk assessment

In this thesis we demonstrated an increased renal cell carcinoma (RCC) risk in IBD patients with a more complex phenotype, probably as a result of incidental findings (**Chapter 4**). This is supported by a high number of incidentally detected RCC (51%) and consequently a younger age and lower disease stage at RCC diagnosis compared to the general population. Subsequently, this translated into a better survival following RCC independent of immunosuppression and anti-TNFα use.

Implications

Currently, IBD management following a diagnosis of cancer is a relevant topic. Case-by-case management is recommended based on cancer characteristics, the probable impact of IBD therapy on cancer evolution, and IBD severity. However, the body of evidence to guide management after a specific cancer diagnosis is limited at best. Our nationwide study contributes to this field and may aid in guiding IBD management after a diagnosis of RCC. As no adverse effect of IBD therapy on disease free and overall survival was observed, our data suggest that immunosuppression and anti-TNFα use could be considered following RCC.

In addition, our data emphasize that frequent use of the health care system, including abdominal imaging and surgery, may yield incidental findings. Indeed, both NET and RCC are frequently found by incidence. When interpreting data from epidemiological studies that assessed cancer risk in IBD, it could be questioned whether increased cancer risks are the result of a higher prevalence rate or of a higher detection rate.

Reflection

This study is limited by the retrospective character and absence of data regarding the total Dutch IBD population. This hampered us to determine the absolute RCC risk in patients with IBD and to compare it with that in the general population. Furthermore, dose and duration of IBD therapy were not taken into account during risk assessment as these data could not be reliably retrieved for all cases in a retrospective setting. The total dose as well as the interval time between RCC diagnosis and IBD treatment may impact survival and outcome, however we were not able to assess this. Furthermore, the use of different databases and registries may have introduced biases, such as selection bias and slightly different defined variables.

Future perspectives

Data for case-by-case cancer management is limited and more cancer specific data are not only needed for RCC, but for multiple cancer types. Therefore, several studies currently assess specific cancer risks including the effect of IBD therapy on cancer outcome and vice versa. As such, risk assessment is performed by our research group for gastric cancer, head and neck cancer, and melanomas, using similar databases and registries. The comparable study design brings the same limitations; however, many cancers are rare, which makes it difficult to design prospective IBD studies of sufficient size to reach meaningful conclusions.

Since the retrospective character was one of the major limitations of the RCC study, future studies should adopt a prospective study design. This allows for example accurate registration of medical treatment and subsequently evaluation of the impact on cancer outcomes. The CESAME study cohort in France and the South-Limburg cohort in The Netherlands are such prospectively established population-based IBD cohorts.[12, 13] However, the numbers of index cancers in these cohorts are small, which impedes cancer site specific analyses. Future studies may benefit from comprehensive prospective registries that register all IBD patients with newly diagnosed cancers including medical treatment. This will allow the evaluation of IBD treatment on cancer outcome and vice versa, including the effect of dose and duration. Furthermore, the prospective registration of all IBD patients on immunosuppressive and/or anti-TNFα therapy may aid cancer risk assessment in this subgroup of patients. Such a registry is recently started in The Netherlands (IB-DREAM).

It could be questioned whether IBD patients with a prior malignancy are more prone to develop a new cancer. In our IBD and RCC cohort we detected many patients with more than one cancer and it has previously been shown that patients with a history of cancer were at increased risk to develop new or recurrent cancer. Future studies should evaluate whether IBD patients are at increased risk to develop multiple cancers compared to the general population. One could speculate that a certain IBD genotype, and/or phenotype, in combination with specific IBD therapies, could underlie susceptibility to cancer development.

CONCLUSIONS

Cancer development in IBD has become one of the growing concerns in recent decades, especially given the aging population. In this thesis we assessed cancer risks and outcomes

for solid intestinal (both CRC and NET) and extra-intestinal malignancies (RCC). We identified relatively low prevalences of post-colectomy CRC with a history of prior CRC as the most important risk factor for IPAA, IRA and rectal stump cancer development. Furthermore, NETs and RCCs were frequently detected by incidence. This translated into a better survival in IBD patients with RCC compared to the general population, independent of immunosuppressive and anti-TNFα use. In general, epidemiological studies describe disease patterns, risk factors, and outcomes in defined study populations, which may shape evidence-based practice and policy decisions. Indeed, our findings may lead to more optimized and evidence-based surveillance and treatment strategies in IBD management.

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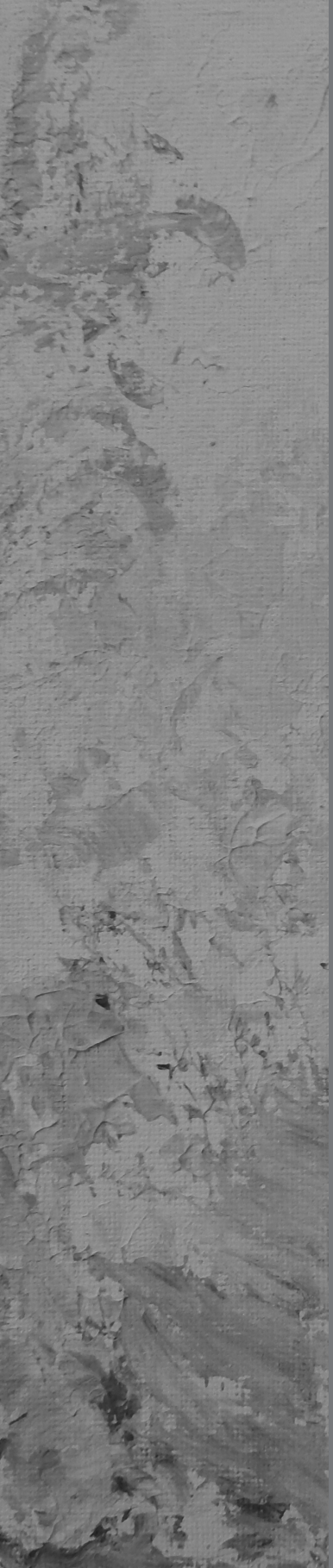

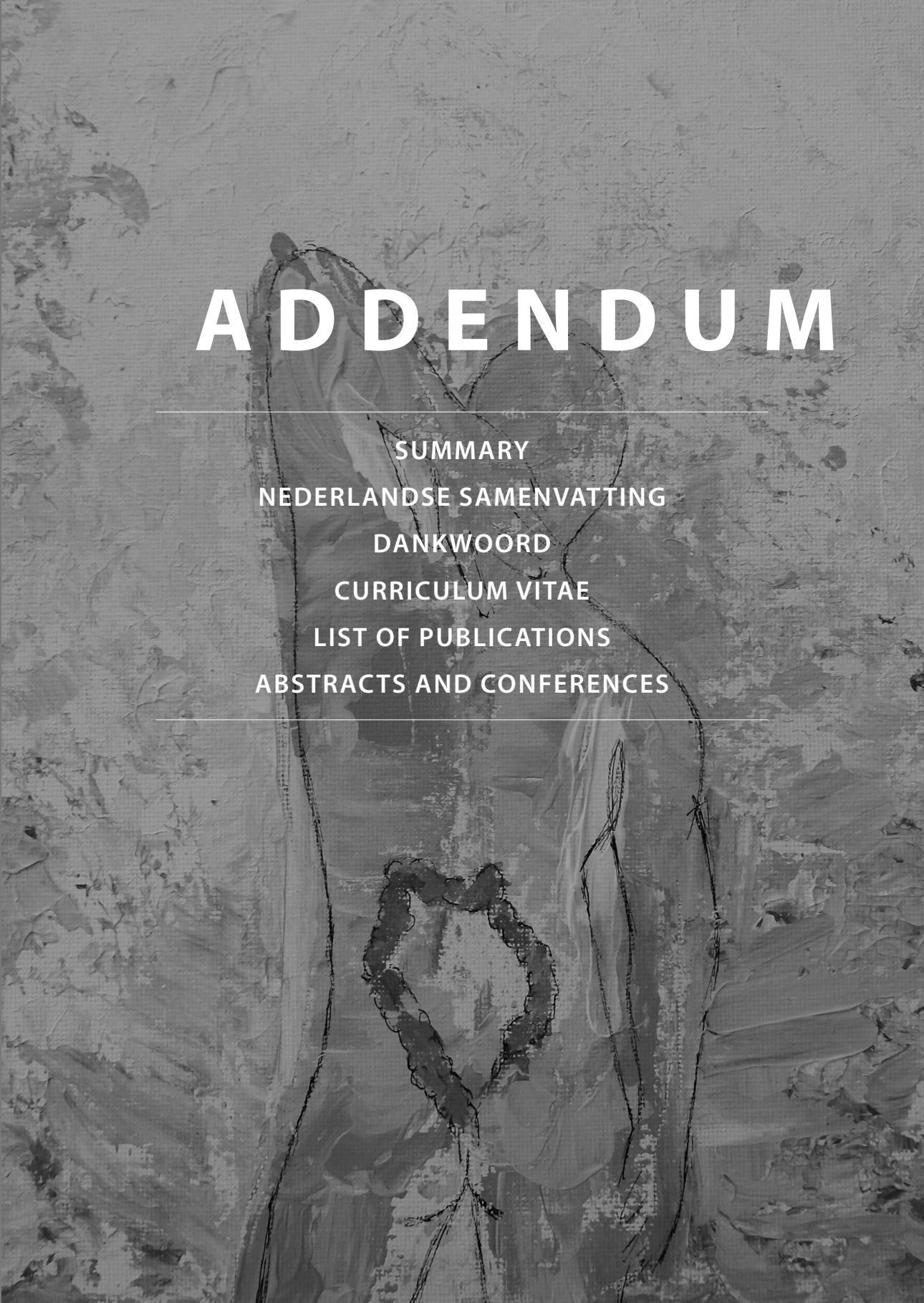

ADDENDUM

SUMMARY

Malignancies in inflammatory bowel disease

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory disorders affecting the gastro-intestinal tract. They are associated with both an increased intra- and extra-intestinal cancer risk, which can be mainly attributed to chronic inflammation as well as immunosuppressive therapies. Intestinal malignancies, such as colorectal cancer (CRC), are especially associated with chronic inflammation. Therefore, control of mucosal inflammation with (immunosuppressive) therapy is warranted. By contrast, these therapies may promote or inhibit the development of (extra-)intestinal malignancies by impairing immunosurveillance of tumor cells or inducing DNA damage. Further evidence is required to optimize management strategies that can achieve reduction of chronic inflammation with an acceptable safety profile while reducing cancer risk. To this end, this thesis provides epidemiological risk assessment of solid intra- and extra-intestinal malignancies and translation of risk profiles into recommendations for daily clinical practice.

In **Chapter 2** CRC risk is assessed in patients with both IBD and Lynch syndrome (LS). Both conditions are associated with an increased CRC risk due to inflammatory and genetic factors, although it is unknown whether this risk is further increased in patients with both IBD and LS. In our multicenter LS cohort, consisting of 1046 patients, 15 patients also carried a diagnosis of IBD (1.4%). Four of these 15 patients (26.7%) developed CRC, which was comparable to LS patients without IBD (311/1031, 30.2%). However, patients with both IBD and LS were younger and thus had less time to develop CRC (median 38.0 y versus 52.0 y, $p = 0.001$). Patients with both IBD and LS in our cohort developed CRC at a younger age (median 36.0 y versus 46.0 y, $p = 0.045$) and especially patients with UC were at increased risk. These findings may contribute to surveillance and treatment recommendations, although limited by the relative small number of cases. For example, we recommend careful compliance to existing IBD and LS surveillance recommendations since one of our cases developed multiple CRC due to insufficient follow-up.

Chapter 3 describes neuro-endocrine tumor (NET) risk in IBD patients since inflammation may cause hyperstimulation of enteroendocrine cells leading to hyperplasia and neoplasia. Indeed, an association between IBD and NET has been described in the literature, however contradicting results exist. Using the Dutch Pathology Registry (PALGA) we identified 51 IBD patients who developed colonic NET in a 20-year period (1991–2011), resulting in a prevalence of 60.4–89.3 per 100,000 patients. Colonic NET was more prevalent in IBD patients compared to the general population (prevalence rate ratio 2.8–4.1), which may be attributed to a high rate of incidental NET as IBD patients frequently undergo intestinal surgery. To this end, we compared NET prevalence in colonic resection specimens between IBD cases and non-IBD controls (diverticulitis and ischemia). Adjusted for resection type, sex and age, IBD patients had a lower NET prevalence in colonic resection specimens compared to diverticulitis and ischemia. This supports our hypothesis that frequent incidental NET detection during surgery may results in increased NET prevalences in IBD patients compared to the general population.

Chapter 4 is focused on extra-intestinal malignancies since certain cancer types occur more commonly in IBD. We investigated renal cell carcinoma (RCC) risk and outcome in IBD patients, with focus on the impact of immunosuppression and anti-TNFα agents. 180 IBD patients who developed RCC between 1991 and 2013 were identified with PALGA. First, clinical characteristics of these patients were compared with a population-based IBD cohort (IBD South Limburg cohort) to identify risk factors for RCC development. Second, RCC characteristics and survival were compared between IBD cases and the general population (identified from the Eindhoven Cancer Registry, maintained by the Netherlands Comprehensive Cancer Organization). This study demonstrated that IBD patients with a complex phenotype (including Montreal E3 UC, penetrating CD and/or IBD related surgery) were at increased risk to develop RCC. This may be the result of more frequent and intensive use of the health care system, including abdominal imaging. Consequently, IBD patients were significantly younger at RCC diagnosis ($p < 0.001$) and had a lower RCC stage (N-stage, $p = 0.025$; M-stage, $p = 0.020$) compared to the general population. This translated into a better survival ($p = 0.026$; hazard ratio 0.7) independent of immunosuppression. As no adverse effect of IBD therapy on survival was observed, our data suggest that immunosuppressive agents may be considered following RCC.

Part II of this thesis describes CRC risk in IBD in different post-surgical scenarios following colectomy, including the permanent end ileostomy and rectal stump, ileorectal anastomosis (IRA), and ileal pouch-anal anastomosis (IPAA). Currently, the increased CRC risk in IBD patients with an intact colon is taken into account in endoscopic surveillance guidelines. A colectomy substantially reduces CRC risk, however it is unknown how this should impact surveillance strategies. To this end, we established risk profiles for CRC development following colectomy and translated this into surveillance recommendations.

In **Chapter 5** the risk to develop ileoanal pouch neoplasia in patients with IBD is investigated. All IBD patients with IPAA in the Netherlands were identified between 1991 and 2012 using PALGA (n = 1200). Sixteen out of 1200 patients developed pouch carcinoma resulting in a cumulative pouch carcinoma incidence of 0.6%, 1.4%, 2.1%, and 3.3% after respectively 5, 10, 15, and 20 years. Subsequently, a case control study was performed to identify risk factors for pouch neoplasia development. Prior colorectal dysplasia and prior CRC were associated with an approximate 4- and 25-fold increase in risk, respectively, to develop pouch neoplasia.

Chapter 6 includes a systematic review and meta-analysis establishing CRC risk in IBD patients post-colectomy. Based on 13 studies about CRC development in the rectal stump, 35 IRA studies and 33 IPAA studies, we calculated CRC prevalences. The cancer prevalence appeared to be dependent on the type of surgery and was highest in IRA patients (2.4%), followed by patients with a rectal stump (2.1%), and lowest in IPAA patients (0.5%). This resulted in an odds ratio of 6.4 to develop CRC for patients with a residual rectum (rectal stump, IRA) compared to IPAA patients. In line with **Chapter 5**, prior CRC was the most important risk factor for developing rectal or pouch carcinoma (IRA group: odds ratio 12.8; IPAA group: odds ratio 15.0). Furthermore, we identified IBD duration and a diagnosis of UC rather than CD as risk factors.

Chapter 7 translates our findings from **Chapter 5** and **Chapter 6** into surveillance recommendations for IBD patients who underwent colectomy and IPAA. Given the available data, we proposed a strategy comprising risk stratification based on a history of colorectal neoplasia before colectomy. We recommend yearly surveillance in those with prior CRC and the withholding of surveillance in IBD patients without a history of colorectal neoplasia. Although many questions remain regarding surveillance, the implementation of a widely supported guideline for pouch surveillance would be a first step towards improved surveillance in IBD patients following IPAA construction.

In conclusion, this thesis assesses cancer risks and outcomes for solid intestinal (both CRC and NET) and extra-intestinal malignancies (RCC) in IBD patients. Risk profiles for cancer development and outcome are established and subsequently translated into treatment and surveillance recommendations. More cancer specific data enable an individualized approach and may in future contribute to case-by-case management of IBD patients with malignancies.

NEDERLANDSE SAMENVATTING

Maligniteiten bij inflammatoire darmziekten

Inflammatoire darmziekten (IBD) waaronder colitis ulcerosa (CU) en de ziekte van Crohn (ZvC) zijn chronische ontstekingsziekten van het maag-darmstelsel. Ze zijn geassocieerd met een verhoogd risico op zowel intra- als extraintestinale maligniteiten. Dit is hoofdzakelijk toe te schrijven aan chronische ontsteking en immunosuppressieve behandelstrategieën. Intestinale maligniteiten, zoals het colorectaal carcinoom (CRC), zijn met name geassocieerd met chronische ontsteking. Om deze reden is het beperken van de mucosale ontsteking middels (immunosuppressieve) behandeling van groot belang. Daarentegen kunnen deze therapieën de ontwikkeling van (extra-)intestinale maligniteiten ook juist stimuleren door verstoorde immuunsurveillance van tumorcellen of door het veroorzaken van DNA schade. Meer wetenschappelijk bewijs is nodig voor optimalisering van de behandelstrategieën leidend tot adequate reductie van de chronische ontsteking, een acceptabel veiligheidsprofiel en een verminderd risico op maligniteiten. Dit proefschrift omvat een epidemiologische risico analyse betreffende het ontwikkelen van solide intra- en extra-intestinale maligniteiten en een vertaling van deze risicoprofielen naar aanbevelingen voor de dagelijkse klinische praktijk.

In **Hoofdstuk 2** is het risico op CRC onderzocht bij patiënten met IBD en het Lynch syndroom (LS). Beide aandoeningen zijn geassocieerd met een verhoogd risico op CRC door inflammatoire en genetische factoren. Het is echter onbekend of dit CRC risico hoger is bij patiënten met zowel IBD als LS. In ons multicenter LS cohort, bestaande uit 1046 patiënten, hadden 15 patiënten ook IBD (1,4%). Vier van deze 15 patiënten (26,7%) ontwikkelden CRC, wat vergelijkbaar was met de LS patiënten zonder IBD (311/1031, 30,2%). Echter, de patiënten met zowel IBD als LS waren jonger en hadden dus minder tijd om CRC te ontwikkelen (mediaan 38,0 jaar versus 52,0 jaar, p = 0,001). De patiënten met zowel IBD als LS in ons cohort ontwikkelden CRC op een jongere leeftijd (mediaan 36,0 jaar versus 46,0 jaar, p = 0,045) en met name de patiënten met CU hadden een hoger risico. Deze bevindingen kunnen bijdragen aan aanbevelingen voor surveillance en behandeling, hoewel dit wordt gelimiteerd door het beperkte aantal cases. Ons advies is om nauwgezet de bestaande surveillance richtlijnen op te volgen aangezien één van onze patiënten multipele CRC ontwikkelde ten tijde van inadequate follow-up.

Hoofdstuk 3 beschrijft het risico op neuro-endocriene tumoren (NET) bij patiënten met IBD. Inflammatie kan zorgen voor hyperstimulatie van entero-endocriene cellen, mogelijk leidend tot hyperplasie en neoplasie. In de literatuur wordt inderdaad een associatie beschreven tussen IBD en NET, hoewel er tegenstrijdige resultaten worden gerapporteerd. Middels de Nederlandse Pathologie Database (PALGA) hebben we 51 IBD patiënten geïdentificeerd die een NET in het colon ontwikkelden gedurende een periode van 20 jaar (1991–2011). Dit resulteerde in een prevalentie van 60,4-89,3 per 100.000 patiënten. Een NET in het colon kwam vaker voor bij IBD patiënten in vergelijking met de algemene bevolking (prevalentie ratio 2,8-4,1). Dit is mogelijk te wijten aan een hoog percentage per toeval gevonden NET aangezien IBD patiënten vaak darmoperaties ondergaan. Om deze reden

hebben we de NET prevalentie in colon resectiepreparaten van IBD patiënten vergeleken met die van niet-IBD controle patiënten (diverticulitis en ischemie). Gecorrigeerd voor resectie type, geslacht en leeftijd, hadden patiënten met IBD een lagere NET prevalentie in colon resectiepreparaten vergeleken met patiënten met diverticulitis en ischemie van het colon. Dit ondersteunt onze hypothese dat de frequente vondst van NET als toevalsbevinding gedurende operaties kan resulteren in een verhoogde NET prevalentie bij patiënten met IBD vergeleken met de algemene bevolking.

Hoofdstuk 4 is gericht op extra-intestinale maligniteiten omdat bepaalde vormen van kanker vaker voorkomen bij IBD. We onderzochten het risico op, en de uitkomst van niercelcarcinoom (Renal Cell Carcinoma, RCC) bij IBD patiënten, met specifiek aandacht voor de invloed van immuunsuppressiva en anti-TNFα medicamenten. 180 IBD patiënten die een RCC ontwikkelden tussen 1991 en 2013 werden geïdentificeerd middels PALGA. Ten eerste werden klinische karakteristieken van deze patiënten op bevolkingsniveau vergeleken met het IBD Zuid-Limburg cohort om risicofactoren te idenficeren voor het ontwikkelen van een RCC. Ten tweede werden RCC karakteristieken en overleving vergeleken tussen IBD patiënten en de algemene bevolking (geïdentificeerd middels het Integraal Kankercentrum Zuid, onderdeel van Integraal Kankercentrum Nederland). Onze studie liet zien dat IBD patiënten met een complex fenotype (waaronder Montreal E3 CU, penetrerende ZvC en/of IBD gerelateerde operaties) een hoger risico hadden om een RCC te ontwikkelen. Dit kan het gevolg zijn van vaker en intensiever gebruik van de gezondheidszorg, met hierbij het verrichten van abdominale beeldvorming. Inderdaad waren IBD patiënten significant jonger ten tijde van RCC diagnose ($p < 0,001$) en hadden ze een lager stadium RCC (N-stadium, $p = 0,025$; M-stadium, $p = 0,020$) in vergelijking met de algemene bevolking. Dit vertaalde zich naar een betere overleving ($p = 0,026$; hazard ratio 0,7), onafhankelijk van immuunsuppressiva gebruik. Aangezien er geen nadelige effecten werden geobserveerd van de IBD behandeling op de overleving, suggereren onze data dat immuunsuppressiva overwogen kunnen worden na RCC.

Deel II van dit proefschrift beschrijft het risico op CRC bij IBD in verschillende post-operatieve scenario's na colectomie, waaronder het permanente eindstandige ileostoma met rectumstomp, de ileorectale anastomose (IRA) en de ileoanale pouch (ileal pouch-anal anastomosis, IPAA). Momenteel zijn de huidige endoscopische surveillance richtlijnen gebaseerd op het CRC risico bij IBD patiënten met een intact colon. Een colectomie reduceert het risico op CRC substantieel, echter is het onbekend hoe dit verwerkt kan worden in een post-operatieve surveillance strategie. Om deze vraagstelling te beantwoorden, hebben we risicoprofielen opgesteld voor het ontwikkelen van CRC na een colectomie en deze profielen vertaald naar surveillance aanbevelingen.

In **Hoofdstuk 5** is het risico op het ontwikkelen van een ileoanale pouch neoplasie onderzocht. Alle IBD patiënten met IPAA in Nederland tussen 1991 en 2012 werden geïdentificeerd middels PALGA ($n = 1200$). Zestien van de 1200 patiënten ontwikkelden een pouch carcinoom, wat resulteerde in een cumulatieve pouch carcinoom incidentie van 0,6%, 1,4%, 2,1% en 3,3% na respectievelijk 5, 10, 15 en 20 jaar. Vervolgens werd een case-control studie verricht met als doel het identificeren van risicofactoren voor het ontwikkelen

van pouch neoplasie. Een voorgaande colorectale dysplasie en een voorgaand CRC waren respectievelijk geassocieerd met een 4- en 25-voudige toename van het risico op het ontwikkelen van een pouch neoplasie.

Hoofdstuk 6 betreft een systematische review en meta-analyse waarin het risico op CRC bij IBD patiënten na colectomie werd onderzocht. Hierin werd de CRC prevalentie berekend, gebaseerd op 13 studies over CRC ontwikkeling in de rectumstomp, 35 IRA studies en 33 IPAA studies. De prevalentie van CRC bleek af te hangen van het type operatie en was het hoogst in IRA patiënten (2,4%), gevolgd door patiënten met een rectumstomp (2,1%), en was het laagst in IPAA patiënten (0,5%). Dit resulteerde in een odds ratio van 6,4 op het ontwikkelen van CRC bij patiënten met een resterend rectum (rectumstomp of IRA) in vergelijking met IPAA patiënten. Zoals ook beschreven in **Hoofdstuk 5**, bleek een voorgaand CRC de belangrijkste risicofactor voor het ontwikkelen van een rectum of pouch carcinoom (IRA groep: odds ratio 12,8; IPAA groep: odds ratio 15,0). Daarnaast bleken de duur van IBD en een CU diagnose in plaats van ZvC risicofactoren voor CRC ontwikkeling.

Hoofdstuk 7 vertaalt onze bevindingen in **Hoofdstuk 5** en **Hoofdstuk 6** naar surveillance aanbevelingen voor IBD patiënten die een colectomie met IPAA ondergingen. Gezien de beschikbare data hebben we een strategie voorgesteld met risicostratificatie op basis van voorgaande colorectale neoplasie. We raden jaarlijkse surveillance aan in patiënten met een voorgaand CRC en onthouding van surveillance bij patiënten zonder voorgaande colorectale neoplasie. Hoewel vele vragen resteren omtrent surveillance, zou de implementatie van een breed gedragen richtlijn voor pouch surveillance een goede eerste stap zijn op weg naar optimalisatie van de surveillance in IBD patiënten met IPAA.

Concluderend beschrijft dit proefschrift kanker risico's en uitkomsten van solide intestinale (zowel CRC als NET) en extra-intestinale maligniteiten (RCC) bij IBD patiënten. Risicoprofielen voor de ontwikkeling en uitkomst van maligniteiten zijn opgesteld en vervolgens vertaald naar aanbevelingen voor behandeling en surveillance. Meer kanker specifieke data zijn van essentieel belang voor een geïndividualiseerde benadering. Dit kan in de toekomst bijdragen aan 'case-by-case' management van IBD patiënten met een maligniteit.

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Lauranne Derikx
Nijmegen, oktober 2016

CURRICULUM VITAE

Lauranne Derikx werd geboren op 18 juli 1988 te Oud en Nieuw Gastel (Noord-Brabant). Zij behaalde in 2006 cum laude haar Gymnasium diploma aan het Norbertuscollege te Roosendaal (Noord-Brabant). In datzelfde jaar startte zij met de opleiding Geneeskunde aan de Radboud Universiteit Nijmegen. Nadat zij zowel haar propedeuse (2007) als bachelor (2009) had ontvangen met het predicaat cum laude, behaalde zij in 2013 haar artsexamen.

Gedurende haar opleiding volgde Lauranne een wetenschappelijke stage aan de afdeling Maag-, Darm-, Leverziekten van het Radboud Universitair Medisch Centrum te Nijmegen onder begeleiding van dr. F. Hoentjen. Ze onderzocht het risico op pouch neoplasieën bij patiënten met inflammatoire darmziekten en de hieruit volgende publicatie werd bekroond met verschillende onderzoeksprijzen (Onderwijs- en Opleidingsregio Oost Nederland Onderzoeksprijs 2014, PALGA prijs 2014, Best Paper Award 2014). Na aanvankelijk 4 maanden werkzaam te zijn geweest als ANIOS Maag-, Darm-, Leverziekten in het Radboudumc, vervolgde zij haar wetenschappelijke stage met een promotietraject. Hierin onderzocht zij het risico op verschillende intra- en extra intestinale maligniteiten bij patiënten met inflammatoire darmziekten.

In het kader van haar opleiding tot Maag-, Darm-, Leverarts, begon Lauranne op 1 oktober 2015 aan haar vooropleiding Interne Geneeskunde in het Jeroen Bosch Ziekenhuis te 's Hertogenbosch (opleider mw. dr. W. Smit).

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